Asian Journal of Pharmaceutical Sciences 15 (2020) 661–684

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/AJPS

Review

Recent trends on wound management: New therapeutic choices based on polymeric carriers

Mehmet Evren Okur[a], *Ioannis D. Karantas*[b], *Zeynep Şenyiğit*[c], *Neslihan Üstündağ Okur*[d,*], *Panoraia I. Siafaka*[e,**]

[a] *Department of Pharmacology, Faculty of Pharmacy, University of Health Sciences, Istanbul TR-34668, Turkey*
[b] *Hippokration General Hospital, 2nd Clinic of Internal Medicine, Thessaloniki 54124, Greece*
[c] *Department of Pharmaceutical Technology, Faculty of Pharmacy, İzmir Katip Çelebi University, İzmir, Turkey*
[d] *Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Health Sciences, Istanbul TR-34668, Turkey*
[e] *Department of Chemistry, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece*

ARTICLE INFO

Article history:
Received 11 September 2019
Revised 13 November 2019
Accepted 27 November 2019
Available online 23 January 2020

Keywords:
Wound
Infection
Dressings
Scaffolds
Biomaterials
Wound healing

ABSTRACT

Wound healing is an unmet therapeutic challenge among medical society since wound assessment and management is a complex procedure including several factors playing major role in healing process. Wounds can mainly be categorized as acute or chronic. It is well referred that the acute wound displays normal wound physiology while healing, in most cases, is seemed to progress through the normal phases of wound healing. On the other hand, a chronic wound is physiologically impaired. The main problem in wound management is that the majority of wounds are colonized with microbes, whereas this does not mean that all wounds will be infected. In this review, we address the problems that clinicians face to manage while treat acute and chronic wounds. Moreover, we demonstrate the pathophysiology, etiology, prognosis and microbiology of wounds. We further introduce the state of art in pharmaceutical technology field as part of wound management aiming to assist health professionals to overcome the current implications on wound assessment. In addition, authors review researches which included the use of gels and dermal films as wound healing agents. It can be said that natural and synthetic drugs or carriers provide promising solutions in order to meet the wound management standards. However, are the current strategies as desirable as medical society wish?

* Corresponding authors. University of Health Sciences, Department of Pharmaceutical Technology, Istanbul TR-34668, Turkey
** Corresponding authors. Aristotle University of Thessaloniki, School of Chemistry, Thessaloniki 54124, Greece.
E-mail addresses: neslihanustundag@yahoo.com (N. Üstündağ Okur), siafpan@gmail.com (P.I. Siafaka).
Peer review under responsibility of Shenyang Pharmaceutical University.

https://doi.org/10.1016/j.ajps.2019.11.008

1. Introduction

From ancient years till now, wound assessment is a challenge beyond medical society. In most cases, wounds are associated with increased morbidity as well as substantial mortality [1,2]. As wounds are any disruptions or injuries of anatomical structure and function due to severe breakage in organs such as skin. This break can extend further to other tissues and structures such as subcutaneous tissue, muscles, tendons, nerves, vessels as well as bone. It can be said that the skin, the largest human organ is mostly exposed to damage since can be easily burned or injured either by trauma or surgery. Wounds are mainly classified as acute or chronic; acute wounds processed through the normal phases of wound healing as well as exhibit well-defined signs of healing within four weeks, whereas chronic wounds do not show normal progress through the healing stages and healing is not obvious within four weeks.

Wound healing is one of the most complex processes in multicellular organisms, involving multi phases during process which include hemostasis/inflammation phase, proliferation phase, and remodeling phase [3]. Unbalancing one or more of these phases could lead to two distinct damaging outcomes: either chronic wound development or the formation of a hypertrophic scar/keloid [4]. It can be said that the healing process relies upon local wound factors, systemic mediators, any underlying disease as well as the injury type [5]. Clinicians recommend that the primary intention of wound healing associates with the closure of wound edges via sutures, clips or skin adhesive. The secondary intention arises, when the edges cannot be approached so the wound remains open and the defected area slowly being filled with connective tissue. These wounds healed slowly and are susceptible to infections. Commonly, this happens to patients with underlying conditions such as vascular, diabetic or pressure ulcers as well as in patients with post-surgical wound infections, haematomas or mechanical tension. Finally, tertiary intention, or delayed primary intention, includes wound to left open until the removal of non-viable tissue due to any infection or contamination, then the wound edges are approached. Finally, the healing carries on similarly to primary intention [6].

1.1. *Classification of wounds*

Acute wounds are associated with the external corruption of intact skin and consist of surgical wounds, bites, burns, minor cuts and abrasions as well as severe traumatic lacerations or caused by crush or gunshot injuries. It has been well documented acute wounds expect to heal within a predictable time regardless the nature of cutaneous injury. However, the decided healing treatment will be modified in accordance with the type, site and depth of a wound. The primary closure of a clean, surgical wound requires minimal intervention to enable healing to progress naturally and quickly. Nonetheless, in a more severe traumatic injury such as a burn or gunshot wound, the presence of devitalized tissue and contamination with viable and nonviable foreign material requires surgical debridement and antimicrobial therapy. This fact allows healing progress through the natural process, including inflammation and granulation, to final re-epithelization and remodeling.

On the other hand, chronic wounds are most frequently generated by endogenous mechanisms due to a predisposing condition which ultimately compromises dermal and epidermal tissue integrity. The formation of chronic wounds such as leg ulcers, foot ulcers, and pressure sores could be a consequence of impaired arterial supply (peripheral vascular disease) or impaired venous drainage (venous hypertension) and metabolic diseases such as diabetes mellitus. Chronic ulceration could also be exacerbated by advancing age, obesity, smoking, poor nutrition, and immunosuppression associated with disease (e.g., AIDS) or drugs (e.g., chemotherapy or radiation therapy). On the contrary, the formation of pressure or decubitus ulcers is caused by sustained external skin pressure, most commonly on the buttocks, sacrum and heels. Nevertheless, the underlying pathology is often responsible for the chronicity, and in this situation, pressure sores, like all chronic wound types, heal slowly in an unpredictable manner [7].

1.2. *Microbiology of chronic wounds*

The main problem arise on chronic wounds is that this type of wounds are easily contaminated by bacteria. In most cases, wound healing can occur despite the presence of bacteria. Indeed, some bacteria appear to promote wound healing. However, it seems that the interaction between the presence of the bacteria and the patient determines their influence on wound healing. Clinicians should be able to differentiate wound contamination, colonization and finally infection.

Wound contamination: All chronic wounds are contaminated. These contaminants come from the indigenous microbiota and/or the environment.

Wound colonization: Colonization is defined as the presence of proliferating bacteria without a host response and this is a very common procedure. Most of these organisms are normal skin microbiota like *Staphylococcus epidermidis*, other coagulase negative *Staphylococcus Corynebacterium* sp., *Brevibacterium* sp., *Proprionibacterium acnes*, *Pityrosporum*sp [1,7].

Wound Infection: At this point, proliferating bacteria invaded not only on the surface of the wound but into deeper, healthy viable tissue on the periphery of the wound, eliciting host response. Primarily pathogens found when wound is infected *Staphylococcus aureus* (*S. aureus*), Beta-hemolytic *Streptococcus* (*Streptococcus pyogenes, Streptococcus agalactiae*), *Escherichia coli* (*E. coli*), *Proteus, Klebsiella, Pseudomonas, Acinetobacter, Stenotrophomonas* (*Xanthomonas*) [7,8]. It has been reported that in early acute wound the normal skin microbiota is predominate. *S. aureus*, and Beta-hemolytic *Streptococcus* follow soon. These are common organisms found in diabetic foot ulcers.

After about 4 weeks: Facultative anaerobic gram negative rods like *Proteus, E. coli, and Klebsiella* will colonize the wound. As the wound deteriorates deeper structures are affected. Very often infections are polymicrobial [1].

Long-term chronic wounds often contain more anaerobes than aerobes. For example, *Pseudomonas, Acinetobacter as well as Stenotrophomonas (Xanthomonas)* are commonly found on chronic wounds [7,9].

2. Phases during wound healing process

2.1. Haemostasis

Haemostasis is the normal response of vessel to injury by forming a clot that limits hemorrhage. The decreased blood flow mediated by arteriolar narrowing in a few minutes induces tissue hypoxia and acidosis. At the same time, histamine releases from mast cells. This can also enhance vasodilatation and vascular permeability, helping inflammatory cells to enter the extracellular space of wound [10]. The coagulation involves thrombocytes aggregation and platelets in a fibrin network, confiding on the action of specific factors through the activation and aggregation of these cells. In addition to reestablish homeostasis and establish a barrier against the invasion of microorganisms, the fibrin network organizes the transient matrix necessary for cell migration, restoring skin function as a protective barrier for the integrity of the skin [11].

2.2. Inflammation

Inflammatory response is triggered immediately after the passive exposure of circulating neutrophils from damaged blood vessels into wounds. The inflammatory response carries on with active neutrophils and then macrophages from nearby vessels recruitment, which is orchestrated by growth factor signals from the resident cells and serum, as well as by foreign epitopes such as the lipopolysaccharides (LPS) of invading microorganisms [11,12].

It is known that pro-inflammatory cytokines and active antimicrobial substances, such as reactive oxygen species (ROS), cationic peptides and proteases at the location of the lesion are expressed by neutrophils. Recruitment of activated neutrophils in answer to the activation of complement system, platelet degranulation and bacterial degradation products provides continuance of the inflammatory response [13]. Then, neutrophils are primary activated and collected cells that play a role in clearing the tissue and at the same time contribute to the death of the invading agents [2]. Only a few hours after the formation of lesion, a large quantity of neutrophils transmigrate through endothelial cells present in blood capillary walls, which are activated by pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), IL-1 β and interferon gamma (IFN-γ) at the location of lesion [11]. Neutrophils are either phagocytosed by macrophages or undergo apoptosis, or even get exuded from the wound surface. Macrophages are large phagocytic cells with high number of growth factors, such as platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), TGF-α, fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF) which achieve the highest concentration in the wound, at 2-3 d after injury [14]. These growth factors are of high importance for the regulation of inflammatory response, stimulation of angiogenesis as well as for the formation of granulation tissue [10].

2.3. Proliferation

Proliferative phase occurs between 4 to 21 d, and represents angiogenesis, extracellular matrix (ECM) formation and epithelization. ECM formation starts with platelet degranulation, because PDGF is a known promoter of proteoglycan and collagen formation [15]. During the proliferative phase, wound defect is filled with highly vascular connective tissue, commonly known as 'granulation tissue' [6]. Angiogenesis starts when the haemostatic plug has formed due to release of TGF-β, PDGF and FGF by platelets. VEGF and other cytokines are released in response to hypoxia, and then lead to endothelial cells to promote neovascularization and the damaged blood vessels repair [10]. TGF-β has been described as a potent growth factor involved in wound healing. Furthermore, fibroblasts proliferation is provoked by growth factors released from haemostatic clot and then migrate to the wound [6]. Migration of epithelial cells starts from wound edges within a few hours of wounding. A single layer of cells initially forms over the defect, accompanied by a marked increase in epithelial cell mitotic activity around the wound edges. When advancing epithelial cells meet, migration stops and basement membrane starts to form [14].

2.4. Remodeling

Remodeling which is the third phase of healing, starts two to three weeks after the onset of the lesion and can continue for one year or more [2,16]. Remodeling occurs after the formation of fibrin clot in the early inflammatory phase which is replaced by the granulation tissue that is abundant with collagen III and blood vessels during the proliferative phase. Consequently, it is reintegrated by a collagenous scar rich in type I collagen with much less mature blood vessels [16,17]. The main key points of wound repairing process are the growth factors which are polypeptides released by several activated cells at the wound site and trigger cellular proliferation as well as attract new cells to the wound [18]. Fig. 1 summarizes the phases of wound healing.

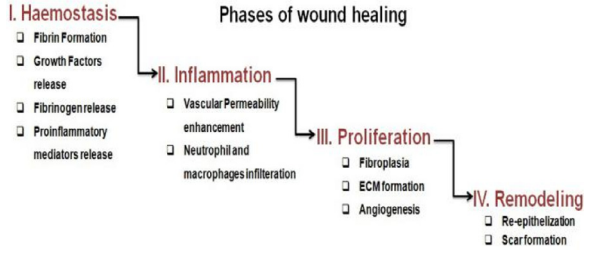

Fig. 1 – Phases of wound healing.

3. Important factors in wound healing process

It has been reported that many wounds might be rapidly healed while other type of wounds tend to become chronic and trapped in the inflammatory phase. Many factors play role for such compromise. First of all, high levels of inflammatory mediators emerged damage to growth factors and the extracellular matrix which are essential for healing. A major problem during wound healing process is the possibility of a wound to be rapidly colonized by bacteria or fungi. This is because wound infection reduces growth factors and degrades the essential fibrin for healing. In addition, bacteria induce the inflammatory response and thus chronic wounds often have high levels of bacteria. Obviously, by reducing the bacterial healing process will be improved [19]. In further, biofilm which is a complex structure that can adhere to a surface, involved in the production and maintenance of the chronic wound environment. Among others, hypoxia hinders wound healing process by impeding fibroblast proliferation and collagen production and allows certain negative entities, such as bacteria, to flourish. It seems that common chronic conditions such as cardiovascular disease [20], smoking, pulmonary diseases and peripheral vascular disease (PVD) result in hypoxia. So, the proper management of these conditions can improve wound healing [21]. Furthermore, smoking hampers wound healing since it can affect chemotaxis, migratory function as well as oxidative bactericidal mechanisms during the inflammatory phase [22]. Many drugs that debilitate the inflammatory response can also disrupt the healing process. For instance, oral steroids found to diminish cytokine concentrations, inducing decreased collagen deposition [10]. Diabetes is one of the metabolic diseases which hinder the wound healing process [23,24]. Moreover, elderly patients are in higher risk to develop chronic wounds or complications since they present a thinner epidermal layer and show slower inflammatory, migratory and proliferation responses and they are also more likely to have chronic disease [10]. Finally, poor nutrition with low protein levels can delay wound healing. To conclude, these factors affect the wound healing process and so clinicians have to manage and overcome any barriers so as the wound healing process terminated easily [25].

3.1. *Wound assessment-management*

A very significant factor which the physician has to consider when assess the wounds is to identify treatment objectives at any given time [26]. According to Russell, it is significant to understand that wound management and wound healing have different meanings. It can be said that the actual granulation tissue generation is normally done by the patient and depends more on nutrition than the applied dressings [27]. Consequently, 'Ideal Dressing' cannot be found easily but it should be selected by the physician after wound assessment, intended treatment outcome, patient preference from previous experience and several points [28]. The key factor of wound management is to provide a warm, moist, non-toxic environment, which is ideal for natural wound healing. Among others, the clinician should treat the patient all his medical problems since coexistent diseases can hinder the wound healing process. Wound management should be accomplished alongside the treatment of any other medical problems and should be evaluated accordingly so as to compensate for their effects [29]. Summarizing, the properties of the ideal dressing for a wound it can be said that it should be safe, non-irritant, easy to apply, pain-free, cost-effective and highly absorbent.

4. Biomaterials for wound management

Biopolymers, polymers that produced by living microorganisms are commonly used as wound management. Nevertheless, seems that some polymers gain more attention than the others as wound dressings. Wound dressings should be designed to facilitate and accelerate the healing process; this can be achieved by protecting the wound from factors such as contaminations and moisture-loss that could delay or impair its healing. The used materials in wound dressings involve films, sponges, fibers or hydrogels from natural and synthetic polymers and their combinations (Fig. 2). Ideal wound-dressing should provide efficient oxygen permeability, but most importantly mimic the structural and biological characteristics of skin extracellular matrix (ECM) [30].

4.1. *Wound dressings from naturally-occurred polymers*

Naturally-occurring polymers are generally chosen for wound management over synthetic polymers because they are economical, non-toxic to human body and environmental-friendly (Fig. 3). Polysaccharides are natural polymers which are frequently applied as wound dressing materials. Cellulose, chitosan, pullulan, starch and β-glucan, as well as collagen, hyaluronic acid and alginate are among the most used polymers as wound dressings.

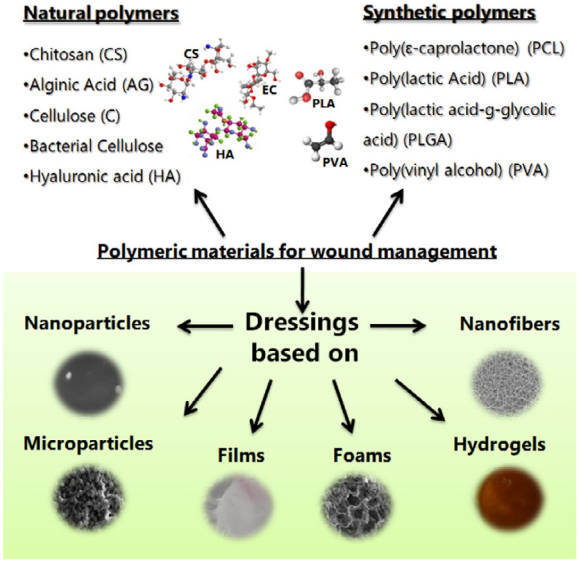

Fig. 2 – Biomaterials for wound management (photos from personal archive).

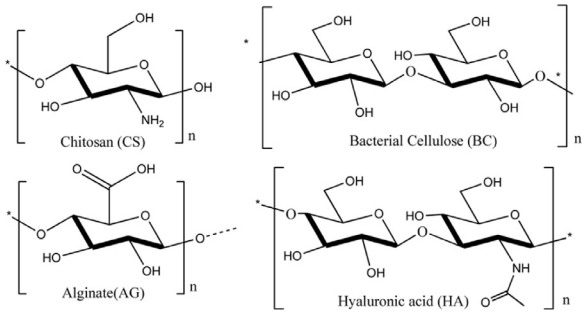

Fig. 3 – Natural polymers used in wound dressing applications.

4.1.1. *Chitosan based wound dressings*

Chitosan (CS) is a well studied natural polymer, frequently used in biomedical applications because of its antimicrobial activity and healing stimulation. It also promotes drainage, prevents the buildup of exudates, and serves as auto-grafting bed in wound therapy. Furthermore, CS promotes gas exchange which is essential in wound healing process [1,31–34]. CS based delivery systems for wound management can be widely found in literature. From nano or micro particles containing CS to wound dressings and hydrogels, this leading polymer may have the solution for the treatment of chronic and acute wounds.

The chemical properties of CS allow the formation of gels in acid media. The hydrogels exhibit good swelling behavior absorbing significant amount of water, while the developed Three-dimensional (3D) network structure when exposed to aqueous medium is a great feature for CS used as wound dressings [35]. CS-based hydrogels have been intensively engaged in wound healing since they are biocompatible and present activity against pathogenic microorganisms. For example, Ferreira et al. [36] developed and characterized CS gel system associated with chlorhexidine (2% and 4%). The antibacterial properties and healing activity of this hydrogel system were studied showing 100% inhibition of bacterial growth when strain *S. aureus* was applied. Animals were treated with CS hydrogel containing 2% chlorhexidine and the histological evaluation results revealed healing on the 14th day. Healing was better with 4% chlorhexidine groups in which all other lesions were closed on the 14th day. The results indicate that a promising material was obtained as healing agent with antibacterial properties.

The main disadvantages which limited the use of CS-based hydrogel are their poor mechanical properties and unsatisfied anti-bacterial performance. Therefore, many research groups are working on the use of CS in combination with other polymers to further improve its hydrophilic nature, increase antibacterial effect and enhance mechanical properties. Martínez Ibarra et al. [37] prepared a porous hydrogel with mixtures of CS and xyloglucan which is a vegetable-derived polysaccharide and act as soluble fiber. These porous hydrogels were characterized in terms of their mechanical, hydrophilic, structural and morphological properties as well as their biodegradability and antimicrobial activity. The pore sizes of porous hydrogels were found to be 32.8-101.6 µm and their water retention capacity is improved as the added amount of xyloglucan increased. Dynamic degradation of hydrogels showed progressive weight loss during 14 d with lysozymes. The results demonstrated that the incorporation of xyloglucan to hydrogels improved the mechanical properties of CS without affecting its antimicrobial capacity. Therefore, biomaterials based on CS and xyloglucan were found to be promising for hydrogel wound dressings.

In another study, a hydrogel system was synthesized with a chemical reaction of CS and carboxymethylcellulose polymers and with a crosslinker (N,N'-methylenebisacrylamide). Alpha-tocopherol was loaded to this hydrogel and characteristic features such as release profile were determined. In addititon, cell adhesion and proliferation was observed by 3-[4,5-dimethyl-2-thiazolyl]-diphenyltetrazolium bromide (MTT) method. The results indicate that alpha-tocopherol loaded hydrogels are effective for stimulating the healing process [35].

Mukherjee et al. [38] developed hydrogel dressings with interpolymeric complexation method to enhance wound healing activity in excision wound model. CS was cross-linked with polyvinyl alcohol, sodium alginate and Pluronic F68 at different ratios. Wound was created onto the rat dorsom with a biopsy punch and the efficacy of hydrogel dressing was evaluated based on the complete healing time of wounds. The hydrogel characterization studies showed that the formulations prepared with CS and sodium alginate exhibited the highest water vapor transmission value. CS and polyvinyl alcohol hydrogel formulation exhibited high tensile strength. CS and Pluronic F68 hydrogels exhibited better rate of wound healing when compared to other formulations within 15 d. The overall result showed that the hydrogel dressings using the blend of CS and hydrophilic polymers substantiated to be a potential wound dressing.

Yao et al. [39] prepared CS-based hydrogels by grafting poly(acrylic acid) and poly(hydroxyethyl methacrylate), and the epidermal growth factor (EGF) was incorporated to stimulate the wound healing effect. The physical characterization of hydrogels depicted their high hydrophilicity with adequate wound dressing properties. The biological characterization studies showed that CS-based hydrogel retains its thrombogenic and antibacterial properties. *In vivo* wound healing experiment demonstrates that the EGF incorporated hydrogel system has better wound healing rate than other dressings.

Hydrogels with self-healing capacity can undergo self-repair, establishing safer and longer-lasting products and provide better wound protection. Therefore, in another study, Schiff base reactions were utilized to design injectable self-healing hydrogels with CS and konjac glucomannan. The results indicate that in addition to injectable and self-healing properties, the hydrogels also had adhesive and antibacterial properties which were biocompatible, and promoted wound healing. These findings established a novel injectable hydrogel material that significantly shortened wound recovery time in a full-thickness skin defect model [40]. Similarly, konjac glucomannan was acetylated with different degrees of substitution and electrospun to nanofibrous structures. The nanofibrous film showed biocompatibility and good adhesion force between Raw264.7 cells. Moreover, the nanofibrous film revealed accelerating wound healing properties by promoting

re-epithelialization, tissue remodeling and collagen deposition, and thus can be used as wound dressings [41].

Liang et al. [42] developed a water-soluble carboxymethylcellulose sodium/sodium alginate/CS composite hydrogel system for burn wound dressing applications. It was found out that the hydrogel dressing presents desirable water vapor permeability which can contribute to enhance healing of deep second-degree burns in Sprague–Dawley rats. The results indicated that, the produced hydrogel dressing shows significant self-regulatory and anti-adhesive properties and can be safely applied in clinical practice for burn healing.

In respect to the relatively unsatisfied anti-bacterial performance of CS, Song et al. developed a self-healable cordycepin/CS hydrogel dressing by cross linking with non-covalent bonds. The hybrid hydrogel system exhibited excellent biocompatibility, suitable swelling, desired mechanical strength and remarkable antimicrobial effect with no side effects. In addition, the self-healable property of this hydrogel enables to adapt irregularly shaped wound defects without pre-molding. *In vivo* experiments confirmed that hydrogel dressing served as a quicker re-epithelization of skin wounds and an apparent increasing collagen deposition compared with CS hydrogels [43].

As it was mentioned previously, CS hydrogels show poor mechanical properties and this situation may hinder their use. Xie et al. prepared CS hydrogel by using LiOH/urea solvent system to overcome this problem. The incorporation of Ag nanoparticles (AgNPs) into these CS hydrogel networks, showed improvement on the mechanical and antibacterial properties of 3D porous network. In addition, the increment on the re-epithelization rate and collagen deposition induced wound healing. Consequently, the prepared hydrogel is advantageous for wound healing applications [44]. In another study, active wound dressing hydrogel system comprised from Punica granatum peel crude extract (PGPC), ethyl acetate fraction (PGPEA) and their silver nanoforms was designed for chronic wound healing applications. The methacrylated CS hydrogel was crosslinked by divinylsulfone and showed acceptable cytotoxicity against fibroblast human cells for PGPC and PGPEA fraction over the silver nanoforms. *In vivo* studies using rat as animal model revealed the desirable properties of dressing on diabetic wounds. Finally, the developed CS system was efficient as chronic wound dressings due to the significant intensity of immune-positivity signals of transforming growth factor beta and nuclear factor kappa-light-chain-enhancer of activated B cells in the epidermal cells [45].

Long et al. demonstrated a 3D printed CS-pectin hydrogel as possible wound dressing. The hydrogels were prepared by physical crosslinking of CS and pectin polysaccharides, and the local anesthetic drug lidocaine hydrochloride was incorporated to this biopolymeric hydrogel. Scaffolds were pextruded via a 3D printer followed by lyophilisation. The 3D hydrogels exhibited good printability, dimensional integrity and self-adhesion to skin as well as high swelling index and water absorption property. These data indicate their possible use as candidates for absorbing exudates and retaining a moist wound environment. This study revealed that the 3D printed hydrogel can be a favorable wound dressing [46].

Non-healing wounds are among the serious complications of type-2-diabetes, associated with bacterial infections, nerve and blood vessel damage and amputation of limbs and organs. Masood et al. study involves the development of Ag NPs loaded CS-poly ethylene glycol (PEG) hydrogel in order to promote wound healing in diabetic patients. CS-PEG-Ag nitrate based hydrogels were formulated to sustain the release of antibacterial AgNPs. From the physicochemical evaluation, it was ruled out that the incorporation of AgNPs led to improved porosity, swelling index and higher water vapor transition rate. Moreover, the loaded hydrogels exhibited enhanced antimicrobial and antioxidant properties which are crucial for wound dressing materials. Alongside, the hydrogel release AgNPs in a sustainable manner for at least 7 d. The above showed that the developed hydrogels present quite promising properties important chronic diabetic wounds healing [47].

Very interesting nanocomposite hydrogels were designed in order to be used for burn wound healing. The nanocomposite self-healing hydrogel which can be injected into irregular and deep burn wound beds, consisted of carboxymethyl-CS and rigid rod-like dialdehyde-modified cellulose nanocrystal. The promising hydrogel exhibits high biocompatibility which can generate cell growth (Fig. 4). The study is quite interesting given that the development of dissolvable self-healing hydrogels can accelerate the deep partial thickness burn wound healing, reducing pain when the dressing is frequently changed as well as prevent scar formation [48].

The crucial objective in wound care is to control infections of the injured area, so wound dressings with high antimicrobial activities are required in wound treatment. Regarding this, CS derivative films have been widely studied by many research groups as superficial wound dressings. Halim et al. evaluated the efficacy of CS films as superficial wound dressings via *in vivo* study included 244 patients. A number of 86 patients were treated with CS derivative film whereas 84 of them were treated with hydrocolloid. The main result of this work was that the percentage of epithelization between groups was quite similar. However, patients using CS derivative film felt more pain when the dressing was removed compared to hydrocolloid. In further study, CS derivative film group demonstrated less exudate and fewer odors than the control group. Moreover, similar data were found in terms of adherence, ease of removal, wound drainage, erythema, itchiness, pain, and tenderness between the groups. Finally, it can be said that both CS derivative film and hydrocolloid dressing is a beneficial solution for superficial and abrasion wounds [49].

In many research studies, it was found that CS films were not at the desired level in terms of some features. Therefore, improvement of mechanical properties and biomedical behavior was achieved by combining different polymer groups or NP based drug delivery systems with CS-based polymeric films. AgNPs are one of the most widely studied formulations to improve the antibacterial ability of wound dressings. Shao et al. designed CS membranes embedded with AgNPs so as to examine their efficacy as wound healing agents. The obtained data demonstrated that the inorganic ions hinder the silver release while the proteins block the silver release. More significantly, the AgNPs did not change

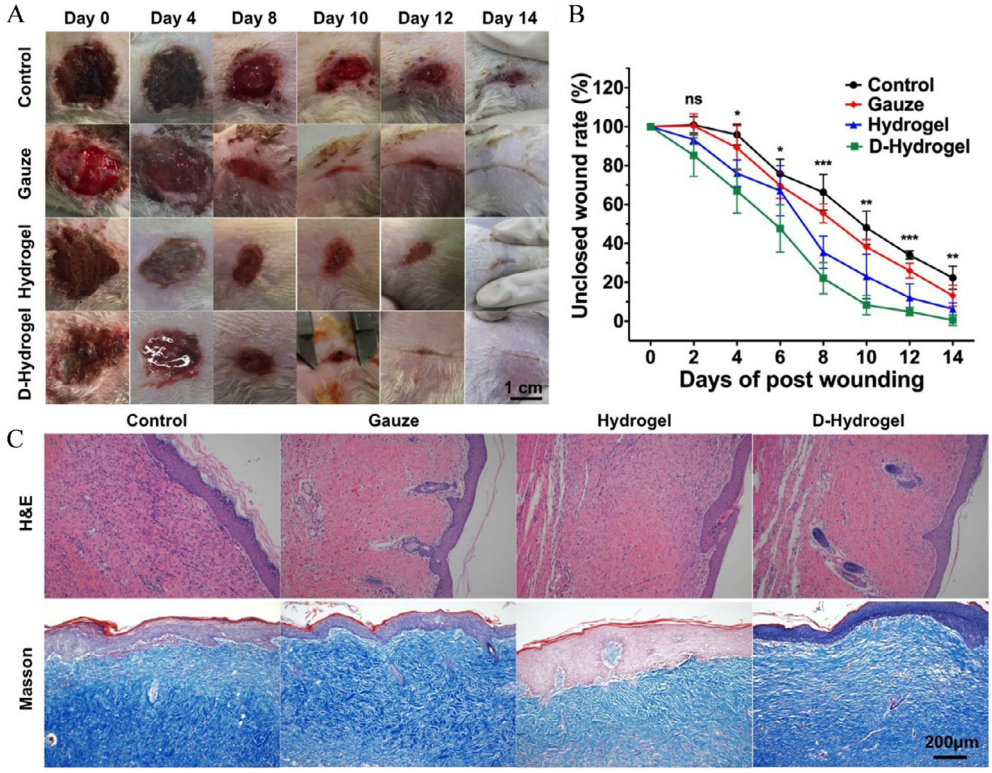

Fig. 4 – Wound healing progress: (A) images of a representative wound site from each group taken on post-injury days 0, 4, 8, 10, 12 and 14. (B) Unclosed wound area rate of initial wound untreated or treated with petrolatum gauze, hydrogel, and hydrogel with glycine at Day 0, 2, 4, 6, 8, 10, 12 and 14 (mean ± SD; $P > 0.05$, $^{*}P \leq 0.05$, $^{**}P \leq 0.01$, $^{***}P \leq 0.001$). (C) H&E staining and Masson's trichrome staining of wounds at Day 14. (Reprinted/adapted with permission from [48]. Copyright (2018) American Chemical Society).

wound healing rate and tissue response although high concentration of AgNPs was needed in order to achieve important *in vivo* antibacterial effects [50].

Shah et al. reported the development of nanocomposite films of CS and chemically reduced silver which further loaded with moxifloxacin. From the evaluation, the nanocomposite films exhibited increased swelling index, reduced tensile strength and great elongation at break compared to neat CS film. The release of moxifloxacin from the films was sustained while the drug permeation was found to be more than 60% in 24 h. The films were applied against *S. aureus*, *P. aeruginosa* and two strains of methicillin-resistant *S. aureus* (MRSA) exhibiting high antimicrobial activity. In summary, this study has proved that CS nanocomposite films have promising antibacterial potential and they might be recommended for their biomedical application as wound dressing [51]. Recently, Shah et al. developed novel moxifloxacin loaded chitosan-pullulan-silver-nanocomposite films with enhanced antibacterial properties, sustained drug release as well as permeability and thus could be employed as promising material in tissue engineering applications [52].

Kaolaor et al. studied how the β-cyclodextrin (β-CD) complexation of curcumin and the quaternization of CS can affect their properties. Quaternized CS containing curcumin (CUR-CS) and the quaternized β-CD grafted with CS containing curcumin (CUR-QCD-g-CS) were further blended with 4% poly(vinylalcohol) (PVA). The crosslinking with glutaraldehyde led to improvement of the mechanical properties of films. The physicochemical evaluation revealed that the developed CD films exhibited higher mechanical properties but lower water swelling and weight loss behaviors than the CUR-QCS/PVA films. Additionally, encapsulation of curcumin in the CD cavity promoted increased release of curcumin with higher antioxidant activity than CUR-QCS/PVA films [53].

Polymeric films, based on CS and gelatin were prepared and the effect of nanocrystalline cellulose (NCC) and calcium peroxide (CP) particles on the film properties were investigated. It was shown that the combination of both CP and NCC improved the mechanical strength of the films. On the other hand, CP and NCC particles decreased the percentage of water vapor transmission rate and swelling of the samples. Addition of CP to film formulation increased the antibacterial activity against *E. coli*. Finally, it was found that the human fibroblast cells growth was escalated during 7 d, showing that the developed films had no toxicity on healthy cells [54].

Wu et al. prepared starch–CS composite films and assessed their potential as wound dressings. Firstly, the amylose content of potato, corn and glutinous starch types were determined and found 35.3%, 30.5% and 9.7%, respectively. The glutinous rice starch–CS composite film, which had lower

amylose content presented a coarser surface, higher swelling rate, tensile strength and elongation at break. The results of MTT assay indicated that glutinous rice starch–CS composite film had greater biocompatibility with mouse fibroblast L929 cells and human keratinocyte HaCaT cells. The enzyme-linked immunosorbent assay indicated that glutinous rice starch–CS film was more capable of alleviating inflammation than other films. Briefly, the results indicated the suitability of the glutinous rice starch–CS film with for wound dressing material [55].

Recently, quaternized CS nanocomposite films were blended with AgNPs to produce effective wound dressing. It was ruled out that the quaternized CS film with and without AgNPs exhibited high antimicrobial activity against both gram-negative and gram-positive bacteria strains. More importantly, all the films showed biocompatibility on HFFF cells indicating that the quaternized CS nanocomposite films can be sufficiently used as wound dressings [56].

As described above, various manufacturing approaches have been employed to generate film dressings. 3D printing is one the newest approaches to fabricate film scaffolds with interesting morphology. In a study, crosslinked CS mats were prepared with 3D printing method. The researchers applied genipin as crosslinker and PEG as plasticizer. Morphology examination revealed the uniform smooth surface of the films whereas their brittle nature was confirmed due to the existence of micro cracks. In addition, the matrices were characterized as mudoadhesive due to their ability to adhere to the epithelial surface. In further, the cytocompatible mats expressed high swelling ability, with increasedwater absorption. The overall results proved that the 3D crosslinked CS dressing can be a promising strategyf for chronic wound healing applications [57].

As outlined here, different CS-based dressings have been developed over years; however, most of them are not fully biodegradable due to the involvement of synthetic polymers during dressing fabrication. In addition, the preparation method of these dressings is generally laborious, and may damage the fragile therapeutic molecules. Lai et al. performed a study to address these problems by developing a tunable, biocompatible, and biodegradable CS-based dressing for wound treatment. The dressing was prepared with electrostatic interactions between CS and carmellose. By changing CS/carmellose ratio; the swelling properties, erosion behavior, loading efficiency and drug release sustainability properties of the dressings were easily changed. The dressing was loaded with minocycline hydrochloride to protect the wound from infection and enhances wound closure. Regarding its high tunability and promising *in vivo* performance, this user-friendly dressing was found to be promising for use in wound care [58].

Biranje et al. successfully developed an effective, economic and biodegradable dressing containing CS NPs. NPs were developed via by ionic gelation method and impregnated into CS porous dressing using lyophilization. Patial enzymatic hydrolysis was seen due to the higher surface area and porosity of the dressing. Moreover, the dressing was biocompatible when hymal fibroblasts were used whereas haemostatic activity demonstrated that the blood when is contacting the dressing contained two-fold higher levels of Human Thrombin-Antithrombin, in comparison to that contacting the standard. From the above, it was indicated that the CS dressing can successfully remove the necrotic tissues and can enhance the haemostasis for sufficient and vigorous wound healing [59].

Melatonin-loaded NLCs and NLC-loaded microspheres were fabricated by hot homogenization technique and spray-drying method so as to design a novel dry powder wound dressing. It was revealed that the system when is in contact with simulated wound fluid provide hydrogel layer. The lipid NPs reduced evaporative water loss showing the desirable optimal hydration. According to the results, the hybrid dressing present excellent cytocompatibility as well as great antimicrobial activity against *S. aureus* and *S. aureus* MRSA strains [60].

In another study, CS NPs were synthesized using ionotropic gelation method optimal conditions to obtain minimum size particles. The nanocomposite hydrogels were prepared using a combination of PVA and CS NPs through freezing-thawing cycles. It was proved that the developed PVA nanocomposite hydrogels loaded with CS NPs showed improved swelling and mechanical strength ability, excellent barrier activity. Thus, the prepared nanocomposites are ideal as good wound dressing [61].

Sharma et al. developed a polyelectrolyte complex using CS and chondroitin sulfate in order to produce in-situ scaffold via spontaneous mixing. The polyelectrolyte complex possessed very high swelling and porosity property, with excellent blood compatibility. In addition, the structure was not haemolytic whereas blood clotting index was low. Two very important factors were the optimal antibacterial activity against both gram-positive and gram-negative bacteria and the biocompatibility. In summary, it was ruled out that the CS-chondroitin sulfate polyelectrolyte complex can trigger wound healing process by stimulating fibroblast growth, and thus is an ideal wound dressing material [62].

Wichai et al., prepared bacterial cellulose/sodium alginate/CS-copper sulfate (BC/AG/CS-Cu) composites with an aim widen the use of BC in wound dressings and to improve antimicrobial activity. The structure and properties (such as weight fraction, tensile strength, swelling ratio, and release characteristics of Cu) of the obtained composites were studied in details. The obtained BC/AG/CS-Cu composites exhibited antibacterial properties against both gram-positive MRSA and gram-negative bacteria *E. coli*. In addition, indirect cytotoxicity test performed with L929 mouse fibroblasts and human dermal fibroblasts showed that the obtained composites were safe to use in contact with living cells. The overall obtained results showed that the BC based composites were promising materials to be used as an antimicrobial wound dressing [63].

Effective wound healing and bleeding control are still very important and can be life saving. However, traditional wound dressings with structural deficiencies are not so effective in bleeding control and promoting the regeneration of functional tissues. Therefore, new kind of wound healing and bleeding control formulations that will eliminate these problems are still needed. Anbazhagan et al. prepared tetracycline HCl loaded fungal CS incorporated with or without aloe vera extract. A constant amount of cumulative tetracycline HCL release was observed from composite sponges at the

phosphate buffer saline (pH 7.4). Also, the developed sponges demonstrated good antibacterial activity against various bacteria. Finally, cell culture studies depicted desirable cell viability, recommending that these sponges can be applied as cost-effective, potential wound dressing material [64]. Xia et al. prepared a novel CS sponge with quaternary ammonium chitosan NPs. They sponge showed improved antibacterial properties and dual wettability. Authors used an *in vivo* chronic wound healing model and showed that the developed sponge promote wound healing and thus it can be a promising candidate in wound dressings [65].

In another study, 3D layered nanofiber sponge based on CS and PVA was prepared so as to increase interfacial interaction between the sponge and blood cells which can lead to accelerated haemostasis. 3D nanofibrous sponge exhibited useful properties such as improved elasticity, high permeability and fluid absorption that might be beneficial for wound healing. In addition, layered nanofiber structure promoted functional dermis regeneration and the restoration of differentiated adipocytes during the early repair phase. *In vivo* studies using model mice have shown that the sponge induces wound healing and reduces scar formation. Due to the easy to produce and significant wound healing properties, the obtained nanofibrous sponges are quite promising for future wound applications [66].

Siafaka et al. fabricated absorbable and non-absorbable sponge dressings via phase separation technique, using CS derivative with 2-hydroxyethylacrylate (CS-g-PHEA). The developed sponge showed enhanced swelling index and mechanical strength whereas the biocompatibility and biodegradability were also high enough. Moreover, the sponge loaded with levofloxacin in order to achieve the greatest antimicrobial activity against MRSA and *P. aeruginosa*. The interesting high porous dressings exhibited a significant inhibition zone of the bacteria indicating their use as wound delivery systems of levofloxacin [1].

CS sponges are widely used as hemostatic dressings as well as wound dressings. The haemostatic effect can easily be improved by modifying chitosan with other polymers, such as PVA. In a current study, CS was crossliniked with PVA and a fast-swelling sponge was obtained. The physicochemical examination showed that PVA-CS sponges present enhanced mechanical strength, vigorous swelling ability and fast absorption speed. The sponges also exhibited high cell viability, proliferation and attachment. Furthermore, *in vivo* evaluation of PVA-CS sponges depicted significant haemostatic ability and enhanced wound healing. The obtained data strongly recommend that these sponges can be applied to stop hemorrhage in acute trauma and injuries [67].

Aubert-Viard et al. aimed to synthesize a wound dressing loaded with chlorhexidine as controlled release with long-lasting antibacterial efficacy. Firstly, the polyethylene terephthalate dressing was modified by CS crosslinked with genipin. Afterwards, the dressing was deposited layer-by-layer with a multilayer system comprised from anionic methyl-β-CD and cationic CS polymers. Authors in order to stabilize the film used thermal treatment whereas the textiles were impregnated with Chlorhexidine. The thermal treatment improved cell viability whereas rapid degradation of the system was found. Chlorhexidine was released in sustainable manner and *in vitro* antibacterial activity against *E. coli* and *S. aureus* was optimal for several weeks [68].

4.2. *Other natural polymeric wound dressings*

Except CS, research groups also study other natural polymers, effective to be fabricated as wound dressings. However, it can be said that most of the studies involve the use of combination of natural polymers. Cellulose is the most abundant natural polymer obtained from renewable sources. Bacterial cellulose (BC) is a biopolymer produced by bacteria with several advantages, such as purity, high porosity and high biocompatibility. Furthermore, BC can be easily modified to obtain antibacterial activity and possible local drug delivery features [69]. Alginate (AG) is readily available anionic biopolymer which is obtained from brown seaweed, and possess high biocompatibility while wound dressings which consist of AG present moist environment and reduced bacterial infections, which are important factors for wound healing [70]. Collagen, which is produced by fibroblasts, is the most existing protein in the human body which triggers cellular migration and contributes to new tissue development. Collagen-based biomaterials stimulate and recruit specific cells, such as macrophages and fibroblasts, so they enhance and influence wound healing [71]. Hyaluronic acid (HA) is a glycosaminoglycan, which is found in high concentrations in several soft connective tissues including skin. In fact, HA plays a vital role in maintaining tissue integrity, as well as in facilitating adhesion and differentiation of cells during inflammation, wound repair and embryonic development. These promising results associate with biocompatibility and biodegradability have led to the development of a range of wound dressing containing HA for human medical use [72].

In a recent study, natural polymers as cellulose acetate (CA), sodium alginate (SA) and carbopol were mixed to prepare mupirocin films in order to explore their use as dermal delivery systems (Fig. 5). The solvent casting films exhibited strong interaction between the components and the drugs. Their morphology was expected whereas their swelling ability was high. The most valuable result was the insignificant percentage of mupirocin which cross the epidermis layer showing that the film can be employed as topical wound dressing. Furthermore, *in vivo* assays demonstrated that the chosen film promotes the regeneration of epidermal layer. Subsequently, it was found that the developed film is more favorable on epithelialization, granulation tissue thickness as well as angiogenesis in comparison with the commercial product [32].

In an interesting study, authors prepared CS NPs, which further loaded into ionic cross-linked films comprised of SA and pectin for the topical delivery of cefazolin. The study focused on preparing films that could sustainably deliver cefazolin at the site of application. Cefazolin was loaded into CS NPs in order to avoid burst release for the drug and further loaded into the cross-linked via calcium chloride films. The cross-linking was able to enhance the mechanical strength of the hydrogel films upon exposure to wound fluid. Authors conclude that 0.5% crosslinked cefazolin loaded films showed significantly better results and are more suitable as wound dressings for the treatment

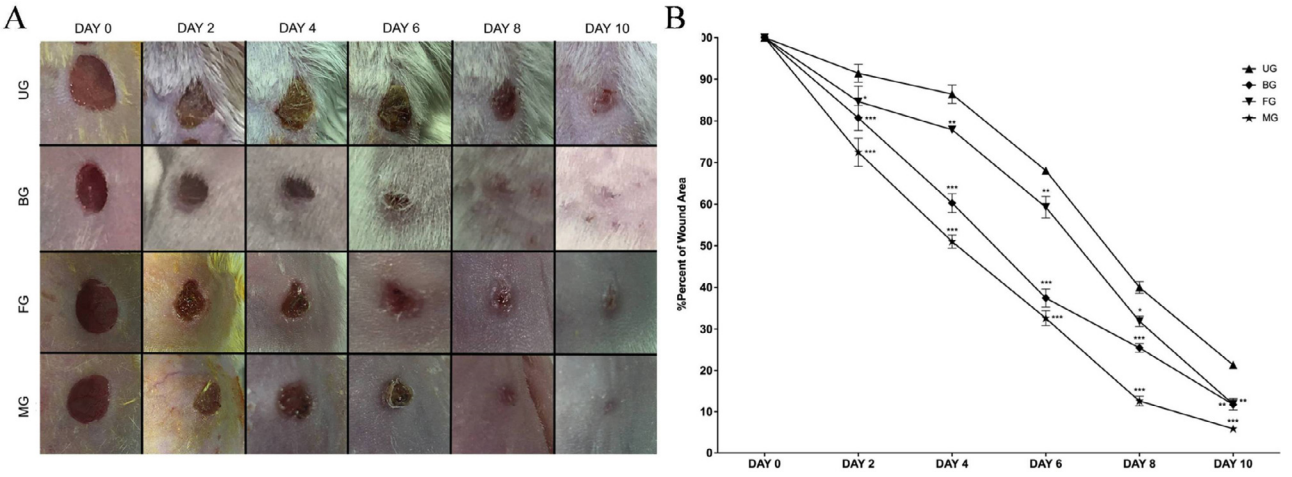

Fig. 5 – (A) Macroscopic examples of untreated (UG), bactroban (BG), blank film (FG) and mupirocin film (MG) groups at Day 0, 2, 4, 6, 8 and 10. (B) Healing percentage of seam area in each group. (Reprinted with permission from [32]. Copyright (2019) Elsevier).

of infections [73]. An interesting study revealed the use of Gauze coated with CS nanofiber and sodium alginate (CAG) forms polyion complex by calcium cross-linkage as dressing for the sustained release of fradiomycin sulfate. The developed CAG showed efficient mechanical properties, water absorption, and biocompatibility while fradiomycin sulphate exhibited a gradual release from the dressing. These properties are beneficial for wound delivery [74]. Similarly, crosslinked alginate-pectin hydrogel was loaded with simvastatin to be applied as topical wound dressing [75]. The hydrogel like film found to have improved mechanical strength, thermal stability and fluid uptake. The sustained release of simvastatin as it was proven by *in vitro* release studies as well as the high biocompatibility demonstrated that the films can be safely applied as non-toxi dressings [75]. AG has been widely used as hemostatic agent due to its efficient hemostatic properties. These properties are highly desirable for wound healing applications. The main obstacle when AG is applied is its low swelling ability. Thus, Tong et al. prepared composite microparticles of AG and the hydrophilic poly(g-glutamic acid) via emulsification/internal gelation method. The microparticles depicted improved swelling capability, thermal stability and increased biocompatibility in L929-fibroblasts. Researchers conclude that the microparticles are promising candidates as wound dressing for hemostasis or rapid removal of exudates [76].

Lukáč et al. prepared an alternative collagen wound dressing using freshwater fish skin (Cyprinus Carpio) collagen type I. The prepared sponges were either cross-linked with carbodiimide or non-crosslinked. In addition, the sponges loaded with gentamicin and lyophilized. It was found that sponges depicted open porosity while the crosslinked products maintained their secondary collagen structure after 168 h. Additionally, gentamicin was rapidly released from all the sponges however gentamicin plasma levels were same with both administration routes (intramuscular and via gentamicin-containing sponges). Gentamicin loaded sponges were of the best clinical results since infection signs have not been seen. Authors strongly believe that the prepared film has interesting properties for the treatment of a surgical wound infection in a rat mode and it is quite promising since Cyprinus Carpio collagen was first time used for the preparation of wound dressings [77]. Biomimetic CS/collagen coated silk fibroin/poly(ε-caprolactone) (SF/PCL) electrospun membranes were developed by Wu et al. The fibrous films showed improved mechanical properties. Moreover, the fibrous materials found to be efficient on promoting cell proliferation and attachement whereas *in vivo* rat models depicted that the promising films can decrease the wound closure time, increase collagen production in dermal ECM and mitigate excessive scar formation through TGF-β/Smad signaling pathways [78]. A bioactive scaffold based on collage, aloe vera and graphene oxide was proposed as an alternative wound dressing. The porous scaffolds showed improved mechanical properties, good antibacterial activity against *E. coli* and *S. aureus* as well as biocompatibility. Moreover, *in vivo* studies in rats showed accelerated wound healing [79]

In another study, carboxymethyl CS (CMC) and collagen were covalently bonding with ciprofloxacin and gentamicin sulfate to produce sustained wound dressings. It was found that dressings demonstrated great water absorption capacity, siginificant water vapor transmission rate, enhanced mechanical property as well as excellent stability. Besides these results, the system found to be cytocompatible in human skin fibroblast cells with enhanced and prolonged antimicrobial activity. Most importantly, the dressings found to trigger wound healing process, re-epithelization, collagen deposition, and angiogenesis. Finally, authors believe that the wound dressings can act superiorly for chronic wounds [80]. Another combination of keratin and CS-azide was applied for the preparation of UV-crosslinked membrane, appropriate for wound healing and other biomedical applications. The novel composite membrane demonstrated sufficient mechanical strength, biocompatibility and biodegradability as well as cell proliferation in L929-mouse fibroblasts. Authors suggest that the novel composite could serve as a desirable wound dressing which benefited by the synergistic effects

of CS and keratin [81]. An alternative approach for wound dressing was proposed by Ying et al. They develop new dressings with spontaneous healing activity, fabricating an injectable hydrogel composed of collagen I and hyaluronic acid (COL-HA). The preparation of hydrogel dressing was performed through *in situ* coupling of phenol moieties of collagen I-hydroxybenzoic acid (COL-P) and hyaluronic-acid-tyramine (HA-Tyr) through horseradish peroxidase (HRP). COL-HA hydrogel exhibited porous surface important for gas, medium and nutrition exchange. In addition, hydrogel showed important proliferation of human microvascular endothelial cells (HMEC) and fibroblasts (COS-7). Furthermore, VEGF was also observed in HMEC cultured hydrogel, and thus vascular regeneration is possible. Finally, full-thickness wound, the healing ratio and validity of wound treated with COL-HA hydrogel were extremely enhanced compared to commercial drug and individual COL-P hydrogel [82].

As it was mentioned, HA wound dressing is of great interest, in recent years. Nonetheless, the main problem of these dressings, are their poor mechanical properties. Consequently, researchers instead of using HA alone add several reinforcing agents. An agent like this is NCC which can enhance the mechanical properties of the dressing. In recent years, HA as wound dressing have gained more attention but its poor mechanical properties limited its clinical applications. In some studies, HA-based wound dressings were incorporated with reinforcing agents, such as NCC, to improve their mechanical properties. In a novel study, NCC reinforced HA-based composite loaded with CS NPs was developed as an effective wound dressing and characterized in terms of its physicochemical characteristics such as mechanical properties, high swelling ability and drug release. The results showed that by delivering in controlled manner, growth factors to the wound can improve the healing process. *In vivo* results depicted that, after 13 d an almost full wound closure and complete re-epithelization was achieved when the wounds covered with NPs compared to control group. In addition, NP applied wounds showed sufficiently lower inflammatory reaction, improved re-epithelization as well as enhance granulation tissue formation. The results suggest that the prepared dressing can be potentially applied in clinical practice for wound treatment [83].

Film dressings of cornstarch/hyaluronic acid/ ethanolic extract of propolis (CS/HA/EEP) were fabricated via solvent-casting by Eskandarinia et al. The films showed high antibacterial activity against *S. aureus*, *E. coli* and *S. epidermidis* and non cytotoxicity for L929 fibroblast cells. The acceleration of wound healing process was proven when Wistar rats' skin model was applied. Subsequently, the prepared film can be a potential product for wound healing [84]. An alternative wound healing system comprised from AG, HA and Chitlac-AgNPs was proposed by Tarusha et al. Calcium anions were used as crosslinking agents. The obtained data showed that the release of HA can accelerate the wound healing while the improved cell viability and antibacterial activity was considered as important characteristics. In further, the membranes had the capability to inhibit metalloproteinases evidencing that the dressing could be used as antibacterial wound dressing [85]. HA core-shell particles were developed in order to deliver platelet lysate and the anti-infective vancomycin hydrochloride (VCM) and growth factors, to chronic skin ulcers. HA particles were coated with calcium AG, embedded in VCM containing AG matrix and characterized for their properties. It was revealed that the dressings had desirable mechanical strength and swelling ability. *In vitro* fibroblasts viability was also high and *ex vivo* (on skin biopsies) biological activity was also optimal. The obtained results showed that the dressings are able to improve skin ulcers healing [86].

Novel membranes from CS and CS-HA containing new arginine derivatives with thiazolidine-4-one were fabricated into scaffolds via ionic cross-linking method. Their porous morphology, as confirmed by SEM, is a desirable characteristic for burn wound healing since it can differentiate the fluid absorption, rate of colonization, cell structure and angiogenesis process. Physicochemical evaluation revealed that the membranes had enhanced swelling index, improved hydrophilicity, and cell viability. Finally, the membranes exhibited impressed healing effects on the burn wound rat model as well as complete reepithelization after 15 d of experiment [87].

Hydrogels of HA as wound healing products can be widely found throughout literature. A composite hydrogel composed of polyvinyl alcohol, SA and HA was developed by Jiang et al. The fabricated hydrogels showed porous or fibrous structure depended on the content of SA. In further, SA improves the hydrophilicity and water vapor transmission, important characteristics for wound healing agents [88]. In similar way, a topical HA/SA film loaded with sulfadiazine and/or AgNPs and crosslinked with Ca^{2+}, Zn^{2+} or Cu^{2+} metal cations was studied by Abou-Okeil et al. It was revealed that antimicrobial activity was strongly correlated with the addition of sulfadiazine and AgNPs whereas the highest antimicrobial ability has the film with the combination of sulfadiazine and AgNPs. Homeostasis skin tissue restoration of albino rats was also confirmed [89]. Hybrid hydrogels comprised from aminoethyl methacrylate hyaluronic acid (HA-AEMA) and methacrylated methoxy polyethylene glycol (mPEG-MA) were further embedded with chlorhexidine diacetate nanogels (CLNs) for improved haemostasis and antibacterial activity. The HA-AEMA and mPEG-MA hybrid hydrogel loaded with CLNs exhibited microporous structure. Physicochemical characterization displayed excellent swelling, mechanical property, and enhanced cell viability. The antibacterial drug was sustainably released up to 240 h and the antibacterial property over 10 d. *In vivo* mouse model displayed that the hydrogels can act as rapid haemostatic and wound healing agents, thus are desirable candidates for wound healing market [90].

A very interesting research, involved the application of HA and adipose-derived stem cells (HA/ASCs) dressing on burn wounds and the injured area was then covered by an acellular dermal matrix dressing in a rat model (ADM-HA/ASCs). The histopathological, histomorphometrical, molecular, biochemical, and scanning electron microscopy assessments on Day 7, 14 and 28 post-wounding showed reduced inflammation, improved angiogenesis and enhanced granulation tissue formation. In further, basic fibroblast growth factor (bFGF) expression increased and TGF-β1 level on the 28th post-wounding day decreased indicating the anti-scarring activity of ASCs. The aforementioned

hydrogel is an innovative product for wound healing field [91]. In similar skeptic, a new wound-healing peptide known as REGRT (AES16-2 M, denoted as REG), inspired by erythroid differentiation regu-lator1 (Erdr1) was loaded in HA-based hydrogel dressing for the enhancement of acute excisional wound repair. The HA hydrogels are grafted with the REG peptide, demonstrating cell motility-stimulating ability, by releasing the peptide in sustained and prolonged manner. Histological examination showed that the HA dressing accelerates re-epithelization in skin wound healing, particularly by promoting migration of fibroblasts, keratinocytes and endothelial cells. The peptide-grafted HA hydrogel system can be considered as state of the art technology for wound repair [92].

Tranexamic acid, antibleeding agent was impregnated into composite alginate/hyaluronan (AG/HA) sponge dressings. The sponges like dressings were soft, flexible and nonbrittle. Morphology of sponges were studied via SEM which confirmed their porosity whereas HA addition played vital role by decreasing the porosity, modifying the water uptake kinetic, and increasing the resistance to compression. A controlled release of tranexamic acid up to 3 h was confirmed and found to be altered by the addition of HA. *In vitro* clotting test performed on human whole blood revealed that the HA-loaded sponges significantly decrease the blood clotting index by 30%. Given the above, the dressins can act as hemostatic agents [93].

Gelatin, HA and NCC were fabricated in hydrogles by cross-linking and freeze-drying for skin wound repair. The porous spongy hydrogels were physicochemically studied and found to have interesting swelling ability whereas FTIR depicted that amide bond and hydrogen bonding formed between the components. *In vitro* cytotoxicity studies on NIH-3T3 cells showed cell attachment, grow and proliferation on the hydrogels which is highly recommended for wound healing applications [94].

Gelatin is ideal as wound dressing due to its easy a film-formation, air-permeability, biocompatibility, non-toxicity and haemostatic properties. Consequently, crosslinked foam based on starch and gelatin with borax were prepared by Tavakoli et al. Erythromycin was further loaded to enhance antimicrobial ability. Their results revealed that foams can be applied as wound coatings due to their porous morphology high swelling capacity as well as low cytotoxicity in L929 cells. Furthermore, the foams present improved mechanical strength while erythromycin release was altered by borax addition. More specifically, erythromycin releases in less than 3 h when low borax density was used, whereas drug release controlled by increasing borax concentration to 40% [95]. In a different study, gelatin microspheres were used as carrier for neurotensin, a neuropeptide which can accelerate wound healing process, an ability essential to treat diabetic foot ulcers. The silk fibroin (SF) scaffolds impregnated gelatin microspheres loaded with neurotensin to improve wound healing. Morphology of the scaffolds found to be porous, suitable for wound healing regeneration whereas gelatin microspheres release the drug in controllable manner. Besides this, the composite scaffold exhibited promising results in terms of macroscopic healing and l in fibroblast accumulation in tissue granulation, collagen expression and deposition at the wound site. It can be strongly recommended the use of the above scaffolds as diabetic foot ulcers treatment [96]. Yang et al., prepared a novel SF scaffold containing also HA/SA by freeze-drying. The porous scaffolds were soft and present elasticity while other analyses depicted that they had improved mechanical strength and thermal stability. Moreover, the composite scaffolds demonstrate attachment, grow and proliferation of NIH-3T3 fibroblast cells. Finally, wound healing analysis in a rat full-thickness burn model demonstrated increased improved re-epithelization and improved extracellular matrix remodeling. The above results might provide an alternative wound dressing for wound healing [97]. SF and PCL electrospun fibrous structures were produced in order to be applied as wound membrane. The bi-layered membrane consisted of SF and PCL whereas the bottom layer was developed by SF and HA enclosed the herbal drug (thymol). Physicochemical characterization showed improved mechanical strength, porous structure, wettability and cell viability of human's fibroblasts. Furthermore, the loading of thymol improved the antioxidant and antibacterial properties of the membrane. The prepared wound dressing possess desirable properties for wound healing field [98]. Bacterial cellulose-based hydrogels are widely used as wound dressing given their biocompatibility. The *in vivo* study using athymic mice of bacterial cellulose/acrylic acid (BC/AA) hydrogel containing human epidermal keratinocytes and human dermal fibroblasts produced extremely high acceleration on burn wound healing, followed by treatment with hydrogel alone, compared with the untreated group. Results of wound healing showed that the percentage wound reduction on day 13 in the mice treated with BC/AA hydrogel loaded with cells (77.34% $\pm$ 6.21%) was significantly high. In addition, in histological analysis, the expression of collagen type I via immunohistochemistry, and transmission electron microscopy showed a greater deposition of collagen in the mice treated with hydrogel loaded with cells and thus BC/AA hydrogel can act as a promising wound dressing and a cell carrier [99]. A composite membrane comprised from natural BC, PEG and polyhexamethylene biguanidine (PHMB) through new synthetic approaches was developed as wound dressing by Wang et al. Physicochemical examination revealed desirable transparency, water retention ability, flexibility and anti-adhesion. Additionally, the membrane showed cell viability and high antimicrobial activity. *In vivo* results depicted that the composite could accelerate wound healing and regeneration [100]. In similar skeptic, a hybrid membrane of BC and copolymer of 3-hydroxybutyric and 4-hydroxybutyric acids [P(3HB/4HB)] were loaded with drugs to accelerate the wound healing process and epidermal cells differentiation from multipotent adipose-derived mesenchymal stem cells. Actovegin loaded films found to effective for fibroblasts growing while *in vivo* studies on laboratory animals with model third-degree skin burns showed wound healing promotion [101]. A recent study included the use of graphene oxide as antibiofilm agents. The prepared grahene oxide was formulated into NaCMC hydrogels to form rGO hydrogel. *In vitro* (XTT tests) and *in vivo* using nematodes *C. elegans* results exhibited that the rGO hydrogels decreased biofilm formation by *S. aureus* (81%–84%) and *P. aeruginosa* (50%–62%) while fluorescence

intensity showed inhibition of biofilm bacteria in *C. elegans* experiments. This interesting study is of great importance for wound healing applications [102]. Finally, a novel approach in wound healing field is the use of curcumin. Curcumin is a herbal supplement with many properties, like antioxidant and antibacterial activities. A hinder for curcumin use is its high hydrophobicity which was overcame by using CD complexation. In the study of Gupta et al. biosynthetic cellulose produced by *Gluconacetobacter xylinus* was loaded with water soluble curcumin: hydroxypropyl-β-cyclodextrin (HP-β-CD) supramolecular inclusion complex to develop hydrogel dressings. The results revealed that HP-β-CD enhanced the aqueous solubility of curcumin and allowed loading into bacterial cellulose hydrogels. It was found that the hydrogels showed improved haemocompatibility, cell viability, antimicrobial activity against *Staphylococcus* and antioxidant properties. Thus, curcumin: HP-β-CD-loaded-bacterial cellulose as hydrogel dressings can be effective for skin wound healing [103]. In further, Zhang et al. developed a novel biomaterial loading tannic acid and $MgCl_2$ to BC and examinate its use as wound dressing application. *In vitro* release studies exhibited the improved release of tannic acid and desirable antibacterial activity against *S. aureus, E. coli* and *P. aeruginosa*. Thus the biomaterial can be applied as antibacterial wound dressing [104].

CA fibrous scaffolds embedded with silver sulfadiazine were studied for the treatment of burn wound infections by Khan et al. The scaffolds exhibited uniformity of silver sulfadiazine into the nanofibrous structure whereas FTIR demonstrated the existence of strong chemical interactions between silver sulfadiazine and CA. In addition, the nanofibers depicted water absorption and high antimicrobial activity against *E. coli* and *B. subtilis* bacteria. Consequently, the films can be used wound dressings applications [105]. Similarly, CA nanofibrous scaffolds loaded with gallic acid (GA) were developed via electrospinning whereas solvent casting films of CA-GA were produced for comparison. High release rate was recorded by the total immersion and the transdermal diffusion through a pigskin method in acetate buffer solution (pH 5.5) or normal saline (pH 7.0) at either 32 or 37 °C, respectively. The films also present high antioxidant and antibacterial activity against *S. aureus*, which showed the potential for use as wound dressing materials [106].

Alpha-cellulose from wheat bran nanofibrous structures loaded with ciprofloxacin were prepared via electrospinning method. Results demonstrated that the scaffolds showed increased zone inhibition after 24 h against *S. aureus*. From the physicochemical characterization, pathology tests on rats, it can be said that α-cellulose nanofibers are effective as wound dressings because they can easily be applied to the wound, whereas no adhesion to wound was found. Meanwhile, morphology and porosity of the nanofibrous scaffolds were appropriate for wound healing applications. Finally, the nanofibers can reduce the wound area and improvement time, as it has optimized drug-release capabilities [107].

4.3. *Wound dressings from synthetic polymers*

Synthetic polymers like PCL, poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA) as well as PVA (Fig. 6) are widely used as biomaterials since they exhibit high biocompatibility and biodegradabilityas well as active groups (-OH) which can covalently linked or conjugated with several receptors so as to improve cellular uptake, increase the circulation time to RES [108,109]. The above polymers are found in the form of micro- or nano-particles, electrospun fibrous structures, sponges etc and they are applied as wound dressings for acute or chronic wounds. Mostly, the polymeric formulations contain antibiotics, growth factors or natural components like honey, cinnamaldehyde etc.

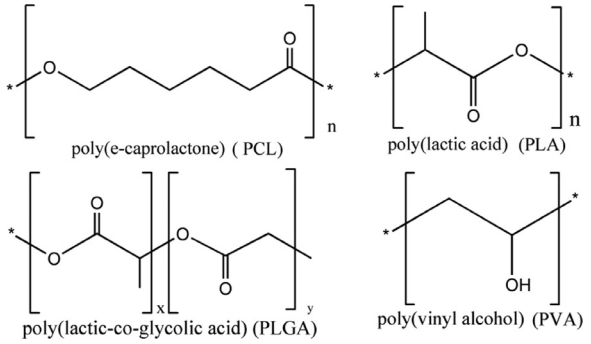

Fig. 6 – Synthetic polymers used in wound dressing applications.

4.3.1. *PCL based systems*

PCL is aliphatic polyester which is used extensively in pharmaceutical applications due to its favorable biocompatibility, biodregrability and mechanical properties [110,111]. However, as the majority of aliphatic polyesters presents high hydrophobicity and high crystallinity hindering its application as wound dressing materials. Thus, in most cases PCL is blended with hydrophilic substances in order to resolve the problems that aroused by its hydrophobicity [30]. Many researchers studied the use of PCL as wound dressing material. As it was mentioned above, PCL is hydrophobic but biocompatible. So many studies focused on PCL electrospun fibers or micro-/nano- particles which contain active ingredients, like growth factors or antibiotics or they use PCL blends with hydrophilic polymers like CS, PEG etc.

Except the conditional active ingredients as antibiotics, many researchers investigate the use of extracts from medicinal plants or other natural ingredients. Egri et al. prepared Hypericum perforatum oil loaded electrospun PCL fibers knowing that it presents curative effect on wound-healing process. Nonetheless, the dressing consisted by two layers one from PCL so as to maintain membrane integrity and mechanical strength, whereas the layer which will be applied to the wound was formed by electrospraying and electrospining of PEG/H. perforatum oil. The study revealed that the dressing possess interesting antimicrobial activity as well as high biocompatibility, properties that are quite important for wound management [112]. In further, similar PCL nanofibrous structures imbedded with ciprofloxacin and quercetin by Ajmal et al. The developed fibrous mats with 101.59 ± 29.18 nm average diameter exhibited prolonged *in vitro* release (for 7 d) demonstrated the capability of the dressing to inhibit any probable infection and

oxidative damage. Furthermore, haemocopatibility and cytocompatibility studies showed accelerated wound healing with complete re-epithelization and improved collagen deposition within 16 d while antimicrobial assay depicted that the wound dressing hinder the bacterial colonization. Authors conclude that the prepared functionalized PCL nanofibers can act as a potential wound dressing material [113]. Accordingly, another study involved the preparation of PCL wound dressing by using a small amount of hydrophilic surface modifying macromolecule (LSMM) which was functionalized with PEG and aminated zeolitic imidazolate frameworks (MZIF-8) as a drug carrier for curcumin to accelerate the healing process while improve drug loading and controlled release. The results showed that the prepared dressing is biocompatible and present improved mechanical strength. Fibroblast cell adhesion evaluation depicted that it was increased when 1% LSMM was added [114]. Similarly, Ravichandran et al. synthesize novel nanofibrous PCL mats loaded with ethyl acetate extract of medicinal plant Clerodendrumphlomidis L.F (CP). GC-MS analysis of the non polar solvent extract of CP, revealed that more than 40 phyto constituents such as terpenoids, flavonoids, phytol, hexadecanoic acid and palmitic acid. Physicochemical studies demonstrated the successful incorporation of CP into the fibrous mats. In further, antibacterial studies confirmed its superior antimicrobial activity whereas a prolonged release was achieved. Thus, authors recommend the use of prepared mat as antimicrobial wound dressing with antioxidant activity [115]. Likewise, Calendula officinalis (C. officinalis) and gum arabic loaded PCL nanofibrous scaffolds were prepared via electrospinning. The porous mats exhibited improved hydrophilicity compared to neat PCL scaffold. The increased porosity was critical for fibroblast proliferation whereas the nanocomposite scaffold found to have important degradability and antimicrobial activity. In further, gum arabic and C. officinalis promoted cell attachment and proliferation. The research group confirm that the nanofibrous calendula-loaded PCL/gum arabic scaffolds are suitable for tissue regeneration dressings [116]. Analogously, PCL-gelatin electrospun nanofibers containing lawsone (2-hydroxy-1,4-naphthoquinone) which is found on the leaves of the henna plant (Lawsoniainermis) were prepared. It was proved that by adding 1% lawsone to the mat, cell attachment and proliferation were improved significantly. Among others, the lawsone loaded scaffolds in rat wound model revealed that the PCL/Gel/Law 1% exhibit high impact on healing by increasing re-epithelization of the wound after 14 d. It was concluded that the prepared mat has excellent characteristics and can be safely applied as wound dressing material [117]. In addition, novel dexpanthenol-loaded nanofiber mats for wound healing were formulated by Tanrıverdi at al. Authors examined the use of three synthetic polymers (PCL, poly(ethylene oxide) (PEO), PLGA) as wound dressings loaded with dexpanthenol. However, from the physicochemical properties (morphology, swelling, *in vitro* release, cell viability), PCL dressings present many disadvantages compared to the other polymers [118].

Many antibacterial drugs (mupirocin, ciprofloxacin, etc) have been incorporated into PCL fibrous mats to improve their antimicrobial activity. Multilayered electrospun fibrous mats were formed from mupirocin and lidocaine hydrochloride homogeneously incorporated into PCL as the first layer of scaffolds and CS as the second layer of scaffolds nanofibers through electrospinning. The successful incorporation of the drugs into the layers was confirmed by FTIR while thermogravimetric analysis indicated the thermal stability of the mats. Antibacterial assay displayed the superior antibacterial activity against *S. aureus*, *E. coli* and *P. aeruginosa* while toxicity to fibroblasts wasn't identified. The excellent hydrophilicity, cytocompatibility, sustained drug release and antibacterial activity, are desirable properties for wound dressing applications and thus the prepared mats are excellent candidates as wound dressing materials [119]. In parallel manner, multilayered nanofibrous mats of PCL in the bottom, CS/PEO in the middle, and PCL/collagen in the top layer were synthesized. The CS/PEO was loaded with EGF and bFGF, while PCL layer incorporated silver sulfadiazine in the bottom layer as an anti-infection factor. The authors conclude that the composite nanofibrous mat could be an optimal dynamic and effective candidate for wound dressing [120]. Huang et al. fabricated also a novel bilayered wound dressing with excellent antibacterial activity through electrospinning and *in situ* cross-linking polymerization. More specifically, [2-(methacryloyloxy)ethyl] trimethylammonium, (MTA) was first polymerized and cross-linked in the presence of PCL to form PCL/PMTA composites. Then, PCL was electrospun as the biocompatible inner layer that directly contacts the wound, while the hydrophilic PCL/PMTA layer was placed as the external layer as the antibacterial layer with strong activity *E. coli* and *S. aureus*. The electrospun bilayered fibrous mats did not release any toxic agents and so are promising candidates for antimicrobial wound dressings [121]. PCL/sulfonated keratin co-electrospun fibrous membranes were prepared and studied as wound dressing candidates. The mats revealed optimal cell and blood compatibility [122].

As it was already mentioned, PCL low hydrophilicity forces the researchers to blend it with other more hydrophilic ingredients to improve the characteristics. Accordingly, ciprofloxacin loaded PCL/PEG blended fibrous structures were produced as wound dressing. The results showed that the addition of PEG improved the hydrophilicity of the mats and also affected the release mechanism. Ciprofloxacin loaded composite fiber mats showed antibacterial activities with different efficiency due to the addition of PEG [123]. PCL/gelatin hybrid nanofibrous scaffolds loaded with trimethoxysilylpropyloctadecyldimethyl ammonium chloride (QAS), were fabricated as antibacterial wound dressing. Sufficient mechanical strength as well as antibacterial activity against *S. aureus* (gram-positive) and *P. aeruginosa* (gram-negative) bacteria, suggest that the prepared membranes can be efficiently applied as an antibacterial wound dressing [124]. In another study, plasma treated electrospun PCL mats were coated with AgNPs which were previously embedded in gelatin by multi-immersion technique. This technique was applied so as to improve the antibacterial activity and reduce wound-scaffold adhesion of the mats. The obtained *in vitro* and *in vivo* data also proved that that the greater number of gelatin-Ag coating times, the more significant the antibacterial property of the membrane was. To conclude, the EsPCLGelAg mats present desirable propertied and prevent removal-induced damage for wound dressing applications

[125]. Souza et al. synthesize semipermeable bioactive electrospun fibers as wound dressings containing silver sulfadiazine. Silver sulfadiazine was previously complexed with β-CD and loaded to PCL nanofibrous matrix aiming to reduce the direct contact between silver and skin and to modify the drug release. The fibrous mats were found to be semipermeable with water vapor transmission and moderate hydrophilicity. Although, the matrices present modulated drug release adequately during 24 h they also exhibit a high hemolytic index. The complexation of sulfadiazine with CD decrease the hemolytic index and drug release but show improved antimicrobial activity. Consequently, PCL fibrous mats loaded with β-CD/silver sulfadiazine inclusion complexes are a promising pharmaceutical dosage form for wound healing [126].

Using growth factors and their combinations has been suggested as a promising treatment to promote wound healing. Some of the most important factors, like EGFs, PDGF, TGF, VEGF and FGF-2, present at different healing stages with certain functionalities [127]. In a similar skeptic, EGF and bFGF were encapsulated into PCL-PEG coaxial core-shell fibers. The conjugation of EGF to PCL-PEG shell showed no negligible release in 7 d showed a slow release of 2% in a week whereas the bFGF showed a high initial burst in 24 h. Human primary keratinocyte and fibroblast cells cultivated on the nanofibrous meshes showed the highest cellular proliferation on mesh composed of bFGF and EGF [128]. Furthermore, others have synthesized PCL fibrous mats with connective tissue growth factor (CTGF) [129], so as to promote cell proliferation, which benefits wound healing. Molecularly engineered antimicrobial peptides have been applied as active molecules for biofilm treatment. The molecularly engineered human cathelicidin peptide 17BIPHE2 was impregnated into pluronic F127 and PCL core-shell nanofibrous structures. A sustained release was depicted for over 4 week's period while MRSA as well as *Klebsiella pneumoniae* and *Acinetobacter baumannii* was effectively killed while cytotoxicity to skin cells and monocytes was not observed (Fig. 7). The developed biodegradable nanofibrous wound dressings are able to sufficiently deliver peptides to treat chronic wounds [130]. Finally, electrospun nanocomposite meshes based on PCL and titanium dioxide nanorods (TNR) were also developed by electrospinning technique. The obtained *in vitro* and *in vivo* data demonstrated that the presence of TNR in the PCL meshes greatly improved the cell migration, proliferation, angiogenesis and wound healing [131].

Except, electrospinning technique wound dressing membranes can be prepared by other techniques. CS was blended with methoxy PEG-PCL copolymer (mPEG-PCL) to prepare gentamicin wound-dressing membranes via solvent evaporation. All gentamicin-loaded membranes inhibited *S. aureus* and *E. coli* growth, and demonstrated color, moisture and thermal stability. Therefore, mPEG-PCL/CHI-genipin membranes showed important features for potential wound dressing and drug delivery applications [132]. An interesting tissue-engineered skin substitute, based on gelatin, collagen, and PCL, was fabricated by impregnation of lyophilized gelatin/collagen (GC) mats with PCL solutions, followed by solvent evaporation. The fibrous structures present good cytocompatibility when incubated with primary human

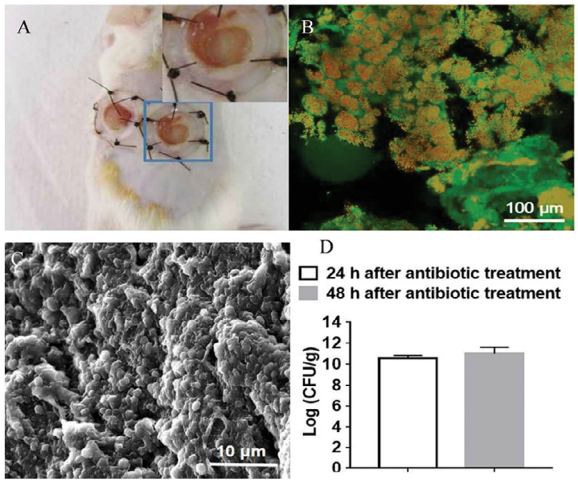

Fig. 7 – MRSA USA300 biofilm formation in chronic wounds based on type II diabetic mice. (A) Wounds were created and fixed with splint, and MRSA was inoculated for 24 h. (B)LIVE/DEAD staining for the tissue collected from wounds after 24 h of MRSA inoculation and subsequent 24 h Mupirocin 2% treatment. (C) SEM observation of the tissue collected from wounds after 24 h of MRSA inoculation and subsequent 24 h Mupirocin 2% treatment. (D) Quantification of bacterial load in the wound after 24 h of MRSA inoculation and subsequent 24 h and 48 h Mupirocin 2% treatment). (Reprinted with permission from [130]. Copyright (2019) American Chemical Society).

epidermal keratinocytes, human dermal fibroblasts and ASCs *in vitro*. The biomembranes exhibited similar cell growth and mechanical concluding that the prepared membranes provide an effective and low-cost solution to assist skin regeneration for clinical use [133].

Another, interesting idea for wound healing was the use of hybrid AG hydrogel cross-linked by calcium gluconate crystals deposited in poly(ϵ-caprolactone)-b-poly(ethylene glycol)-b-poly(ϵ-caprolactone) (PCL-PEG-PCL, abbreviated as PCEC) porous microspheres (Fig. 8). The porous structure of the microspheres provided more anchor points for fibroblast attachment and growth, resulting in the enhancement of cell growth in the hybrid hydrogel [134].

4.3.2. PVA

PVA is a neutral hydrogel, with high bio-compatibility, hydrophilic properties and biomechanical characteristics. PVA can easily form hydrogels and widely used in controlled release applications, thus PVA has been advanced as a promising wound dressing material [135]. As expected, PVA electrospun fibers have been found during literature examination. Besides, this is the most easy and inspirational technique to produce structures mimicking the extracellular matrix. Except nanofibrous systems, PVA hydrogels and NPs can be also widely found in the literature.

Tang et al. prepared honey incorporated AG/PVA-based electrospun nanofibrous membrane to develop an efficient wound dressing material. By increasing honey content, the nanofibrous membranes with demonstrated enhanced

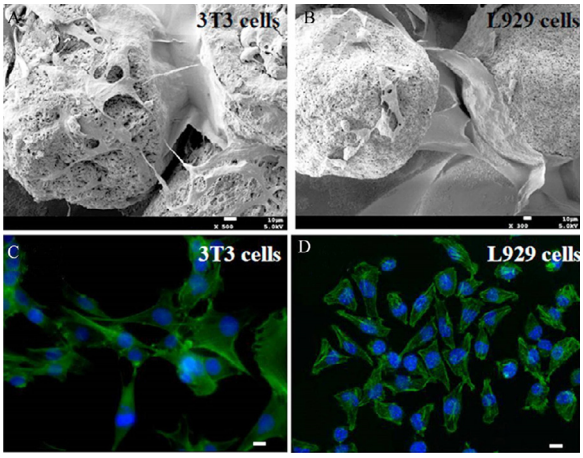

Fig. 8 – SEM images and confocal microscopy images of (A, C) 3T3 cells and (B, D) L929 cells co-immobilized in PCEC porous microspheres/AG hydrogels (scale bars in C and D = 1 μm). Cells stained with 4′,6-diamidino-2-phenylindole (DAPI, nuclei) and FITC-conjugated phalloidin (f-actin) (Reprinted with permission from [134]. Copyright (2018) American Chemical Society).

antioxidant activity, suggesting the ability to control the overproduction of reactive oxygen species whereas antibacterial activity of the honey loaded nanofibers towards *S. aureus* and *E. coli* was also improved. Authors strongly believe that the developed honey/AG/PVA nanofibrous membranes are promising for wound dressings [136]. In further, another group evaluated the use of Carica papaya incorporated PVA blended gelatin nanofibers. The scaffolds demonstrated excellent antibacterial activity against both *S. aureus* and *E. coli* bacteria. In addition, the nanofibrous membranes did not show cytotoxicity against fibroblast cells (NIH 3T3) and thus can be safely applied as wound healing agents [137]. Alternative antimicrobial wound dressings comprised from zinc oxide/SA/ PVA were studied as potential candidates in wound healing field. The electrospun nanofibrous mats demonstrated improved biocompatibility and high antimicrobial activity against *E.coli* and *S. aureus*. The results indicate that the mats are suitable skin tissue regeneration dressings [138]. In further the use of a novel three phase antibacterial wound dressing consisting of carbon nanotubes, AgNPs andPVA nanofibers was produced via electrospinning. The nanofibrous structures exhibited excellent bactericidal and prolonged bacterial growth inhibition properties and thus can be proposed for sustained and safer wound healing applications [139]. PVA nanofibers incorporated Zatariamultiflora (ZM) essential oil, were studied as novel wound dressing. It was found that the nanofiber mat loaded with 10% of ZM essential oil completely inhibited the growth of *S. aureus*, *P. aeruginosa* and *C. albicans* after 24 h of incubation. Swelling investigations showed that the produced nanofibers have a substantial ability to take up water, in the range of 400%–900%. Mechanical properties of the nanofiber mats were studied by tensile testing. Additionally, the prepared agents did not have toxicity on mouse fibroblast (L929) cells and thus can be desirably act as wound healing [140].

The use of non-toxic, super-absorbent and antibacterial hydrogel as a skin wound dressing is very significant as wound healing system. Kim et al. prepared PVA hydrogels loaded with diphlorethohydroxycarmalol (DPHC) which derived from Ishige okamurae. *In vitro* and *in vivo* biocompatibility tests exhibited that the hydrogels were cytocompatible. In further, they show anti-bacterial against *S. aureus* and *P. aeruginosa*. Finally, the PVA hydrogels showed wound healing effect and thus can be used safely in wound-dressing applications [141]. In an interesting study, PVA and starch hydrogel like membranes were loaded with AgNPs which were synthesized using Diospyros lotus fruit extract. The antibacterial activity of the prepared systems was comparable of that of ciprofloxacin, indicating the potential of such membranes to be used in wound dressing application [142]. Tao et al. used a blend of silk sericin (SS) with PVA to prepare a SS/PVA hydrogel through repetitive freeze-thawing. The synthesized porous mat depicted excellent hydrophilicity and swelling behavior. In further steps, authors load gentamicin to the SS/PVA hydrogel to improve the bacteriostatic properties of the mat which had excellent cytocompatibility on mammalian cells. The results criticized as promising [143]. Similarly, nanocomposite hydrogels of PVA and 5%, 10% and 15% CS NPs were prepared through freezing-thawing cycles. It was proved that the prepared system demonstrated characteristics such as favorable swelling and acceptable strength as well as excellent antimicrobial activity [61]. Another promising hydrogel containing PVA/Dextran-aldehyde solution blend was prepared via freeze-thaw method and freeze-drying. The porous hydrogels showed very low hemolysis and no cytotoxicity. Except these findings, the hydrogel indicated complete healing faster by 10 d, and fast regeneration of skin [144]. Among others studies, a very interesting work employed PVA, PVA-sodium carboxymethyl-cellulose (PVA-CMC), PVA-gelatin (PVA-G), and PVA-starch (PVA-S) cryogels loaded with manuka honey as part of burn healing management. The prepared gels, which loaded with honey, exhibit improved swelling capacity, high degradation. Although, neat manuka honey possess bactericidal effect the hydrogels could not manage inhibiting *S. aureus*, and thus authors propose the use of high concentrations of manuka honey into the gels [145]. Nanocomposite PVA hydrogels incorporating nano zinc oxide (ZnO) were produced via freezing-thawing method. The addition of ZnO NPs improved the mechanical properties while the antibacterial properties of the gels significantly increased and the cells viability was also improved. Consequently, the aforementioned wound dressings are biocompatible, anti-bacterial and nontoxic, can absorb the wound fluids and exudates, be safely applied to the wound [146]. A different work, exploited the use of adipose-derived stem cells (ADSCs) onto PVA dressing for wound healing. Authors decide to modify the one side of the PVA dressing with photo-reactive gelatin using ultraviolet irradiation. The surface-modified PVA induced the ADSCs adhesion and proliferation which was essential for wound healing. The protein released tests exhibited that the bioactive agents emitted from ADSCs and penetrate to the wound. *In vitro* and *in vivo* results depicted that hydrogels could promote

the wound healing and can provide an alternative approach for stem cells application in skin tissue engineering field [147]. PVA crosslinked with borax (PB) hydrogels which further loaded with Pluronic F127 micelles-curcumin were examined as wound dressing. The curcumin release rate in PBS solution was investigated. The strong power law correlation between curcumin release rate and viscoelastic properties of PB hydrogel was confirmed. Drug release mechanism showed in initial stages drug diffusion of curcumin loaded Pluronic micelles followed by erosion of hydrogel matrix at later stages. This drug delivery vehicle can be used as a competent wound dressing [148]. PVA/starch/citric acid based composite films for wound dressing applications were studied by Das et al. The findings showed that the prepared polymer films present improved water vapor transmission rate and antibacterial activity against Gram-negative (*E. coli*) and Gram-positive (*L. monocytogenes*) bacteria [149]. CS-PVA soft membranes have been studied for antibacterial and wound healing properties. Moreover, wound healing was studied in second degree burns on rabbits. The results indicated that CS-PVA membranes are significant wound healing agents as normal growth of epidermis was observed and can further accelerate the granule and fibrous connective tissues formation [150]. Da cruz et al. prepared hydrophilic PVA and cationic tannin films as possible wound dressings. They showed that the films present antimicrobial and antioxidant activities while they also trigger the attachment and proliferation of cells [151]. Moreover, Dekina et al. studied PVA/CS films containing Bacillus thuringiensis var. israelensis which were found to be promising wound dressing materials given that the films revealed collagenolytic and elastolytic activities [152].

4.3.3. *PLA and PLGA*

Except PCL, other aliphatic polyesters found in literature as wound dressing candidates are PLA and PLGA. PLA is an important biomaterial for applications such as drug delivery systems, gene transfer, surgical sutures, tissue engineering and regenerative medicine, given its favorable cytocompatibility and biodegradability [153,154]. The blend of PLA and poly(glycolic acid) (PGA) leads to a copolymer known as PLGA. This copolymer presents good biocompatibility, mechanical strength etc. Moreover, PLGA exhibit controllable degradation and mechanical properties accordingly to which PLGA is used. Additionally, when PLGA is used as dressing materials, it can be seen that the degradation rate is synchronized with the epithelization rate and further the healing process [108].

Similar to PCL based wound dressings, PLA and PLGA are also fabricated into electrospun nanofibrous dressings. However, in most cases the aforementioned polymers are blended with other macromolecules. For example, PLA was blended with poly(ethylene succinate) in order to be used as topical mats for skin infection from fungi species. The preliminary results were promising and authors proposed to apply the topical mats for further wound healing studies [155]. Elastic electrospun nanofibrous membranes have been produced by PLA and poly (1, 8-octanediol-co-citric acid) (POC) as raw materials. From their physicochemical properties, the blend consisting of 75% PLA was selected as drug carrier of aspirin. Authors strongly believe that the aspirin loaded film can be used as a desirable carrier for wound applications [156]. In further, electrospun polylactide: poly(vinyl pyrrolidone)/polylactide: PEG core-shell fibers loaded with antimicrobial peptides for efficient burns treatment were also produced by Li et al. The prepared dressings showed fibroblasts adherence and proliferation revealing biocompatibility. Authors claim that the existence of PLA beads mimic the structure of lotus leaves and the interesting architecture presents superhydrophobic property, which leads to inhibition of exogenous bacteria and other microbes. Similarly, electrospun polylactide: poly(vinyl pyrrolidone)/polylactide: PEG core/shell fibers loaded with bioactive agents, were fabricated into functional wound dressing for efficient burns treatment. The lotus-leaf-like super-hydrophobic surface with drugs loaded in fibers expressed desirable antibacterial activity. It can be said that the creation of hierarchically structured surfaces possess improved mechanical strength, effective wound exudate absorption. In addition, the significant biocompatibility and the broad antibacterial activity can promote wound healing which is promising for burn wounds treatment [157]. PLA and PEO nanofibrous membranes with antioxidant properties were successfully fabricated via electrospinning technique. Authors decide to load to the developed structure, grape seed extract (GSE), a rich source of natural antioxidants. *In vitro* culturing studies with human foreskin fibroblast (HFF1) cells demonstrated that the fibrous membranes were biocompatible and present cell attachment and proliferation. In summary, the results suggested that the GSE-loaded membranes are a promising topical drug delivery system and have a great potential for wound dressing applications [158]. PLA and hyperbranched polyglycerol (HPG) loaded with curcumin electrospun nanofibers were studied for their potential as wound dressings. The electrospun scaffolds (PLA/HPG/CUR) exhibit very high hydrophilicity, swelling and drug uptake and promotes better cell viability, adhesion and proliferation when compared to PLA/CUR electrospun nanofibers. Biodegradation study revealed that the morphology of the nanofibers were unaffected even after 14 d immersion in Phosphate Buffered Saline. *In vitro* scratch assay indicates that migration of the cells in the scratch treated with PLA/HPG/CUR is complete within 36 h [153].

PLGA and gelatin (PLGA/Ge) wound dressings were studied as of their use into chronic wounds. The randomly oriented fibers PLGA/Ge scaffolds showed high swelling index, hydrophilicity and degradation rates than pure PLGA. *In vitro* viability studies on Mesenchymal stem cells (MSCs) didn't show cytotoxicity whereas a significant proliferation rate was observed for cells on the PLGA/Ge(7:3) scaffolds. The specific scaffold is suitable for chronic wound dressings [159]. Ciprofloxacin loaded electrospun hydrophobic PLGA fibrous mats were modified with hydrophilic SG microparticles in order to improve the wettability and water absorption capacity, and enhance the release rate of ciprofloxacin from PLGA fibrous mats. The fibrous membranes showed improved antimicrobial effect to the PLGA mats. The results demonstrated that by combining hydrophilic AG and hydrophobic PLGA polymers can be prepared desired wound

dressings [160]. Similarly, nanofibrous wound dressings based on PLA and CA were developed and loaded with the antimicrobial agent, thymoquinone. This drug was used so as to prevent clinical infections, and to accelerate the rate of wound closure and re-epithelization. *In vivo* assessment exhibited that the scaffolds significantly promoted the wound healing process by increasing re-epithelization and controlling the formation of granulation tissue [161]. PLGA nanofibrous membrane that contains recombinant human EGF (rhEGF) and aloe vera extract were successfully fabricated by Garcia-Orue et al. The obtained nanofibers were of 356.03 ± 112.05 nm average diameter while *in vitro* viability studies showed that the membranes containing rhEGF and aloe vera improved fibroblast proliferation, and significantlyaccelerated wound closure and re-epithelization in an *in vivo* full thickness wound healing assay carried out in db/db mice. Consequently, the combination of rhEGF and aloe vera extract onto PLGA nanofibers can be beneficial for the treatment of chronic wounds [162].

Polymeric nanofibers containing montelukast as anti-inflammatory agent were fabricated by using different ratios of the blend of poly(methyl vinyl ether-co-maleic acid) (PMVEMA) and PLGA. *In vitro* viability studies showed that montelukast nanofibers don't present cytotoxicity on L929 cells. The nanofibers also caused increased platelet adhesion compared to the negative control group. Authors suggest that the PLGA/PMVEMA nanofibers of montelukast can be a good candidate for preparation of nontoxic wound dressings with haemostatic effects [163]. Electrospun sandwich-structured composite (SSC) membranes with well-antibacterial and antioxidant properties were prepared and comprised from three layers, including the bottom polyvinylidene fluoride fibrous layer, the middle curcumin/PLA microsphere layer, and the top enrofloxacin/PLA fibrous layer, respectively. It was established that SSC membranes exhibited excellent antioxidant activity against OH and DPPH free radicals as well as antibacterial activity against *S. aureus*, *E. coli*, *S. pneumoniae*, *P. aeruginosa* and *C. albicans*. The scaffolds can be characterized as ideal for wound dressings [164].

Many researchers suggest the use of electrospun fibers containing NPs. This method can lead to more functional dressings. Lysozyme NPs (Lyso- NPs) obtained by electrospray were incorporated to PLGA fibrous mats. Nearly negligible cytotoxicity of all the membranes on mouse fibroblast cells (L929) was observed according to MTT study. Furthermore, it was observed that the L929 cells grew well on the Lyso-EFMs, especially those with the modification of PEG that was added to improve the hydrophilicity of the fibrous membranes. The membranes were found suitable to produce functionalized wound dressings to promote wound healing [165]. In similar thought, β-CD was used to encapsulate cinnamaldehyde. The complex was further incorporated intoPLA electrospun fibers. It was found that the mechanical properties and hydrophilicity of the fibrous structures were improved. Also, the antibacterial activity against *E. coli* and *S. aureus* was enhanced whereas their low cytotoxicity led to researchers to characterize them safe wound dressings [166]. PLGA nanofibrous wound dressing incorporated with andrographolide (Andro)-loaded mesoporous silica NPs (MSNs) were also produced by electrospinning. The PLGA/Andro-MSNs membrane showed a sustained release of Andro while the cell culture and *in vivo* tests exhibited that PLGA/Andro-MSNs membrane can promote epidermal cell adhesion and reduce inflammation process [167].

Another category widely prepared as wound dressing systems are the type hydrogels systems. More specifically, PVA hydrogels containing ciprofloxacin hydrochloride-loaded PLGA NPs as antibacterial materials capable of supporting the treatment of infected pressure ulcers were produced by Choipang et al. The spherical PLGA NPs were of diameter between 625.3–957.9 nm. In later stages, PVA hydrogels encapsulated ciprofloxacin/PLGA NPs and found to provide an effective antimicrobial response when exposed to *E. coli* and *S. aureus*. The absence of cytotoxicity reveal that the system can be safely applied as wound membrane [168]. A novel system comprised from tetrahydrocurcumin-loaded MPEG-PLA NPs found to accelerate the wound healing. Afterwards, the research group study the use of SA/CS dressings containing the prepared NPs on wound healing. The results demonstrated that tetrahydrocurcumin-loaded MPEG-PLA NPs could promote cutaneous healing by increasing the synthesis of collagen I and III, revascularization and improving the migration of fibroblasts [169]. A hybrid system based on double crosslinked HA and PLGA/dexamethasone sodium phosphate (PLGADEX) NPs was designed to act as injectable hydrogel system and authors recommend its use as novel wound dressings [170]. Furthermore, a thermogelling dressing system composed of two triblock copolymers of PLGA-PEG-PLGA was developed to deliver teicoplanin, a glycopeptide antibiotic, for cutaneous wound repair. *In vitro* studies exhibited that the thermogel system presents desired tissue adhesiveness while from gross and histopathologic observations it was found reduced inflammation response, promoted disposition of collagen, enhanced angiogenesis, and accelerated wound closure and maturity of rats. Consequently, the thermogel can be successfully applied wound dressing for full-thickness excision wound healing [171].

Another study involved the use of Mg reinforced PLA composites as potential biocompatible and bioabsorbable materials for biomedical applications. The films show biodegradable properties and bioactive behavior due to the presence of Mg^{2+} ions, offering a promising strategy on wound healing field. Moreover, *in vitro* behavior of PLA/Mg films demonstrated that Mg^{2+} ions increase the fibroblast cells growth [172]. Alternating block polyurethanes and random block polyurethanes based on biodegradable PLA and PEG were synthesized in the form of foam dressings. Authors suggest that the rat skin was fully covered with new epithelium without any significant adverse reactions and that from the histological examination the dressings suppress the infiltration of inflammatory cells and accelerate fibroblast proliferation. This study is very interesting given that by only using polymers without bioactive agents, it can be provided wound healing effect [173].

4.4. *Medicinal plants as wound healing agents*

For centuries, plants have been used in both traditional and popular medicine to treat and prevent diseases [174]. Many

plants have been used as wound repairing herbs. Aloe vera has been applied as remedy for ulcers and skin lesions, however, its action mechanism is still unclear [175–177]. Capparis ovata var. palaestina fruit extract has been studied recently for its antidiabetic properties [178] but also for its wound healing activity. The results of wound healing were quite promising [179]. Another plant, Prunus spinosa L. was applied in the form of gel and demonstrated improved wound healing rates by promoting granulation tissue, epidermal regeneration and angiogenesis [180]. Other plants known for their wound healing property are the following: Anethum graveolens, Eucalyptus, Securigera securidaca, Trigonella foenum, Nelumbo nucifera, Chamomile, Rosemary officinalis, Allium sativum, Vitis vinifera, Calendula officinalis, Pistacia atlantica, curcumin etc [181]. To conclude numerous are the medicinal plants which authors believe that can act as traditional and economical home remedies. However, there is a big unanswered question whether the herbal plants will ever be applied in clinical routine.

5. Conclusions and future perspectives

Almost everyone has faced an open wound during his life. Most of these wounds were treated easily while other needed medical attention. Wound management is among most significant medical field given that infected wound can lead to serious complication. In this review, authors aimed to conclude the current knowledge of wound management and assessment in order to help researchers, clinicians as well as everyone interested on wound field to understand the complex phenomenon of wound healing. The authors' group introduced the principals for wound treatment, paid attention to recent guidelines whereas focused on novel drug delivery systems as wound dressings. Among the existent drug delivery systems, authors pointed out to biomaterials prepared by natural polymers as CS, HA etc as well as synthetic polymers of PCL, PVA and PLGA. It can be strongly argued that CS and its derivatives are the leading polymers applied as wound dressings. Its numerous properties (cost-effective, biocompatible, swelling index) and various ways to be fabricated into delivery systems (electrospun fibers, NPs, hydrogels etc) lead to be the favorable choice between researchers. Besides CS, the other natural and synthetic polymers can also be effective as wound dressings for specific type of wounds. Except the desirable wound dressing, the selection of the topical antibiotic or growth factors is also significant. However, the clinicians strongly believe that other factors such as nutrition and coexisting diseases play important role on the healing process. Thus, patient should be treated for all of the disorders not only the wound. Nutrition elements should be prescribed along with other factors. Among others there is an increasing interest of using medicinal plants because they low side effects and are cheaper than the marketed products. However, the use of medicinal herbs for wound treatment is a holistic approach and it is still in premature levels.

Apart from regional treatment choices, stem cell and RNA therapy have also been suggested as potentional therapeutic choices, which however lack of large scale trials. Nowadays, the state of the art of technology is the use of 3D printing biomaterials, which mimic the extracellular matrix. In future perspective, the use of 3D printed skin on the wound might offer a promising solution on wound treatment field. It can be said that by understanding the mechanism of wound healing, wound microbiology as well as the current wound dressings could be very helpful for medical and pharmaceutical society to produce more efficient wound dressings for individual patients.

Conflicts of interest

The authors declare that there is no conflicts of interest.

REFERENCES

[1] Siafaka PI, Zisi AP, Exindari MK, Karantas ID, Bikiaris DN. Porous dressings of modified chitosan with poly(2-hydroxyethyl acrylate) for topical wound delivery of levofloxacin. Carbohydr Polym 2016;143:90–9.
[2] Gonzalez ACde O, Costa TF, Andrade Zde A, Medrato ARAP. Wound healing - a literature review. An Bras Dermatol 2016;91:614–20.
[3] Wang PH, Huang BS, Horng HC, Yeh CC, Chen YJ. Wound healing. J Chin Med Assoc 2018;81:94–101.
[4] Kiritsi D, Nyström A. The role of TGFβ in wound healing pathologies. Mech Ageing Dev 2017;172:51–8.
[5] Schreml S, Szeimies RM, Prantl L, Landthaler M, Babilas P. Wound healing in the 21st century. J Am Acad Dermatol 2010;63:866–81.
[6] Beldon P. Basic science of wound healing. Surgery 2010;28:409–12.
[7] Bowler PG, Duerden BI. Wound microbiology and associated approaches to wound management. Clin Microb Rev 2001;14:244–69.
[8] Ovington L. Bacterial toxins and wound healing. Clinical Microbiology Reviews 2003;49:8–12.
[9] Edwards R, Harding KG. Bacteria and wound healing. Curr Opin Infect Dis 2004;17:91–6.
[10] Singh S, Young A, McNaught CE. The physiology of wound healing. Surg (United Kingdom) 2017;35:473–7.
[11] Shaw TJ, Martin P. Wound repair at a glance. J Cell Sci 2009;122:3209–13.
[12] Eming SA, Krieg T, Davidson JM. Inflammation in wound repair: molecular and cellular mechanisms. J Invest Dermatol 2007;127:514–25.
[13] Gurtner GC, Werner S, Barrandon Y, Longaker MT. Wound repair and regeneration. Nature 2008;453:314–21.
[14] Elnar TV, Ailey TB. The wound healing process : an overview of the cellular and molecular mechanisms. J Int Med Res 2009;37:1528–42.
[15] Childs DR, Murthy AS. Overview of wound healing and management. Surg Clin North Am 2017;97:189–207.
[16] Li J, Chen J, Kirsner R. Pathophysiology of acute wound healing. Clin Dermatol 2007;25:9–18.
[17] Welch MP, Odland GF, Clark RA. Temporal relationships of F-actin bundle formation, collagen and fibronectin matrix assembly, and fibronectin receptor expression to wound contraction. J Cell Biol 1990;110:133–45.
[18] Sorg H, Tilkorn DJ, Hager S, Hauser J, Mirastschijski U. Skin wound healing: an update on the current knowledge and concepts. Eur Surg Res 2017;58:81–94.
[19] Anderson K, Hamm RL. Factors that impair wound healing. J Am Coll Clin Wound Spec 2012;4:84–91.

[20] Okur ME, Karantas ID, Okur NÜ, Siafaka PI. Hypertension in 2017: update in treatment and pharmaceutical innovations. Curr Pharm Des 2017;23(44):6795–814.
[21] Han G, Ceilley R. Chronic wound healing: a review of current management and treatments. Adv Ther 2017;34:599–610.
[22] Campos AC, Groth AK, Branco AB. Assessment and nutritional aspects of wound healing. Curr Opin Clin Nutr Metab Care 2008;11:281–8.
[23] Okur ME, Karantas ID, Siafaka PI. Diabetes mellitus: a review on pathophysiology, current status of oral medications and future perspectives. Acta Pharm Sci 2017;55(1):61–82.
[24] Galiano RD, Tepper OM, Pelo CR, Bhatt KA, Callaghan M, Bastidas N, et al. Topical vascular endothelial growth factor accelerates diabetic wound healing through increased angiogenesis and by mobilizing and recruiting bone marrow-derived cells. Am J Pathol 2004;164:1935–47.
[25] Molnar JA, Underdown MJ, Clark WA. Nutrition and chronic wounds. Adv Wound Care 2014;3:663–81.
[26] Heinrichs E, Llewellyn M, Harding K. Assessment of the patient with a wound. Wound healing: a systematic approach to advanced wound healing and management. Gray D, Cooper P, editors. Aberdeen: Wounds UK; 2005.
[27] Russell L. Understanding physiology of wound healing and how dressings help. Br J Nurs 2000;9:10–21.
[28] Hampton S. The role of alginate dressings in wound healing. Diabet Foot 2004;7:162–6.
[29] Simões D, Miguel SP, Ribeiro MP, Coutinho P, Mendonça AG, Correia IJ. Recent advances on antimicrobial wound dressing: a review. Eur J Pharm Biopharm 2018;127:130–41.
[30] Ehterami A, Salehi M, Farzamfar S, Vaez A, Samadian H, Sahrapeyma H, et al. *In vitro* and *in vivo* study of PCL/COLL wound dressing loaded with insulin-chitosan nanoparticles on cutaneous wound healing in rats model. Int J Biol Macromol 2018;117:601–9.
[31] Siafaka PI, Titopoulou A, Koukaras EN, Kostoglou M, Koutris E, Karavas E, et al. Chitosan derivatives as effective nanocarriers for ocular release of timolol drug. Int J Pharm 2015;495:249–64.
[32] Üstündağ Okur N, Hökenek N, Okur ME, Ayla Ş, Yoltaş A, Siafaka PI, et al. An alternative approach to wound healing field; new composite films from natural polymers for mupirocin dermal delivery. Saudi Pharm J 2019;27:738–52.
[33] Siafaka PI, Üstündağ Okur N, Karavas E, Bikiaris DN. Surface modified multifunctional and stimuli responsive nanoparticles for drug targeting: current status and uses. Int J Mol Sci 2016;17:1440.
[34] Filippousi M, Siafaka PI, Amanatiadou EP, Nanaki SG, Nerantzaki M, Bikiaris DN, et al. Modified chitosan coated mesoporous strontium hydroxyapatite nanorods as drug carriers. J Mater Chem B 2015;3:5991–6000.
[35] Bayindir Bilgic M, Lacin NT, Berber H, Mansuroglu B. *In vitro* evaluation of alpha-tocopherol loaded carboxymethylcellulose chitosan copolymers as wound dressing materials. Mater Technol 2019;34:386–93.
[36] Ferreira MOG, de Lima IS, Morais AÍS, Silva SO, de Carvalho RBF, Ribeiro AB, et al. Chitosan associated with chlorhexidine in gel form: synthesis, characterization and healing wounds applications. J Drug Deliv Sci Technol 2019;49:375–82.
[37] Martínez-Ibarra DM, Sánchez-Machado DI, López-Cervantes J, Campas-Baypoli ON, Sanches-Silva A, Madera-Santana TJ. Hydrogel wound dressings based on chitosan and xyloglucan: development and characterization. J Appl Polym Sci 2018;136:47342.
[38] Mukherjee D, Azamthulla M, Santhosh S, Dath G, Ghosh A, Natholia R, et al. Development and characterization of chitosan-based hydrogels as wound dressing materials. J Drug Deliv Sci Technol 2018;46:498–510.
[39] Yao HY, Lin HR, Sue GP, Lin YJ. Chitosan-based hydrogels prepared by UV polymerization for wound dressing. Polym Polym Compos 2019;27:155–67.
[40] Chen H, Cheng J, Ran L, Yu K, Lu B, Lan G, et al. An injectable self-healing hydrogel with adhesive and antibacterial properties effectively promotes wound healing. Carbohydr Polym 2018;201:522–31.
[41] Wang C, Li B, Chen T, Mei N, Wang X, Tang S. Preparation and bioactivity of acetylated konjac glucomannan fibrous membrane and its application for wound dressing. Carbohydr Polym 2020;229:115404.
[42] Liang M, Chen Z, Wang F, Liu L, Wei R, Zhang M. Preparation of self-regulating/anti-adhesive hydrogels and their ability to promote healing in burn wounds. J Biomed Mater Res Part B Appl Biomater 2019;107:1471–82.
[43] Song R, Zheng J, Liu Y, Tan Y, Yang Z, Song X, et al. A natural cordycepin/chitosan complex hydrogel with outstanding self-healable and wound healing properties. Int J Biol Macromol 2019;134:91–9.
[44] Xie Y, Liao X, Zhang J, Yang F, Fan Z. Novel chitosan hydrogels reinforced by silver nanoparticles with ultrahigh mechanical and high antibacterial properties for accelerating wound healing. Int J Biol Macromol 2018;119:402–12.
[45] Ragab TIM, Nada AA, Ali EA, Shalaby ASG, Soliman AAF, Emam M, et al. Soft hydrogel based on modified chitosan containing *P. granatum* peel extract and its nano-forms: multiparticulate study on chronic wounds treatment. Int J Biol Macromol 2019;135:407–21.
[46] Long J, Etxeberria AE, Nand AV, Bunt CR, Ray S, Seyfoddin A. A 3D printed chitosan-pectin hydrogel wound dressing for lidocaine hydrochloride delivery. Mater Sci Eng C 2019;104:109873.
[47] Masood N, Ahmed R, Tariq M, Ahmed Z, Masoud MS, Ali I, et al. Silver nanoparticle impregnated chitosan-PEG hydrogel enhances wound healing in diabetes induced rabbits. Int J Pharm 2019;559:23–36.
[48] Huang W, Wang Y, Huang Z, Wang X, Chen L, Zhang Y, et al. On-demand dissolvable self-healing hydrogel based on carboxymethyl chitosan and cellulose nanocrystal for deep partial thickness burn wound healing. ACS Appl Mater Interfaces 2018;10:41076–88.
[49] Halim AS, Nor FM, Mat Saad AZ, Mohd Nasir NA, Norsa'adah B, Ujang Z. Efficacy of chitosan derivative films versus hydrocolloid dressing on superficial wounds. J Taibah Univ Med Sci 2018;13:512–20.
[50] Shao J, Wang B, Li J, Jansen JA, Walboomers XF, Yang F. Antibacterial effect and wound healing ability of silver nanoparticles incorporation into chitosan-based nanofibrous membranes. Mater Sci Eng C 2019;98:1053–63.
[51] Shah A, Yameen MA, Fatima N, Murtaza G. Chemical synthesis of chitosan/silver nanocomposites films loaded with moxifloxacin: their characterization and potential antibacterial activity. Int J Pharm 2019;561:19–34.
[52] Shah A, Ashames AA, Buabeid MA, Murtaza G. Synthesis, *in vitro* characterization and antibacterial efficacy of moxifloxacin-loaded chitosan- pullulan-silver-nanocomposite films. J Drug Deliv Sci Technol 2020;55:101366.
[53] Kaolaor A, Phunpee S, Ruktanonchai UR, Suwantong O. Effects of β-cyclodextrin complexation of curcumin and quaternization of chitosan on the properties of the blend films for use as wound dressings. J Polym Res 2019;26:43.
[54] Akhavan-Kharazian N, Izadi-Vasafi H. Preparation and characterization of chitosan/gelatin/nanocrystalline cellulose/calcium peroxide films for potential wound dressing applications. Int J Biol Macromol 2019;133:881–91.

[55] Wu WC, Hsiao PY, Huang YC. Effects of amylose content on starch-chitosan composite film and its application as a wound dressing. J Polym Res 2019;26:137.
[56] Rahimi M, Ahmadi R, Samadi Kafil H, Shafiei-Irannejad V. A novel bioactive quaternized chitosan and its silver-containing nanocomposites as a potent antimicrobial wound dressing: structural and biological properties. Mater Sci Eng C 2019;101:360–9.
[57] Hafezi F, Scoutaris N, Douroumis D, Boateng J. 3D printed chitosan dressing crosslinked with genipin for potential healing of chronic wounds. Int J Pharm 2019;560:406–15.
[58] Lai WF, Hu C, Deng G, Lui KH, Wang X, Tsoi TH, et al. A biocompatible and easy-to-make polyelectrolyte dressing with tunable drug delivery properties for wound care. Int J Pharm 2019;566:101–10.
[59] Biranje SS, Madiwale PV, Patankar KC, Chhabra R, Dandekar-Jain P, Adivarekar RV. H.emostasis and anti-necrotic activity of wound-healing dressing containing chitosan nanoparticles. Int J Biol Macromol 2019;121:936–46.
[60] Duvnjak Romić M, Špoljarić D, Šegvić Klarić M, Cetina-Čižmek B, Filipović-Grčić J, Hafner A. Melatonin loaded lipid enriched chitosan microspheres – hybrid dressing for moderate exuding wounds. J Drug Deliv Sci Technol 2019;52:431–9.
[61] Farzinfar E, Paydayesh A. Investigation of polyvinyl alcohol nanocomposite hydrogels containing chitosan nanoparticles as wound dressing. Int J Polym Mater Polym Biomater 2019;68:628–38.
[62] Sharma S, Swetha KL, Roy A. Chitosan-Chondroitin sulfate based polyelectrolyte complex for effective management of chronic wounds. Int J Biol Macromol 2019;132:97–108.
[63] Wichai S, Chuysinuan P, Chaiarwut S, Ekabutr P, Supaphol P. Development of bacterial cellulose/alginate/chitosan composites incorporating copper (II) sulfate as an antibacterial wound dressing. J Drug Deliv Sci Technol 2019;51:662–71.
[64] Anbazhagan S, Thangavelu KP. Application of tetracycline hydrochloride loaded-fungal chitosan and aloe vera extract based composite sponges for wound dressing. J Adv Res 2018;14:63–71.
[65] Xia G, Zhai D, Sun Y, Hou L, Guo X, Wang L, et al. Preparation of a novel asymmetric wettable chitosan-based sponge and its role in promoting chronic wound healing. Carbohydr Polym 2020;227:115296.
[66] Zhang K, Bai X, Yuan Z, Cao X, Jiao X, Li Y, et al. Layered nanofiber sponge with an improved capacity for promoting blood coagulation and wound healing. Biomaterials 2019;204:70–9.
[67] Zhao YF, Zhao JY, Hu WZ, Ma K, Chao Y, Sun PJ, et al. Synthetic poly(vinyl alcohol–chitosan as a new type of highly efficient hemostatic sponge with blood-triggered swelling and high biocompatibility. J Mater Chem B 2019;7:1855–66.
[68] Aubert-Viard F, Mogrovejo-Valdivia A, Tabary N, Maton M, Chai F, Neut C, et al. Evaluation of antibacterial textile covered by layer-by-layer coating and loaded with chlorhexidine for wound dressing application. Mater Sci Eng C 2019;100:554–63.
[69] Portela R, Leal CR, Almeida PL, Sobral RG. Bacterial cellulose: a versatile biopolymer for wound dressing applications. Microb Biotechnol 2019;12:586–610.
[70] Aderibigbe BA, Buyana B. Alginate in wound dressings. Pharmaceutics 2018;10(2):42.
[71] Fleck CA, Simman R. Modern collagen wound dressings: function and purpose. J Am Col Certif Wound Spec 2010;2:50–4.
[72] Longinotti C. The use of hyaluronic acid based dressings to treat burns: a review. Burn Trauma 2014;2(4):162–8.
[73] Shahzad A, Khan A, Afzal Z, Umer MF, Khan J, Khan GM. Formulation development and characterization of cefazolin nanoparticles-loaded cross-linked films of sodium alginate and pectin as wound dressings. Int J Biol Macromol 2019;124:255–69.
[74] Nagasawa F, Yoshikawa Y, Tanida I, Osawa S. Development of wound dressing with sustained-release of drug using natural polymer. J Soc Mater Sci Jpn 2018;67:918–23.
[75] Rezvanian M, Ahmad N, Mohd Amin MCI, Ng SF. Optimization, characterization, and *in vitro* assessment of alginate-pectin ionic cross-linked hydrogel film for wound dressing applications. Int J Biol Macromol 2017;97:131–40.
[76] Tong Z, Chen Y, Liu Y, Tong L, Chu J, Xiao K, et al. Preparation, characterization and properties of alginate/poly(γ-glutamic acid) composite microparticles. Mar Drugs 2017;15(4):91.
[77] Lukáč P, Hartinger JM, Mlček M, Popková M, Suchý T, Šupová M, et al. A novel gentamicin-releasing wound dressing prepared from freshwater fish Cyprinus carpio collagen cross-linked with carbodiimide. J Bioact Compat Polym 2019;34:246–62.
[78] Wu G, Ma X, Fan L, Gao Y, Deng H, Wang Y. Accelerating dermal wound healing and mitigating excessive scar formation using LBL modified nanofibrous mats. Mater Des 2020;185:108265.
[79] Rethinam S, Vijayan S, Aruni AW, Basaran B, Alagumuthu T, Ramamoorthy R. Enhanced tissue regeneration using an nano- bioactive scaffold- a novel perspective. Mater Chem Phys 2020;240:122303.
[80] Hu S, Cai X, Qu X, Yu B, Yan C, Yang J, et al. Preparation of biocompatible wound dressings with long-term antimicrobial activity through covalent bonding of antibiotic agents to natural polymers. Int J Biol Macromol 2019;123:1320–30.
[81] Lin CW, Chen YK, Lu M, Lou KL, Yu J. Photo-crosslinked keratin/chitosan membranes as potential wound dressing materials. Polymers (Basel) 2018;10:987.
[82] Ying H, Zhou J, Wang M, Su D, Ma Q, Lv G, et al. *In situ* formed collagen-hyaluronic acid hydrogel as biomimetic dressing for promoting spontaneous wound healing. Mater Sci Eng C 2019;101:487–98.
[83] Karimi Dehkordi N, Minaiyan M, Talebi A, Akbari V, Taheri A. Nanocrystalline cellulose–hyaluronic acid composite enriched with GM-CSF loaded chitosan nanoparticles for enhanced wound healing. Biomed Mater 2019;14:035003.
[84] Eskandarinia A, Kefayat A, Rafienia M, Agheb M, Navid S, Ebrahimpour K. Cornstarch-based wound dressing incorporated with hyaluronic acid and propolis: *in vitro* and *in vivo* studies. Carbohydr Polym 2019;216:25–35.
[85] Tarusha L, Paoletti S, Travan A, Marsich E. Alginate membranes loaded with hyaluronic acid and silver nanoparticles to foster tissue healing and to control bacterial contamination of non-healing wounds. J Mater Sci Mater Med 2018;29:22.
[86] Rossi S, Mori M, Vigani B, Bonferoni MC, Sandri G, Riva F, et al. A novel dressing for the combined delivery of platelet lysate and vancomycin hydrochloride to chronic skin ulcers: hyaluronic acid particles in alginate matrices. Eur J Pharm Sci 2018;118:87–95.
[87] Iacob AT, Drăgan M, Gheţu N, Pieptu D, Vasile C, Buron F, et al. Preparation, characterization and wound healing effects of new membranes based on chitosan, hyaluronic acid and arginine derivatives. Polymers (Basel) 2018;10:607.
[88] Jiang Y, Hou Y, Fang J, Liu W, Zhao Y, Huang T, et al. Preparation and characterization of PVA/SA/HA composite hydrogels for wound dressing. Int J Polym Anal Charact 2019;24:132–41.

[89] Abou-Okeil A, Fahmy HM, El-Bisi MK, Ahmed-Farid OA. Hyaluronic acid/Na-alginate films as topical bioactive wound dressings. Eur Polym J 2018;109:101–9.
[90] Zhu J, Li F, Wang X, Yu J, Wu D. Hyaluronic acid and polyethylene glycol hybrid hydrogel encapsulating nanogel with hemostasis and sustainable antibacterial property for wound healing. ACS Appl Mater Interfaces 2018;10:13304–16.
[91] Alemzadeh E, Oryan A, Mohammadi AA. Hyaluronic acid hydrogel loaded by adipose stem cells enhances wound healing by modulating IL-1β, TGF-β1, and bFGF in burn wound model in rat. J Biomed Mater Res Part B Appl Biomater 2020;108(2):555–67.
[92] Wang SY, Kim H, Kwak G, Yoon HY, Jo SD, Lee JE, et al. Development of biocompatible HA hydrogels embedded with a new synthetic peptide promoting cellular migration for advanced wound care management. Adv Sci 2018;5:1800852.
[93] Catanzano O, D'Esposito V, Formisano P, Boateng JS, Quaglia F. Composite alginate-hyaluronan sponges for the delivery of tranexamic acid in postextractive alveolar wounds. J Pharm Sci 2018;107:654–61.
[94] Yin F, Lin L, Zhan S. Preparation and properties of cellulose nanocrystals, gelatin, hyaluronic acid composite hydrogel as wound dressing. J Biomater Sci Polym Ed 2019;30:190–2013.
[95] Tavakoli J. Physico-mechanical, morphological and biomedical properties of a novel natural wound dressing material. J Mech Behav Biomed Mater 2017;65:373–82.
[96] Liu J, Yan L, Yang W, Lan Y, Zhu Q, Xu H, et al. Controlled-release neurotensin-loaded silk fibroin dressings improve wound healing in diabetic rat model. Bioact Mater 2019;4:151–9.
[97] Yang W, Xu H, Lan Y, Zhu Q, Liu Y, Huang S, et al. Preparation and characterisation of a novel silk fibroin/hyaluronic acid/sodium alginate scaffold for skin repair. Int J Biol Macromol 2019;130:58–67.
[98] Miguel SP, Simões D, Moreira AF, Sequeira RS, Correia IJ. Production and characterization of electrospun silk fibroin based asymmetric membranes for wound dressing applications. Int J Biol Macromol 2019;121:524–35.
[99] Mohamad N, Loh EYX, Fauzi MB, Ng MH, Mohd Amin MCI. *In vivo* evaluation of bacterial cellulose/acrylic acid wound dressing hydrogel containing keratinocytes and fibroblasts for burn wounds. Drug Deliv Transl Res 2019;9:444–52.
[100] Wang Y, Wang C, Xie Y, Yang Y, Zheng Y, Meng H, et al. Highly transparent, highly flexible composite membrane with multiple antimicrobial effects used for promoting wound healing. Carbohydr Polym 2019;222:114985.
[101] Volova TG, Shumilova AA, Nikolaeva ED, Kirichenko AK, Shishatskaya EI. Biotechnological wound dressings based on bacterial cellulose and degradable copolymer P(3HB/4HB). Int J Biol Macromol 2019;131:230–40.
[102] Ali NH, Amin MCIM, Ng S-F. Sodium carboxymethyl cellulose hydrogels containing reduced graphene oxide (rGO) as a functional antibiofilm wound dressing. J Biomater Sci Polym Ed 2019;30:629–45.
[103] Gupta A, Keddie DJ, Kannappan V, Gibson H, Khalil IR, Kowalczuk M, et al. Production and characterisation of bacterial cellulose hydrogels loaded with curcumin encapsulated in cyclodextrins as wound dressings. Eur Polym J 2019;118:437–50.
[104] Zhang ZY, Sun Y, Zheng YD, He W, Yang YY, Xie YJ, et al. A biocompatible bacterial cellulose/tannic acid composite with antibacterial and anti-biofilm activities for biomedical applications. Mater Sci Eng C 2020;106:110249.
[105] Khan MQ, Kharaghani D, Sanaullah, Shahzad A, Saito Y, Yamamoto T, et al. Fabrication of antibacterial electrospun cellulose acetate/silver-sulfadiazine nanofibers composites for wound dressings applications. Polym Test 2019;74:39–44.
[106] Wutticharoenmongkol P, Hannirojram P, Nuthong P. Gallic acid-loaded electrospun cellulose acetate nanofibers as potential wound dressing materials. Polym Adv Technol 2019;30:1135–47.
[107] Yazdanbakhsh MF, Rashidi A, Rahimi MK, Khajavi R, Shafaroodi H. The effect of impregnated alpha-cellulose nanofibers with ciprofloxacin hydrochloride on *Staphylococcus aureus in vitro* and healing process of wound in rat. Regen Eng Transl Med 2018;4:247–56.
[108] Mir M, Ali MN, Barakullah A, Gulzar A, Arshad M, Fatima S, et al. Synthetic polymeric biomaterials for wound healing: a review. Prog Biomater 2018;7:1–21.
[109] Siafaka P, Üstündağ Okur N, Mone M, Giannakopoulou S, Er S, Pavlidou E, et al. Two different approaches for oral administration of voriconazole loaded formulations: electrospun fibers versus β-cyclodextrin complexes. Int J Mol Sci 2016;17:282.
[110] Siafaka PI, Barmpalexis P, Lazaridou M, Papageorgiou GZ, Koutris E, Karavas E, et al. Controlled release formulations of risperidone antipsychotic drug in novel aliphatic polyester carriers: data analysis and modelling. Eur J Pharm Biopharm 2015;94:473–84.
[111] Filippousi M, Turner S, Leus K, Siafaka PI, Tseligka ED, Vandichel M, et al. Biocompatible Zr-based nanoscale MOFs coated with modified poly(ε-caprolactone) as anticancer drug carriers. Int J Pharm 2016;509:208–18.
[112] Eğri Ö, Erdemir N. Production of *Hypericum* perforatum oil-loaded membranes for wound dressing material and *in vitro* tests. Artif Cells Nanomedicine Biotechnol 2019;47(1):1404–15.
[113] Ajmal G, Bonde GV, Thokala S, Mittal P, Khan G, Singh J, et al. Ciprofloxacin HCl and quercetin functionalized electrospun nanofiber membrane: fabrication and its evaluation in full thickness wound healing. Artif Cells Nanomed Biotechnol 2019;47:228–40.
[114] Ghaee A, Karimi M, Lotfi-Sarvestani M, Sadatnia B, Hoseinpour V. Preparation of hydrophilic polycaprolactone/modified ZIF-8 nanofibers as a wound dressing using hydrophilic surface modifying macromolecules. Mater Sci Eng C 2019;103:109767.
[115] Ravichandran S, Radhakrishnan J, Jayabal P, Venkatasubbu GD. Antibacterial screening studies of electrospun polycaprolactone nano fibrous mat containing Clerodendrum phlomidis leaves extract. Appl Surf Sci 2019;484:676–87.
[116] Pedram Rad Z, Mokhtari J, Abbasi M. Preparation and characterization of calendula officinalis-loaded PCL/gum arabic nanocomposite scaffolds for wound healing applications. Iran Polym J 2019;28:51–63.
[117] Adeli-Sardou M, Yaghoobi MM, Torkzadeh-Mahani M, Dodel M. Controlled release of lawsone from polycaprolactone/gelatin electrospun nano fibers for skin tissue regeneration. Int J Biol Macromol 2019;124:478–91.
[118] Tanrıverdi ST, Suat B, Azizoğlu E, Köse FA. *In vitro* evaluation of dexpanthenol-loaded nanofiber mats for wound healing. Trop J Pharm Res 2018;17:387.
[119] Li X, Wang C, Yang S, Liu P, Zhang B. Electrospun PCL/mupirocin and chitosan/lidocaine hydrochloride multifunctional double layer nanofibrous scaffolds for wound dressing applications. Int J Nanomedicine 2018;13:5287–99.
[120] Nejaddehbashi F, Hashemitabar M, Bayati V, Abbaspour M, Moghimipour E, Orazizadeh M. Application of polycaprolactone, chitosan, and collagen composite as a

nanofibrous mat loaded with silver sulfadiazine and growth factors for wound dressing. Artif Organs 2019;43:413–23.
[121] Huang Y, Dan N, Dan W, Zhao W, Bai Z, Chen Y, et al. Bilayered antimicrobial nanofiber membranes for wound dressings via *in situ* cross-linking polymerization and electrospinning. Ind Eng Chem Res 2018;57:17048–57.
[122] Dou J, Wang Y, Jin X, Li P, Wang L, Yuan J, et al. PCL/sulfonated keratin mats for vascular tissue engineering scaffold with potential of catalytic nitric oxide generation. Mater Sci Eng C 2020;107:110246.
[123] He FL, Deng X, Zhou YQ, Zhang TD, Liu YL, Ye YJ, et al. Controlled release of antibiotics from poly-ε-caprolactone/polyethylene glycol wound dressing fabricated by direct-writing melt electrospinning. Polym Adv Technol 2019;30:425–34.
[124] Shi R, Geng H, Gong M, Ye J, Wu C, Hu X, et al. Long-acting and broad-spectrum antimicrobial electrospun poly (ε-caprolactone)/gelatin micro/nanofibers for wound dressing. J Colloid Interface Sci 2018;509:275–84.
[125] Tra Thanh N, Ho Hieu M, Tran Minh Phuong N, Do Bui Thuan T, Nguyen Thi Thu H, Thai VP, et al. Optimization and characterization of electrospun polycaprolactone coated with gelatin-silver nanoparticles for wound healing application. Mater Sci Eng C 2018;91:318–29.
[126] Souza SOL, Cotrim MAP, Oréfice RL, Carvalho SG, Dutra JAP, de Paula Careta F, et al. Electrospun poly(ε-caprolactone) matrices containing silver sulfadiazine complexed with β-cyclodextrin as a new pharmaceutical dosage form to wound healing: preliminary physicochemical and biological evaluation. J Mater Sci Mater Med 2018;29:67.
[127] Xie Z, Paras CB, Weng H, Punnakitikashem P, Su LC, Vu K, et al. Dual growth factor releasing multi-functional nanofibers for wound healing. Acta Biomater 2013;9:9351–9.
[128] Choi JS, Choi SH, Yoo HS. Coaxial electrospun nanofibers for treatment of diabetic ulcers with binary release of multiple growth factors. J Mater Chem 2011;21:5258.
[129] Olvera D, Sathy BN, Carroll SF, Kelly DJ. Modulating microfibrillar alignment and growth factor stimulation to regulate mesenchymal stem cell differentiation. Acta Biomater 2017;64:148–60.
[130] Su Y, Wang H, Mishra B, Lakshmaiah Narayana J, Jiang J, Reilly DA, et al. Nanofiber dressings topically delivering molecularly engineered human cathelicidin peptides for the treatment of biofilms in chronic wounds. Mol Pharm 2019;16:2011–20.
[131] Augustine R, Hasan A, Patan NK, Augustine A, Dalvi YB, Varghese R, et al. Titanium nanorods loaded PCL meshes with enhanced blood vessel formation and cell migration for wound dressing applications. Macromol Biosci 2019;19(7):e1900058.
[132] Brianezi SFS, Castro KC, Piazza RD, Melo Mdo SF, Pereira RM, Marques RFC, et al. Preparation and characterization of chitosan/mPEG-PCL blended membranes for wound dressing and controlled gentamicin release. Mater Res 2018;21(6):e20170951.
[133] Wei LG, Chang HI, Wang Y, Hsu S, Dai LG, Fu KY, et al. A gelatin/collagen/polycaprolactone scaffold for skin regeneration. PeerJ 2019;7:e6358.
[134] Liao J, Jia Y, Wang B, Shi K, Qian Z. Injectable hybrid poly(ε-caprolactone)-b-poly(ethylene glycol)-b-poly (ε-caprolactone) porous microspheres/alginate hydrogel cross-linked by calcium gluconate crystals deposited in the pores of microspheres improved skin wound healing. ACS Biomater Sci Eng 2018;4:1029–36.
[135] Tavakoli J, Tang Y. Honey/PVA hybrid wound dressings with controlled release of antibiotics: structural, physico-mechanical and *in vitro* biomedical studies. Mater Sci Eng C 2017;77:318–25.
[136] Tang Y, Lan X, Liang C, Zhong Z, Xie R, Zhou Y, et al. Honey loaded alginate/PVA nanofibrous membrane as potential bioactive wound dressing. Carbohydr Polym 2019;219:113–20.
[137] Ahlawat J, Kumar V, Gopinath P. Carica papaya loaded poly (vinyl alcohol)-gelatin nanofibrous scaffold for potential application in wound dressing. Mater Sci Eng C 2019;103:109834.
[138] Paduraru A, Ghitulica C, Trusca R, Surdu VA, Neacsu IA, Holban AM, et al. Antimicrobial wound dressings as potential materials for skin tissue regeneration. Materials(Basel) 2019;12:1859.
[139] Jatoi AW, Ogasawara H, Kim IS, Ni QQ. Polyvinyl alcohol nanofiber based three phase wound dressings for sustained wound healing applications. Mater Lett 2019;241:168–71.
[140] Ardekani NT, Khorram M, Zomorodian K, Yazdanpanah S, Veisi H, Veisi H. Evaluation of electrospun poly (vinyl alcohol)-based nanofiber mats incorporated with Zataria multiflora essential oil as potential wound dressing. Int J Biol Macromol 2019;125:743–50.
[141] Kim MS, Oh GW, Jang YM, Ko SC, Park WS, Choi IW, et al. Antimicrobial hydrogels based on pva and diphlorethohydroxycarmalol (DPHC) derived from brown alga Ishige okamurae: an *in vitro* and *in vivo* study for wound dressing application. Mater Sci Eng C 2020;107: 110352.
[142] Batool S, Hussain Z, Niazi MBK, Liaqat U, Afzal M. Biogenic synthesis of silver nanoparticles and evaluation of physical and antimicrobial properties of AG/PVA/starch nanocomposites hydrogel membranes for wound dressing application. J Drug Deliv Sci Technol 2019;52:403–14.
[143] Tao G, Wang Y, Cai R, Chang H, Song K, Zuo H, et al. Design and performance of sericin/poly(vinyl alcohol) hydrogel as a drug delivery carrier for potential wound dressing application. Mater Sci Eng C 2019;101:341–51.
[144] Zheng C, Liu C, Chen H, Wang N, Liu X, Sun G, et al. Effective wound dressing based on poly (vinyl alcohol)/Dextran-aldehyde composite hydrogel. Int J Biol Macromol 2019;132:1098–105.
[145] Neres Santos A, Duarte Moreira A, Piler Carvalho C, Luchese R, Ribeiro E, McGuinness G, et al. Physically cross-linked gels of PVA with natural polymers as matrices for manuka honey release in wound-care applications. Materials(Basel) 2019;12:559.
[146] Khalilipour A, Paydayesh A. Characterization of polyvinyl alcohol/ZnO nanocomposite hydrogels for wound dressings. J Macromol Sci Part B 2019;58:371–84.
[147] Gao T, Jiang M, Liu X, You G, Wang W, Sun Z, et al. Patterned polyvinyl alcohol hydrogel dressings with stem cells seeded for wound healing. Polymers(Basel) 2019;11:171.
[148] Rezvan G, Pircheraghi G, Bagheri R. Curcumin incorporated PVA-borax dual delivery hydrogels as potential wound dressing materials-Correlation between viscoelastic properties and curcumin release rate. J Appl Polym Sci 2018;135:46734.
[149] Das A, Uppaluri R, Das C. Feasibility of poly-vinyl alcohol/starch/glycerol/citric acid composite films for wound dressing applications. Int J Biol Macromol 2019;131:998–1007.
[150] Bano I, Arshad M, Yasin T, Ghauri MA. Preparation, characterization and evaluation of glycerol plasticized chitosan/PVA blends for burn wounds. Int J Biol Macromol 2019;124:155–62.
[151] da Cruz JA, da Silva AB, Ramin BBS, Souza PR, Popat KC, Zola RS, et al. Poly(vinyl alcohol)/cationic tannin blend films with antioxidant and antimicrobial activities. Mater Sci Eng C 2020;107:110357.

[152] Dekina S, Romanovska I, Sevastyanov O, Shesterenko Y, Ryjak A, Varbanets L, et al. Development and characterization of chitosan/polyvinyl alcohol polymer material with elastolytic and collagenolytic activities. Enzyme Microb Technol 2020;132:109399.
[153] Perumal G, Pappuru S, Chakraborty D, Maya Nandkumar A, Chand DK, Doble M. Synthesis and characterization of curcumin loaded PLA—hyperbranched polyglycerol electrospun blend for wound dressing applications. Mater Sci Eng C 2017;76:1196–204.
[154] Siafaka PI, Barmbalexis Panagiotis, Bikiaris DN. Novel electrospun nanofibrous matrices prepared from poly(lactic acid)/poly(butylene adipate) blends for controlled release formulations of an anti-rheumatoid agent. Eur J Pharm Sci 2016;88:12–25.
[155] Üstündağ Okur N, Filippousi M, Okur ME, Ayla Ş, Çağlar EŞ, Yoltaş A, et al. A novel approach for skin infections: controlled release topical mats of poly(lactic acid)/poly(ethylene succinate) blends containing voriconazole. J Drug Deliv Sci Technol 2018;46: 74–86.
[156] Zou F, Sun X, Wang X. Elastic, hydrophilic and biodegradable poly (1, 8-octanediol-co-citric acid)/polylactic acid nanofibrous membranes for potential wound dressing applications. Polym Degrad Stab 2019;166:163–73.
[157] Li W, Yu Q, Yao H, Zhu Y, Topham PD, Yue K, et al. Superhydrophobic hierarchical fiber/bead composite membranes for efficient treatment of burns. Acta Biomater 2019;92:60–70.
[158] Locilento DA, Mercante LA, Andre RS, Mattoso LHC, Luna GLF, Brassolatti P, et al. Biocompatible and biodegradable electrospun nanofibrous membranes loaded with grape seed extract for wound dressing application. J Nanomater 2019;2019(7–8):1–11.
[159] Vázquez N, Sánchez-Arévalo F, Maciel-Cerda A, Garnica-Palafox I, Ontiveros-Tlachi R, Chaires-Rosas C, et al. Influence of the PLGA/gelatin ratio on the physical, chemical and biological properties of electrospun scaffolds for wound dressings. Biomed Mater 2019;14: 045006.
[160] Liu X, Nielsen LH, Kłodzińska SN, Nielsen HM, Qu H, Christensen LP, et al. Ciprofloxacin-loaded sodium alginate/poly (lactic-co-glycolic acid) electrospun fibrous mats for wound healing. Eur J Pharm Biopharm 2018;123:42–9.
[161] Gomaa SF, Madkour TM, Moghannem S, El-Sherbiny IM. New polylactic acid/ cellulose acetate-based antimicrobial interactive single dose nanofibrous wound dressing mats. Int J Biol Macromol 2017;105:1148–60.
[162] Garcia-Orue I, Gainza G, Gutierrez FB, Aguirre JJ, Evora C, Pedraz JL, et al. Novel nanofibrous dressings containing rhEGF and aloe vera for wound healing applications. Int J Pharm 2017;523:556–66.
[163] Varshosaz J, Jahanian A, Maktoobian M. Montelukast incorporated poly(methyl vinyl ether-co-maleic acid)/poly(lactic-co-glycolic acid) electrospun nanofibers for wound dressing. Fibers Polym 2017;18:2125–34.
[164] Li J, Hu Y, He T, Huang M, Zhang X, Yuan J, et al. Electrospun sandwich-structure composite membranes for wound dressing scaffolds with high antioxidant and antibacterial activity. Macromol Mater Eng 2018;303(2):1700270.
[165] Liu X, Nielsen LH, Qu H, Christensen LP, Rantanen J, Yang M. Stability of lysozyme incorporated into electrospun fibrous mats for wound healing. Eur J Pharm Biopharm 2019;136:240–9.
[166] Liu Y, Liang X, Zhang R, Lan W, Qin W. Fabrication of electrospun polylactic acid/cinnamaldehyde/β-cyclodextrin fibers as an antimicrobial wound dressing. Polymers (Basel) 2017;9:464.
[167] Jia Y, Zhang H, Yang S, Xi Z, Tang T, Yin R, et al. Electrospun PLGA membrane incorporated with andrographolide-loaded mesoporous silica nanoparticles for sustained antibacterial wound dressing. Nanomedicine 2018;13:2881–99.
[168] Choipang C, Chuysinuan P, Suwantong O, Ekabutr P, Supaphol P. Hydrogel wound dressings loaded with PLGA/ciprofloxacin hydrochloride nanoparticles for use on pressure ulcers. J Drug Deliv Sci Technol 2018;47:106–14.
[169] He P, Yan H, Zhao J, Gou M, Li X. An evaluation of the wound healing potential of tetrahydrocurcumin-loaded MPEG-PLA nanoparticles. J Biomater Appl 2019;34(3):315–25.
[170] Mousavi Nejad Z, Torabinejad B, Davachi SM, Zamanian A, Saeedi Garakani S, Najafi F, et al. Synthesis, physicochemical, rheological and *in vitro* characterization of double-crosslinked hyaluronic acid hydrogels containing dexamethasone and PLGA/dexamethasone nanoparticles as hybrid systems for specific medical applications. Int J Biol Macromol 2019;126:193–208.
[171] Xu WK, Tang JY, Yuan Z, Cai CY, Chen XB, Cui SQ, et al. Accelerated cutaneous wound healing using an injectable teicoplanin-loaded PLGA-PEG-PLGA thermogel dressing. Chin J Polym Sci 2019;37(6):548–59.
[172] Ferrández-Montero A, Lieblich M, González-Carrasco JL, Benavente R, Lorenzo V, Detsch R, et al. Development of biocompatible and fully bioabsorbable PLA/Mg films for tissue regeneration applications. Acta Biomater 2019;98:114–24.
[173] Li L, Liu X, Niu Y, Ye J, Huang S, Liu C, et al. Synthesis and wound healing of alternating block polyurethanes based on poly(lactic acid) (PLA) and poly(ethylene glycol) (PEG). J Biomed Mater Res Part B Appl Biomater 2017;105:1200–9.
[174] Lordani TVA, de Lara CE, Ferreira FBP, de Souza Terron Monich M, Mesquita da Silva C, Felicetti Lordani CR, et al. Therapeutic effects of medicinal plants on cutaneous wound healing in humans: a systematic review. Mediators Inflamm 2018;2018:7354250.
[175] Macit Ç, Tatlıpınar ME, Çağlar EŞ, Taner N, Turgut S, Sarıkaya EG. Comparison of 3 doses of aloe vera and burn drugs in market on burnt rat models. ACTA Pharm Sci 2018;56(2):93.
[176] Teplicki E, Ma Q, Castillo DE, Zarei M, Hustad AP, Chen J, et al. The effects of aloe vera on wound healing in cell proliferation, migration, and viability. Wounds Compend Clin Res Pract 2018;30(9):263–8.
[177] Haque SD, Saha SK, Salma U, Nishi MK, Rahaman MS. Antibacterial effect of aloe vera (Aloe barbadensis) leaf gel against *staphylococcus aureus, pseudomonas aeruginosa, escherichia coli and klebsiella pneumoniae*. Mymensingh Med J 2019;28:490–6.
[178] Okur ME, Polat DC, Ozbek H, Yilmaz S, Yoltas A, Arslan R. Evaluation of the antidiabetic property of capparis ovata desf. var. paleastina zoh. extracts using *in vivo* and *in vitro* approaches. Endocr Metab Immune Disord Drug Targets 2018;18(5):489–501.
[179] Okur ME, Ayla Ş, Çiçek Polat D, Günal MY, Yoltaş A, Biçeroğlu Ö. Novel insight into wound healing properties of methanol extract of Capparis ovata DESF. var. palaestina zohary fruits. J Pharm Pharmacol 2018;70(10):1401–13.
[180] Ayla Ş, Günal MY, Sayın-Şakul AA, Biçeroğlu Ö, Özdemir EM, Okur ME, et al. Effects of Prunus spinosa L. fruits on experimental wound healing. Medeni Med J 2017;32:152–8.
[181] Reza Farahpour M. Medicinal plants in wound healing. Wound Heal Curr Perspect IntechOpen 2019:33–47.