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Review article

Recent advances on antimicrobial wound dressing: A review

Déborah Simões[a], Sónia P. Miguel[a], Maximiano P. Ribeiro[a,b], Paula Coutinho[a,b], António G. Mendonça[a,c], Ilídio J. Correia[a,d,*]

[a] CICS-UBI – Centro de Investigação em Ciências da Saúde, Universidade da Beira Interior, Av. Infante D. Henrique, 6200-506 Covilhã, Portugal
[b] UDI-IPG- Unidade de Investigação para o Desenvolvimento do Interior, Instituto Politécnico da Guarda, 6300-559 Guarda, Portugal
[c] Departamento de Química, Universidade da Beira Interior, R. Marquês d'Ávila e Bolama, 6201-001 Covilhã, Portugal
[d] CIEPQPF – Departamento de Engenharia Química, Universidade de Coimbra, Rua Sílvio Lima, 3030-790 Coimbra, Portugal

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ABSTRACT

Skin and soft tissue infections (SSTIs) have high rates of morbidity and mortality associated. Despite the successful treatment of some SSTIs, those affecting the subcutaneous tissue, fascia, or muscle delay the healing process and can lead to life-threatening conditions. Therefore, more effective treatments are required to deal with such pathological situations. Recently, wound dressings loaded with antimicrobial agents emerged as viable options to reduce wound bacterial colonization and infection, in order to improve the healing process. In this review, an overview of the most prominent antibacterial agents incorporated in wound dressings along with their mode of action is provided. Furthermore, the recent advances in the therapeutic approaches used in the clinic and some future perspectives regarding antibacterial wound dressings are also discussed.

1. Introduction

Skin is the largest and outermost organ that covers the entire body. Therefore, above all, skiń s primary function is to protect underlying muscles, bones, ligaments and internal organs from external biological, chemical, mechanical and physical agents [1,2]. Furthermore, skin is also involved in sensation, temperature regulation, immunological surveillance, prevention of water loss (dehydration) and synthesis of vitamin D3 [3]. However, the structure and functions performed by this organ can be affected by cuts, burns, surgical incisions or illnesses, such as diabetes [4]. After skin structure be compromised, its structure and functions must be re-established, as soon as possible to ensure the body homeostasis. To accomplish that, the wound healing process begins almost immediately after a skin injury occurs, in order to avoid the risk of bacterial contamination [5]. Non-healing wounds usually appear after this type of contamination occur [4].

Skin and soft tissue infections (SSTIs) are the most common types of infections and they affect approximately 14 million people every year in the United States [6,7]. Depending on the etiology and severity of the microbial invasion, SSTIs can range from minor superficial to life-threatening infections [8]. In the initial stage of the infectious process, gram-positive organisms such as *Staphylococcus aureus* (*S. aureus*) and *Streptococcus pyogenes* (*S. pyogenes*) are the dominant organisms involved, while gram-negative organisms like *Escherichia coli (E. coli)* and *Pseudomonas aeruginosa (P. aeruginosa)* are only found in later stages of the process, i.e. when a chronic wound is developed [7].

In a healthy human being, infection is avoided, by activating the immune system for abolishing the invading pathogens. In this process, macrophages initiate the migration to the wound site and subsequently perform phagocytosis of the pathogens (which are destroyed in a phagolysosome or by nitric oxide production). In a later stage of infection, the immune response is performed by the activation of lymphocytes T helper which secrete interferon-γ and CD40 ligand to coordinate the immune adaptive and humoral response to kill and remove the invading

Abbreviations: A. iwoffii, *Acinetobacter iwoffii*; AMPS-Na$^+$, 2-acrylamido-2-methylpropane sulfonic acid sodium salt; *B. cereus*, *Bacillus cereus*; *B. subtilis*, *Bacillus subtilis*; BC, Bacterial cellulose; CA, Cellulose Acetate; *C. freundii*, Citrobacter freundii; CMCS, Carboxymethyl Chitosan; CMGG, Carboxymethyl Guar Gum; CS, Chitosan; DHBA, 2,3-dihydroxybenzoic acid; *E.aerogenes*, *Enterobacter aerogenes*; *E.coli*, *Escherichia coli*; EDA, Ethylenediamine; *E. faecalis*, *Enterococcusi faecalis*; GMs, Gelatin Microspheres; HNTs, Halloysite Nanotubes; HA, Hyaluronic acid; *K. pneumoniae*, *Klebsiella pneumoniae*; MMSA, Methicillin susceptible *Staphylococcus aureus*; MRSA, Methicillin resistant *Staphylococcus aureus*; nAg, nano silver; NIPAAm, N-isopropyl acrylamide; OAlg, Oxidized Alginate; *P. aeruginosa*, *Pseudomonas aeruginosa*; PCD, β-cyclodextrin polymer; PCL, Polycaprolactone; PEI, Polyethyleneimine; PEO, Polyethylene oxide; PHEA, Poly(2-hydroxyethylacrylate); PLA, Poly(lactic acid); PLGA, Polylactic-co-glycolic acid; Plur, Pluronic F127; *P. mendocina*, *Pseudomonas mendocina*; PP, Polypropylene; PRP, Platelet rich-plasma; PSSA-MA, Poly(styrene sulfonic acid-co-maleic acid); PU, Polyurethane; PVA, Polyvinyl alcohol; PVP, Polyvinylpyrrolidone; *P. vulgaris*, *Proteus vulgaris*; SA, Sodium Alginate; *S. aureus*, *Staphylococcus aureus*; *S. epidermidis*, *Staphylococcus epidermidis*; *S. haemolyticus*, *Staphylococcus haemolyticus*; *S. pyogenes*, *Streptococcus pyogenes*; *S. typhi*, *Salmonella typhi*; *S. typhimurium*, *Salmonella typhimurium*; SF, Silk Fibroin; *V. vulnificus*, *Vibrio vulnificus*; ZN, Zein

* Corresponding author at: CICS-UBI – Centro de Investigação em Ciências da Saúde, Universidade da Beira Interior, Avenida Infante D. Henrique, 6200-506 Covilhã, Portugal.
E-mail address: icorreia@ubi.pt (I.J. Correia).

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bacteria [9]. However, if the immune system is not able to remove the pathogen, infection occurs and causes the deterioration of granulation tissue, growth factors and extracellular matrix components (collagen, elastin and fibrin), thus compromising the normal wound healing process [10,11]. Therefore, it is fundamental to develop wound dressings that are capable of preventing bacteria penetration into the wound or avoid microorganisms' growth. To accomplish that, different approaches involving materials with intrinsic bactericidal activity, modified surface or incorporating antimicrobial agents, are being used to produce wound dressings displaying bactericidal activity [12].

Herein, an overview of the most prominent antibacterial agents incorporated in wound dressings along with their mode of action is provided. Furthermore, the recent advances in the therapeutic approaches used in the clinic and some future perspectives regarding antibacterial wound dressings are also discussed. Due to the higher prevalence of bacterial infections, this review does not provide any data concerning SSTIs caused by viral, fungal or parasites (protozoa, helminths, and ectoparasites).

2. Wound pathophysiology and the wound healing process

Wounds occur when a tissue is disrupted or the cellular integrity is compromised due to mechanical, physical or metabolism-related issues [13]. According to the duration and nature of the healing process, skin wounds can be classified as acute or chronic. An acute wound occurs suddenly, as a consequence of abrasions, avulsions, burns, incisions, lacerations and punctures, and have associated an healing time that is dependent on the size and number of layers of skin that have been affected [12,14]. Under normal physiological conditions, the restoration of the epidermal structure is highly efficient, however when a chronic wound occur, it is characterized by displaying a defective healing process, that do not allow skin to be repaired in an orderly and timely manner [15]. Based on etiology, the Wound Healing Society classifies chronic wounds into four categories: pressure, diabetic, venous and arterial insufficiency ulcers [16]. Bacterial colonization usually occurs in chronic wounds and it is considered as a primary cause of chronic inflammation [17].

The healing process comprises a cascade of precisely synchronized events in which are involved both resident and migratory cell populations, extracellular matrix components and soluble mediators [18]. This process includes five distinct phases: hemostasis, inflammation, migration, proliferation and remodeling [19]. In the first phase, hemostasis, a fibrin clot is formed to prevent blood loss through vasoconstriction as well as to avoid microbial contamination [20]. The inflammatory phase begins almost simultaneously with hemostasis and it involves the recruitment of neutrophils (that engulf bacteria and decontaminate the wound through proteases and antimicrobial peptides secretion and by producing reactive oxygen intermediates), monocytes/macrophages (monocytes differentiate into macrophages to remove apoptotic neutrophils and other cells and secrete cytokines and multiple growth factors), and lymphocytes that exert a specific response against microbes (B–lymphocytes produce antibodies, while T–lymphocytes secrete cytokines involved in cytolytic activity) [20–22]. The migration and proliferative phases begin with fibroblast migration to the wound site and differentiation into myofibroblasts to produce extracellular matrix components like fibronectin, hyaluronic acid, collagen and proteoglycan, that are involved in the production of extracellular matrix (ECM), new blood vessels and re-epithelization [20]. Maturation, or remodeling, is the last stage of the wound healing process and in this phase all processes that were activated after injury are ceased [19].

In order to ensure an effective wound healing process, it is fundamental to maintain a controlled set conditions at the wound site (i.e. oxygenation, temperature and high availability of vitamins, minerals, and trace elements) that sustain the complex cellular activity during this process [23]. However, chronic wounds, burns, diabetic ulcers and post-surgical wounds have extended healing times and, in some cases, even fail. For example, burn wounds usually display high levels of exudate, which provides a moist and nutrient-rich environment that promotes bacterial growth, namely *Pseudomonas* species [24]. These bacteria produce virulence factors that mediate a number of processes like adhesion, nutrient acquisition, leucocyte killing and bloodstream invasion. Furthermore, these microorganisms are also able to produce endotoxins that promote pro-inflammatory cytokines expression, such as interleukin-1 and tumor necrosis factor-α, that ultimately lead to wound inflammation [25–27]. Wounds exhibiting an extended inflammation, show a high content of metalloproteinases (MMPs) that are involved in the degradation of ECM components, thus avoiding the formation of the granulation tissue and consequently delaying the healing [11,28].

On the other hand, patients suffering from Diabetes mellitus (DM) have an impaired protective sensation and altered pain response, which makes them vulnerable to trauma and extrinsic forces. Diabetic wounds are characterized by their dry and keratinized aspect, that usually crack or suffer fissures more easily, leading to an extended healing time [29]. Therefore, patients with DM are predisposed to cutaneous infections occur, namely those caused by *S. pyogenes* and *S. aureus* [30].

3. Wound dressings displaying antimicrobial activity

In 1987, Gristina came up with the expression "race for the surface" to describe the competition that occurs between cells and bacteria for colonize a surface. Bacteria are inherently favored in this event, due to is natural ability to colonize both biological and non-biological surfaces [31]. An open wound is a favorable niche for microbial colonization [32]. Generally, the majority of infected wounds present polymicrobial and are usually contaminated by pathogens found in the surrounding environment, i.e. endogenous microbes living in the mucous membranes, and by the microflora available on the adjacent skin [33]. In the initial stages of chronic wound formation, gram-positive organisms, specifically *S. aureus*, are predominant. In the later stages, gram-negative *E. coli* and *Pseudomonas* species are observed and tend to invade deeper layers of skin causing significant tissue damage. Furthermore, *Staphylococci* and *Streptococci* species are also found in 50% of chronic wounds [7].

Nowadays, bacterial contamination of skin wounds are responsible for the high rates of morbidity and mortality [34]. To address this health issue, different labs around the world started to develop antimicrobial wound dressings to prevent wound contamination [35]. The wound dressings develop up to now have been produced with different materials (synthetic or natural) and with various physical forms (sponges, hydrogels, hydrocolloids, films, membranes). These different formulations have distinct properties that make them suitable for the treatment of a particular type of wound. For example, sponges exhibit a huge porosity, provide thermal insulation and sustain a moist environment at the wound site. Nonetheless, the sponges are mechanically weak, may provoke skin maceration and are unsuitable for the treatment of third-degree burns or wounds with dry eschar [36,37]. On the other hand, hydrogels are characterized by their capacity to store high amounts of water within their 3D polymeric network, which allow them to provide a moist environment to the wound. However, hydrogels display weak mechanical properties, thus demanding a secondary dressing [38,39]. Furthermore, hydrocolloids are easily removed by saline or sterilized water, non-adherent, present high density and are painless dressings. Nevertheless, hydrocolloids display some disadvantages that may limit their use, i.e. they may be cytotoxic, display an unpleasant odor, present a low mechanically stability and maintain an acid pH at the wound site [40,41]. Films used as wound dressings are impermeable to bacteria, allow healing monitorization and are painless. However, this type of dressing are hard to handle, adhere to the wound bed and cause exudate accumulation [14,40]. In turn, membranes (specially electrospun membranes) are known to act as physical barriers

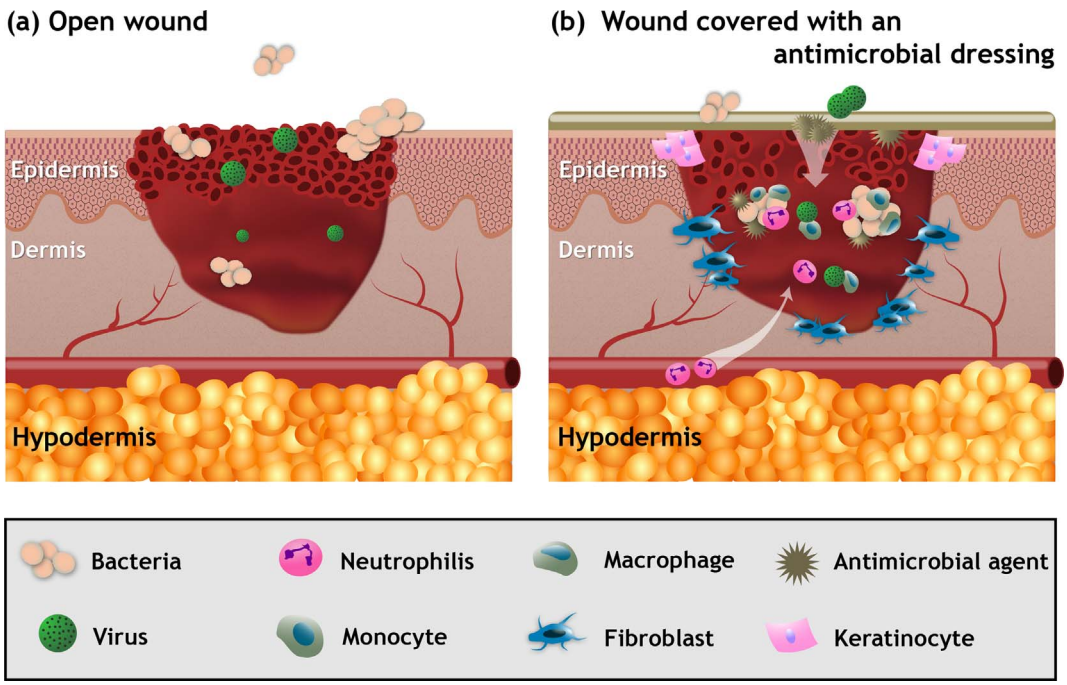

Fig. 1. Representation of the healing process in an open (a) and antimicrobial wound dressing covered (b) wound: The open wound is vulnerable to bacterial contamination, leading to an extended inflammatory phase and an increased expression of metalloproteinases that are involved in the degradation of ECM components and also inhibit the formation of new granulation tissue. When the antimicrobial dressing was used to cover the wound bed, it acts as a physical barrier to prevent pathogens entrance into the wound or to kill the invading microorganisms. In addition, the antimicrobial dressing supports the healing process by stimulating the immune system and fibroblast/keratinocyte migration.

as well as to reproduce the 3D architecture of native ECM. Moreover, their high surface-to-volume ratio and interconnected pores are crucial to assure cell proliferation, gas exchange, nutrient supply, and to control fluid loss. The main drawbacks associated with membrane use are originated by the materials and solvents used in their production [42,43].

So far, to improve dressing antimicrobial properties different agents have been incorporated within their structure. Those antimicrobial agents comprise essentially antibiotics (e.g. tetracycline, ciprofloxacin, gentamicin and sulfadiazine), nanoparticles (e.g. silver nanoparticles) and natural products (e.g. honey, essential oils and chitosan) [33]. A schematic representation of a polymeric antimicrobial dressing, designed to act as a physical barrier that protects the wound from microbial invasion and supports fibroblasts migration and differentiation, is presented in Fig. 1.

4. Antibacterial agents used to functionalize wound dressings

4.1. Antibiotics

The discovery of natural compounds that exhibit antimicrobial activity was a major breakthrough in the treatment of infectious diseases, like SSTIs [44]. Although thousands of antibiotics are known, less than 1% is currently in use in the clinic, due to toxicity related issues or lack of uptake by the host cells [45]. Up to now, only aminoglycosides [46], beta-lactams [47], glycopeptides [48–50], quinolones [51], sulphonamides [52,53] and tetracyclines [54,55] have been used to produce wound dressings displaying antimicrobial activity. The incorporated antibiotics can interfere with a function/feature of the bacteria structure or on their metabolic pathways through one of the following four mechanisms (as represented in Fig. 2):

1. Inhibition of bacterial cell wall synthesis: β-lactams and glycopeptides are among the classes of antibiotics that interfere specifically with the cell wall biosynthesis [56]. For example, β-lactams (including penicillins, carbapenems and cephalosporins) block the crosslinking of peptidoglycan units, by inhibiting the peptide bond formation reaction catalysed by Penicillin Binding Proteins (PBPs). Contrariwise, glycopeptides antibiotics (i.e. vancomycin) inhibit peptidoglycan synthesis, by binding peptidoglycan units and by blocking transglycosylase and PBPs activity [57]. Such events will impact on the shape of the bacteria and eventually lead to their lysis due to the high internal osmotic pressure [58].

2. Blockage of key metabolic pathways: The presence of folate pathway in many pathogenic microorganisms and its absence in mammals, has made this pathway an attractive target for antimicrobial drugs [59]. Some antibiotics mimic the folic acid structure (e.g. sulphonamides) and allow their competitive binding to bacterial enzymes. Such interferes with the production of DNA, RNA and proteins, leading to the disruption of bacteria proliferation [60].

3. Interference on protein synthesis: Antibiotics that interfere with protein synthesis can be divided into two subclasses: the 50S and the 30S inhibitors. According to the data available in literature, only the 30S inhibitors have been used to treat skin infections. Aminoglycosides (i.e. streptomycin) and tetracyclines are antibiotics that act as 30S ribosome-inhibitors, by obstructing the access of aminoacyl-tRNAs to the ribosome [60,61].

4. Inhibition of nucleic acids synthesis: Some antibiotics have the capacity to interfere with nucleic acid synthesis, by inhibiting the replication or transcription processes. Antibiotics that inhibit nucleic acid synthesis usually target topoisomerase II and topoisomerase IV of bacteria and RNA polymerase activity, thereby preventing the production of mRNA [56,60]. The quinolone group of synthetic antimicrobial drugs acts by converting their targets (DNA gyrase and topoisomerase IV), into enzymes that fragment the bacterial chromosome [62].

Among the different antibiotics incorporated so far in wound dressings, tetracycline [63], ciprofloxacin (CIP) [64,65], gentamicin [66] and sulfadiazine [52,67] have been the most used. García et al. developed films based on chitosan (CS), at concentration of 1% (w/v), and modified-hybrids CS-weisocyanate as functional carriers of CIP. The obtained results revealed that these films loaded with antibiotic were able to inhibit *S.aureus* and *P. aeruginosa* growth, and the films' inhibitory activity was proportional to the antibiotic content loaded

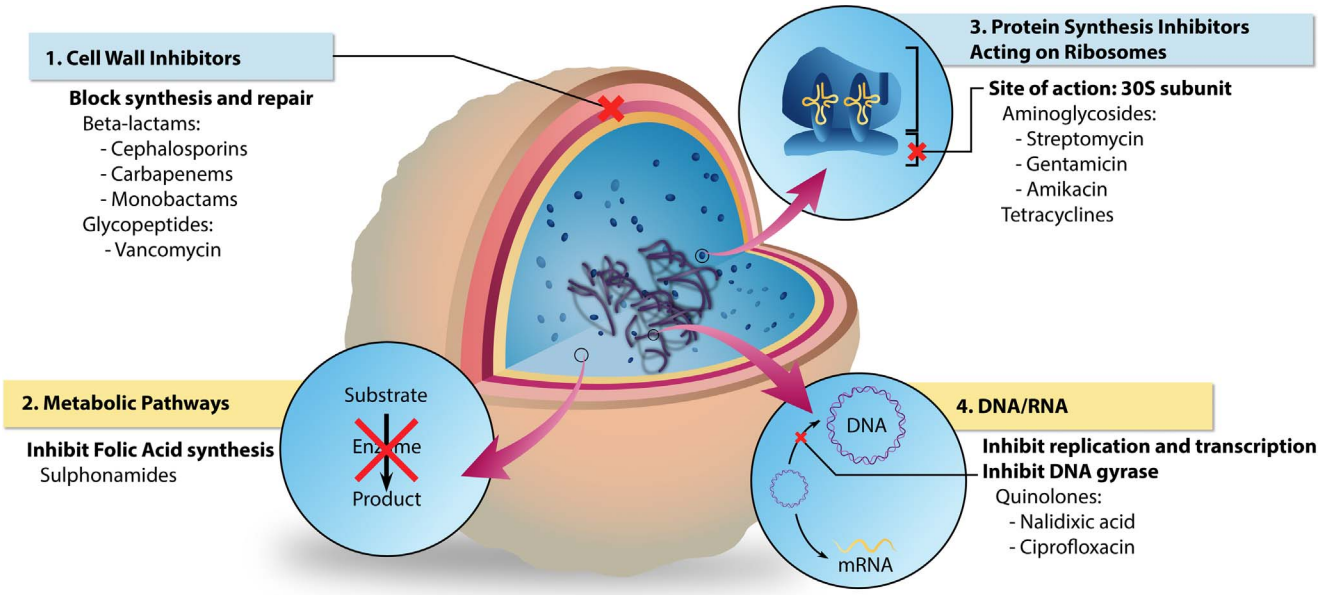

Fig. 2. Representation of the different targets of antibiotic agents within bacteria.

within their structure [68]. Moreover, Heyu Li and co-workers produced electrospun fibers with thermoresponsive polymers, (poly(N-isopropylacrylamide) (PNIPAAm) and poly (l-lactic acid-co-ε-caprolactone) (PLCL)) at different ratios with a total concentration of polymer of 10% (w/v) and loaded them with CIP to confer antibacterial activity to the fibers. Their results showed CIP-loaded fibers displayed similar inhibitory growth effect against *E. coli* and *S. aureus* [69].

On the other hand, Wei Shao and colleagues developed a tetracycline hydrochloride-loaded bacterial cellulose (BC) composite membrane. The antibacterial activity of the produced composite was investigated by both disc diffusion method and plate count method against *E. coli*, *S. aureus* and *Bacillus subtilis* (*B. subtilis*) [55]. The composite membrane presented a higher inhibitory effect against *E. coli* (45.7 mm) than for *S. aureus* (38.5 mm) and *B. subtilis* (34 mm). Regarding the plate counting method, the wound dressing reduce *E. coli* growth by 99.98%, while for *S. aureus* and *B. subtilis* the membrane was able to completely inhibit their growth [55]. Furthermore, Chen et al. fabricated an alginate-CS hydrogel dressing loaded with gelatin microspheres containing tetracycline hydrochloride to be used as a skin substitute. The bactericidal activity assays showed that the composite gel dressing was able to inhibit *E. coli* and *S. aureus* growth [63]. Recently, a semisynthetic derivative of tetracycline (glycylcyclines) was approved for the treatment of SSTIs. Tigecycline was the first member of this new class of antibiotics and presents a similar mechanism of action to that exhibited by tetracycline (30S ribosome-inhibitors), however it was designed to avoid the bacteria efflux-mediated resistance mechanisms [70,71]. Dhanalakshmi and colleagues encapsulated tigecycline within chitosan nanoparticles (CNPs), and used them for treating infected chronic wounds [72]. Subsequently, Nimal et al. incorporated tigecycline loaded chitosan nanoparticles into a chitosan-platelet-rich plasma (PRP) hydrogel. The produced system showed an improved antibacterial activity against *S. aureus* [73].

Monteiro et al. produced a gentamicin-loaded liposome immobilized at the surface of CS nanofibers mesh (NFM), to confer this electrospun membrane antibacterial activity. The obtained results showed that the produced mesh was able to inhibit *E. coli*, *P. aeruginosa* and *S. aureus* growth [66]. Fajardo et al. incorporated silver sulfadiazine (AgSD) into CS/chondroitin sulfate (CHI) film to improve their applicability as a wound dressing. The antibacterial activity of the CHI/CS/AgSD was evaluated through the determination of their capacity to inhibit *P. aeruginosa* and *S. aureus* growth. The produced film presented an inhibitory growth effect against both bacteria, especially against *P. aeruginosa* [74].

Table 1 summarizes different studies where various antibiotics have been incorporated in wound dressings to improve their bactericidal activity.

Despite of several antibiotics be available to treat skin infections, their recurrent use can trigger bacterial resistance [87]. In literature, various studies report that an improper use of antibiotics leads to the development of new resistance mechanisms by bacteria, thus causing their global dissemination [88]. More than 70% of the bacteria that are responsible for wound infections display resistance to at least one of the antibiotics used in the clinic [89]. Methicillin-resistant Staphylococcus aureus (MRSA) and vancomycin-resistant enterococci are two multi-resistant bacteria that are involved in skin infections [88]. Such type of infections are a major health issue, since vancomycin belongs to the latest generation of antibiotics and it is assumed that it is the most effective agent against *S. aureus* [89].

The number of multidrug resistant bacteria is increasing at an alarming rate, i.e. bacteria are gaining resistance to all known classes of natural and synthetic antibiotics leading to an urgent need for new therapeutic alternatives [90]. Nanomedicine tools, particularly nanoparticles, constitute a different approach for the development of new antimicrobial agents [91].

4.2. Nanoparticles as potential antimicrobial agents

Based on the data available in literature, nanoparticles (NPs) are regarded as promising alternatives to conventional antibiotics, since they display bactericidal activity against a large number of strains and are able to minimize the undesirable side effects of drugs and do not trigger microbial resistance [92,93]. Due to the intrinsic properties displayed by NPs, they have been used in different therapeutic approaches that aim to circumvent the problems associated with the acquisition of resistance to antibiotics by bacteria.

NPs alone can perform their bactericidal effect through direct contact with the bacterial cell wall, through the release of toxic metal ions or by the generation of Reactive Oxygen Species (ROS) [94]. When NPs are in contact with bacterial cells walls, the positively-charged NPs are attracted by the negatively-charged groups found in bacteria surfaces (lipopolysaccharides in gram-negative and teichoic acid/peptidoglycan in gram-positive). Then, van der Waals forces, receptor-ligand, and

Table 1
Wound dressings functionalized with antibacterial agents.

	Antibiotic	Wound dressing	Materials	Tested bacteria	Ref.
Beta-lactams	Ceftadizime	Electrospun membrane	SF/Gelatin	*P. aeruginosa*	[75]
		Film	Collagen/CMGG/EDA	*S. aureus*	[76]
				P. aeruginosa	
	Ampicillin	Electrospun membrane	PCL	*S. aureus*	[77]
				K. pneumoniae	
		Hydrogel	PVA/SA	*E. coli*	[78]
	Cefazolin	Electrospun membrane	Gelatin	*S. aureus*	[79]
Aminoglycosides	Streptomycin	Electrospun membrane	PU/CA/ZN	*E. coli*	[80]
				S. aureus	
				S. typhimurium	
				V. vulnificus	
				B. subtilis	
		Hydrogel	PVA/Cellulose	*S. aureus*	[81]
				E. coli	
	Gentamicin	Electrospun membrane	CS	*P. aeruginosa*	[66]
				S. aureus	
				E. coli	
	Neomycin	Electrospun membrane	PSSA-MA/PVA	*S. aureus*	[82]
				E. coli	
Quinolones	Ciprofloxacin	Electrospun membrane	PVP;	*E. coli*	[64,65]
			PU/Dextran	*B. subtilis*	
				S. aureus	
				S. typhimurium	
				V. vulnificus	
	Levofloxacin	Sponge	CS/PHEA	MSSA	[83]
				MRSA	
				P. aeruginosa	
	Norfloxacin	Film	CS	*S. aureus*	[84]
				B. cereus	
				E. coli	
				K. pneumoniae	
	Moxifloxacin	Electrospun membrane	PVA/SA	*P. aeruginosa*	[85]
				S. aureus	
Sulphonamides	Sulfadiazine	Film	BC/SA; CS/CHI	*E. coli*	[53,74]
				S. aureus	
		Sponge	CS	*E. coli*	[67]
				S. aureus	
				B. subtilis	
		Electrospun membrane	PCL/PVA	*S. aureus*	[52]
	Sulfanilamide	Fiber	Alginate	*E. coli*	[86]
				S. aureus	
Tetracyclines	Doxycycline	Film	Collagen/DHBA/GMs	*P. aeruginosa*	[54]
	Tetracycline hydrochloride	Membrane	BC	*E. coli*	[55]
				S. aureus	
				B. subtilis	
		Hydrogel	OAlg/CMCS/GMs	*E. coli*	[63]
				S. aureus	
Glycopeptides	Vancomycin	Hydrogel	SF/GMs	*E. coli*	[50]
				S. aureus	
		Film	Alginate/HNTs/Gelatin	*S. epidermidis*	[49]
				S. aureus	
				S. haemolyticus	
				S. pneumoniae	
				S. pyogenes	
				E. faecalis	

hydrophobic interactions are established and the cell wall permeability is altered through the formation of “pores” at bacteria surface, leading to its disruption and consequent loss of intracellular components [95]. At the same time, NPs can also cross the cell wall and affect metabolic pathways, or even target mitochondria and cause its disruption and, consequently, induce ROS production [96]. In addition, NPs can also affect proton efflux pumps resulting in a serious pH deregulation and on the variation of membrane’s surface charge [94]. Furthermore, NPs can likewise interact with DNA, lysosomes, ribosomes, and enzymes, leading to oxidative stress, electrolyte imbalance, enzyme inhibition, protein deactivation and variations in the gene expression profile [97]. Fig. 3 presents the main bacterial targets of NPs and also some examples of NPs that have been used in the treatment of skin infections.

Among the available NPs, silver nanoparticles (AgNPs) have gained considerable attention owing to their broad inhibitory activity towards nearly 650 species of microbes, and more importantly, against antibiotic resistant bacteria [98]. With the advancement of nanotechnology, the scientific community was able to enhance the antimicrobial properties of silver, and consequently decrease silver NPs minimum inhibitory concentration (MIC), as well as reduce the possible interference of AgNPs in the wound healing process [99]. Such developments trigger the use of AgNPs in the production of wound dressings and their subsequent introduction in the market [100]. Acticoat®, Aquacel Ag® and Silvasorb® are examples of AgNPs containing dressings [101].

In 2013, Jian Wu and collaborators developed a new method to produce a BC hybrid gel-membranes containing AgNPs. The antibacterial activity of AgNP-BC membranes was investigated against gram-negative (*E. coli* and *P. aeruginosa*) and gram-positive (*S. aureus*) bacteria. For comparative purposes, they also used a commercial silver-

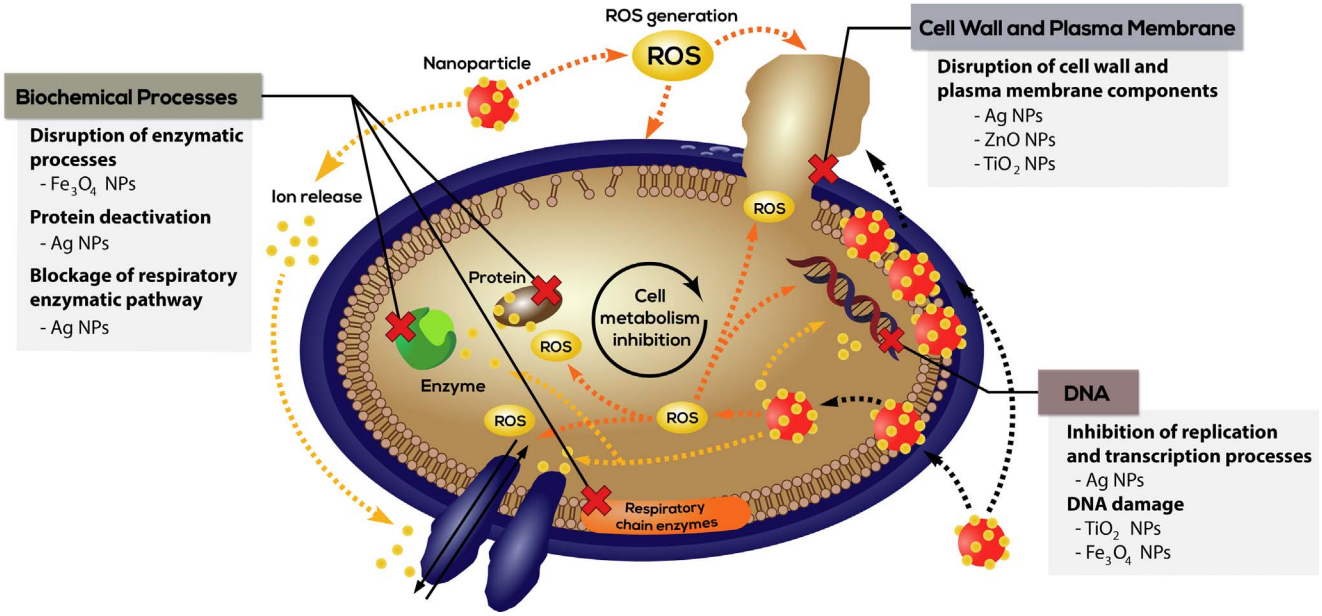

Fig. 3. Representation of NPs targets in the bacteria and some examples of NPs that have been used as antimicrobial agents.

containing dressing (Coloplast®Ag non-adhesive foam dressing). The obtained results revealed that the composite membranes loaded with AgNPs inhibited the growth of all tested bacteria. No inhibitory effect was observed for the pure BC membrane (control), thus demonstrating the crucial role of AgNPs in conferring antimicrobial properties to the produced dressings. In comparison to results obtained for a commercial dressing, no significant difference was observed, meaning that the antimicrobial dressing produced in this study has potential to be used as an effective wound dressing [102]. In another study, Augustine et al. produced a polycaprolactone (PCL) electrospun membranes loaded with AgNPs to be used as wound dressings. The fabricated membranes showed excellent antibacterial activity against both *S. aureus* and *E. coli* [103].

In recent studies, the antimicrobial properties of metallic nanocomposites were combined with natural products, in order to increased their antibacterial effect and biocompatibility [104]. Anisha and their co-workers developed an antimicrobial sponge composed by CS, Hyaluronic acid (HA) and nano silver (nAg) to treat diabetic foot ulcers. The produced sponges showed antimicrobial effect against *E. coli*, *S. aureus*, *P. aeruginosa* and *K. pneumonia*. Further, those sponges loaded with higher nAg (0.005%, 0.01% and 0.02%) concentrations were the most effective in reducing the *in vitro* growth of MRSA [105].

Other studies where AgNPs and other metal nanoparticles have been used to confer antimicrobial properties to the wound dressings are summarized in Table 2.

Despite of the bactericidal activity presented by NPs, some studies report that the same properties that make NPs so unique (small size, large surface area, chemical composition, solubility and geometry) could also be hazard to the human health, i.e. NPs due to their size can easily enter the human body and cross various biological barriers, reaching the most sensitive organs and disrupt the cell normal biochemical pathways [96,117]. Costa et al., demonstrated that AgNPs decrease the activity of mitochondrial respiratory chain complexes I, II, III, and IV from Wistar rats tissues that were analyzed (brain, skeletal muscle, heart and liver) [118]. Furthermore, Botelho et al. demonstrated that TiO_2 NPs induce tumor-like phenotypes in human gastric epithelial cells [119].

Regardless of the several studies available in literature, the cytotoxic profile of a particular NP must be characterized in deeper detail for a particular therapeutic purpose [120]. One strategy that is currently being followed to reduce the possible toxicity associated with NPs use, is based on the obtainment of these carriers from natural sources, namely plant extracts, to be incorporated in wound dressings.

Table 2
Examples of nanoparticles with bactericidal activity that have been incorporated in wound dressings.

Type of nanoparticle	Wound dressing	Materials	Tested bacteria	Ref.
Iron oxide (Fe_3O_4) nanoparticles	Electrospun membrane	CS/Gelatin	*E. coli* *S. aureus*	[106]
Titanium dioxide ($Ti0_2$) nanoparticles	Composite	CS/human ECM sheet; CS/PVP	*E. coli* *S. aureus* *B. subtilis* *P. aeruginosa*	[107,108]
	Electrospun membrane	PVA/Plur/ PEI	*E. coli* *S. aureus* *S. typhi*	[109]
Zinc oxide (ZnO) nanoparticles	Hydrogel	CS; SA/gum acacia	*E. coli* *S. aureus* *B. cereus*	[110,111]
	Composite	BC	*E. coli* *S. aureus* *P. aeruginosa* *C. freundii*	[112]
	Hydrogel	Alginate	*E. coli* *S. aureus* *MRSA*	[113]
Silver (Ag) nanoparticles	Sponge	CS/HA SF/ CMCS	*K. pneumoniae* *MRSA* *E. coli* *S. aureus* *P. aeruginosa*	[105,114]
	Hydrogel	AMPS; PVP	*S. aureus* *P. aeruginosa* *S. epidermidis* *MRSA* *E. coli* *A. iwoffii* *B. cereus* *S. pyogenes*	[115,116]

4.3. Natural products

Nowadays, an increasing number of wound dressings have been functionalized with compounds obtained from natural sources, to

Table 3
Wound dressings containing natural antibacterial agents isolated from plants.

Natural products	Wound dressing	Materials	Tested bacteria	Ref.
Henna (*Lawsonia inermis*)	Electrospun membrane	CS/PEO; gelatin/ oxidized starch	*E. coli* *S. aureus*	[123,124]
St John's-wort EO (*Hypericum perforatum*)	Film	CS	*E. coli* *S. aureus*	[125]
	Electrospun membrane	PCL	*E. coli* *S. aureus*	[126]
Curcumin	Composite	PVA	*E. coli* *S. aureus* *B. subtilis* *P. vulgaris* *E. faecalis* *S. epidermidis* *K. pneumoniae* *E. aerogenes* *P. mendocina*	[127]
	Electrospun membrane	CA/PVP	*S. aureus*	[128]
Aloe vera	Electrospun membrane	PLGA	*S. epidermidis* *S. aureus*	[129]
Thymol	Electrospun membrane	PCL/PLA	*E. coli* *S. aureus*	[130]

increase their antimicrobial activity [121,122]. Table 3 summarizes some studies where natural products displaying bactericidal activity were incorporated into wound dressings.

4.3.1. Honey

Honey has been regarded since the ancient times as a natural healing agent. Due to its antimicrobial activity and capacity to perform the topical nutrition to the wound, debriding activity, minimize inflammation and stimulate angiogenesis, granulation, wound contraction and epithelialization, honey has been incorporated into wound dressings [131,132]. Different honey-impregnated dressings are already available in the market, like MediHoney®, Activon Tulle®, Algivon® and Actilite® [132].

Honey's antimicrobial activity has been attributed to its acidity, low water content, and presence of antimicrobial substances such as hydrogen peroxide, antimicrobial peptide bee defensin-1, flavonoids, and phenolic acids [133–136]. The acidic character exhibited by honey results from the presence of gluconic acid and some authors believe that the acidic pH of honey may aid macrophages to kill bacteria and prevent microbial biofilm formation [137,138]. In turn, the low water content (< 20%) provides an unfavorable environment for microorganism survival and growth. High osmolarity inhibits microbial growth, since water molecules are chemically tied to the sugar molecules, leading to an inappropriate environment for organisms survival [139,140]. Lastly, the production of hydrogen peroxide by honey is responsible for the bacterial growth inhibition, i.e. hydrogen peroxide is able to react with the cell wall, lipids, proteins and nucleic acids available in bacteria [141,142]. In Fig. 4 are illustrated the bacterial activities exhibited by honey.

Although, honey in the presence of catalase (an enzyme that degrades hydrogen peroxide) displays a decreased antimicrobial activity [131]. To surpass this drawback, Manuka Honey (MH), which is obtained from the manuka tree (Leptospermum scoparium), unlike other honeys, contains a non-peroxide component, that is not degraded by catalase, is able to sustain its antibacterial activity in biologic fluids [131,132]. MH inhibits the growth of a broad range of microorganisms (including gram-positive strains such as MRSA and *S. pyogenes*, as well as gram-negative strains like *E. coli*, *Proteus mirabilis (P. mirabilis)*, *Enterobacter cloacae*, and *P. aeruginosa*) and avoids biofilm formation at the wound site [143]. Furthermore, Packer et al. have described that methylglyoxal (MGO), a component of MH, interferes with ribosome and its translational capacity (see further details in Fig. 4) [131].

Bulman et al. incorporated MGO as a functional antibacterial agent into polyvinyl alcohol fibers. The obtained results confirmed that the fibers containing MGO exhibited bactericidal activity against *E. coli* and *S. aureus* [144]. Moreover, Yang et al., incorporated MH in an electrospun membrane produced with silk fibroin (SF), for being used as an antimicrobial wound dressing. The SF/MH fibrous matrices presented antibacterial activity against both gram-positive (MRSA and *S. aureus*) and gram-negative (*E. coli* and *P. aeruginosa*) bacteria [145].

4.3.2. Essential oils

In addition to honey, essential oils (EOs) have been incorporated as antibacterial agents in bioactive wound dressings. Essential oils, also called volatile natural mixtures, are plant secondary metabolites that exhibit antioxidant, antiviral, anticancer, insecticidal, anti-inflammatory, anti-allergic and antimicrobial properties [146].

Different authors stated that the antimicrobial activity of EOs that are usually incorporated in wound dressings is attributed to phenolic compounds, specifically to thymol and carvacrol [131,132,143]. Kavoosi et al., reported that EOs attack the phospholipids present in the cell membranes and the lipids available on the cell wall of the bacteria, leading to an increased permeability and ultimately to cell lysis. Such results in the cytoplasm leakage, pH decrease, and loss of cellular processes, like ATP biosynthesis, DNA transcription and protein synthesis. Moreover, Altiok et al. described that EOs disturbs the function of the cytoplasmic membrane, by disrupting the active transport of nutrients through the cell membrane, and coagulation of bacteria cell contents [147]. In Fig. 5 are illustrated different mechanisms through which EOs exert their antimicrobial activity.

Amongst the different EOs components, cinnamaldehyde, geraniol, thymol analogues, menthol and carvacrol (a major ingredient of Zataria multiflora EO) are the most used for antibacterial purposes. Liakos et al., incorporated 1% and 5% of EOs (cinnamon, lemongrass and peppermint) in cellulose-based fibrous dressings and they noticed that the fibrous dressings were able to inhibit the growth of *E. coli*, even when small amounts of EOs were used [148]. In another study, Liakos et al. prepared polymeric composite films with sodium alginate (NaAlg) incorporating different EOs (chamomile blue, cinnamon, lavender, tea tree, peppermint, eucalyptus, lemongrass and lemon oils) and three different concentrations of EOs were tested (16%, 50% and 66%). They produced dressings able to inhibit *E. coli* growth [149].

4.3.3. Chitosan

Chitosan (CS) and its derivatives display a high antimicrobial activity against fungi, bacteria, algae and viruses [150]. In the literature there are at least three mechanisms proposed for explaining the antibacterial activity of CS (as depicted in Fig. 6) [151]. The most accepted mechanism proposes that CS antimicrobial activity results from the electrostatic interactions occurring between the positively-charged groups of chitosan (amine groups of glucosamines) and the negatively-charged groups available on the bacterial cell wall (surface components like peptidoglycans) [152]. This electrostatic interaction can affect the permeability of the cell wall, thus causing internal osmotic imbalances and consequently inhibit the growth of microorganisms. On the other hand, the electrostatic interactions can induce the hydrolysis of the peptidoglycans of the microorganisms' cell wall, prompting the leakage of intracellular electrolytes [151]. The second proposed mechanism involves the formation of a polymeric envelope around bacteria, leading to the inhibition of cell exchanges and nutrients absorption [152]. The last mechanism includes the chelation of trace metals and oligo-elements that are essential for bacterial growth, i.e. the amino groups of CS might interact with essential trace metals and thereby inhibit the production of toxins and microbial growth [151,152]. These specific properties triggered its use in the production of wound dressings available in the market, such as HidroKi®, Patch®, Chitopack®,

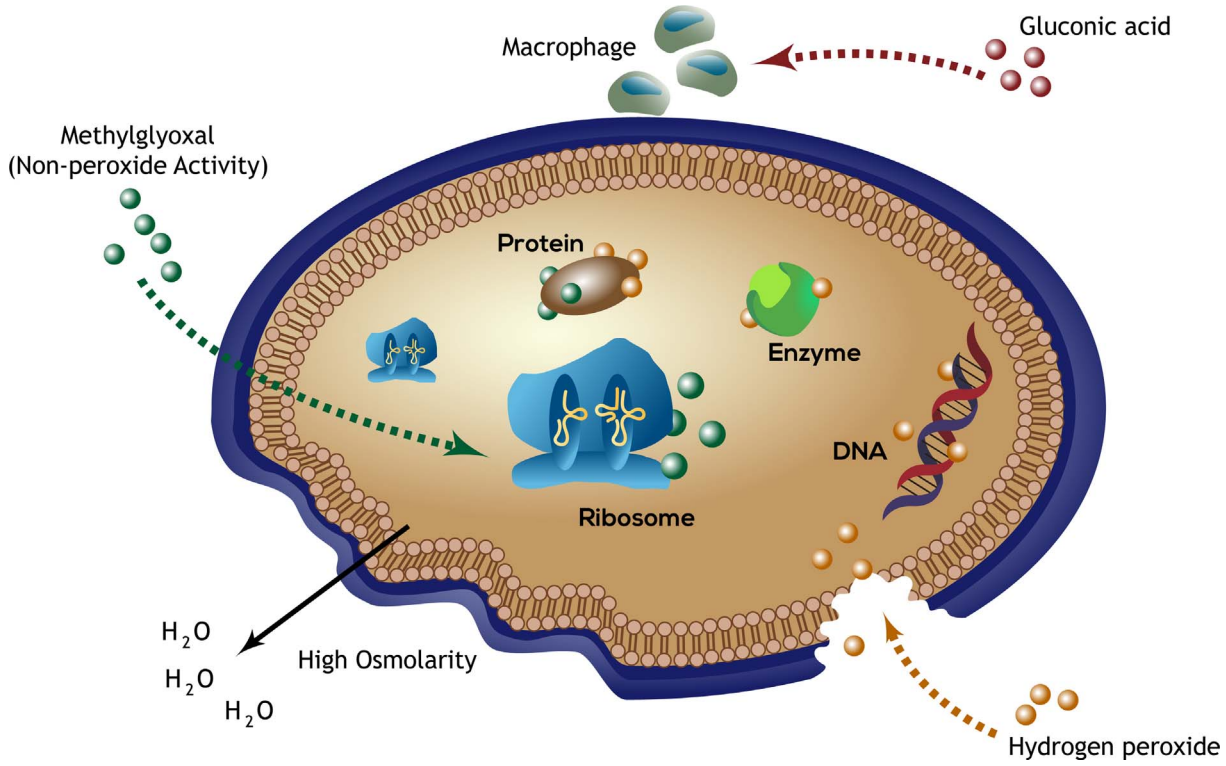

Fig. 4. Representation of the mechanisms proposed to explain the bactericidal activity exhibited by Honey and MH.

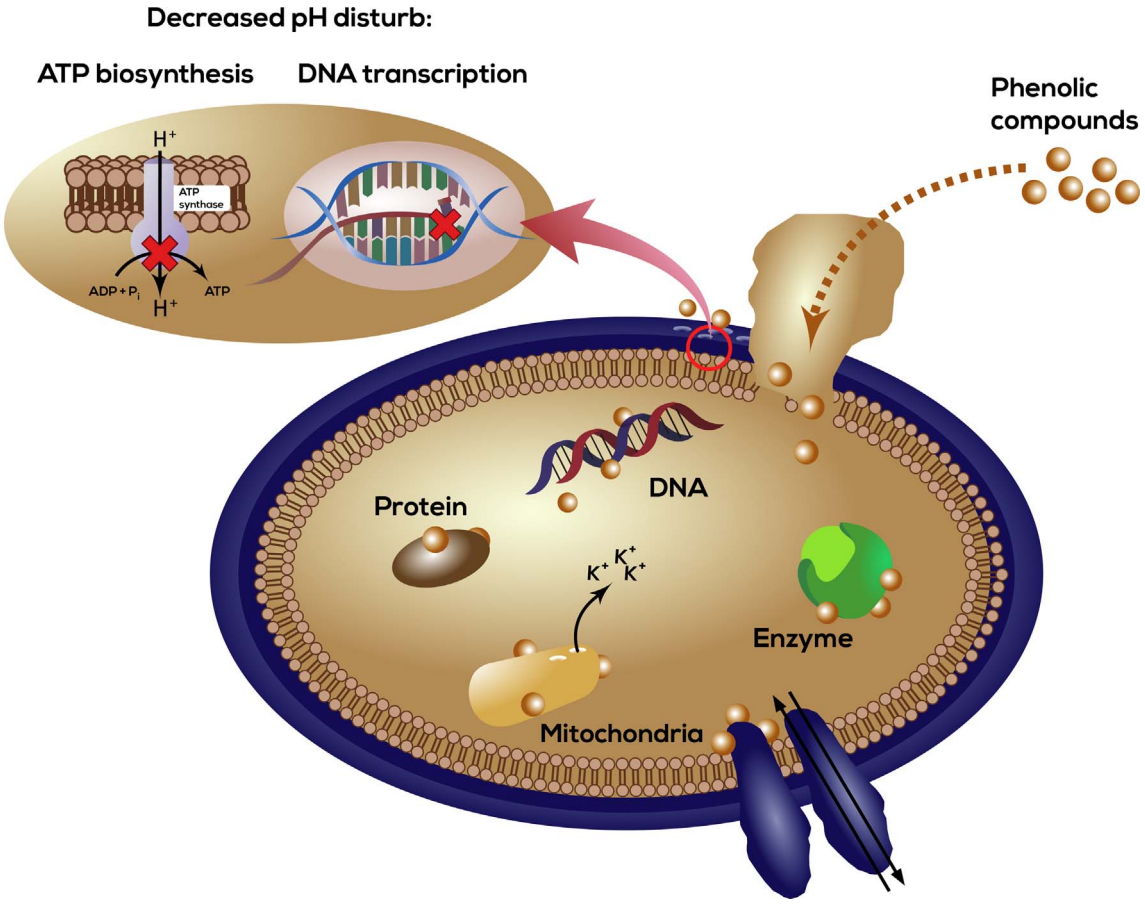

Fig. 5. Representation of phenol (active component of essential oils) targets in bacteria.

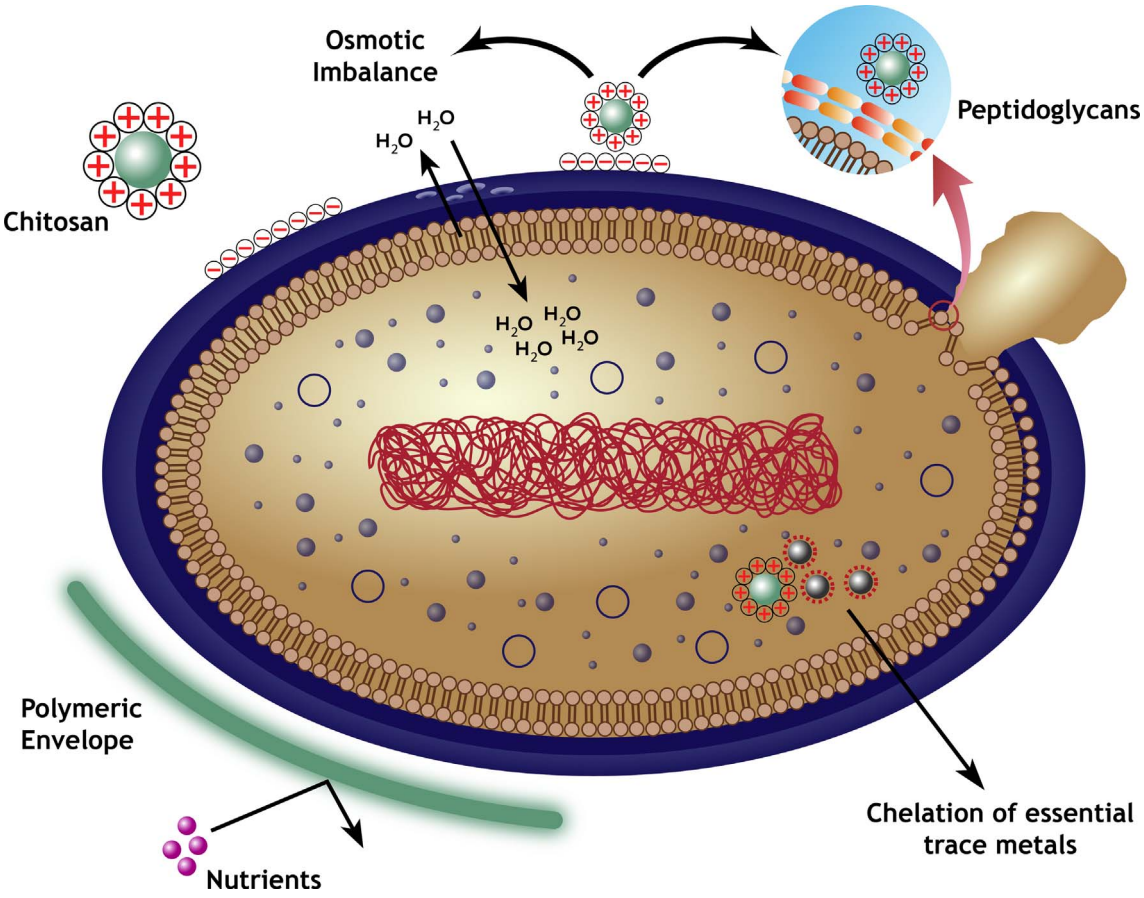

Fig. 6. Representation of the mechanisms proposed to explain the antibacterial activity of Chitosan.

Table 4
Chitosan-based wound dressings for skin regeneration applications.

Chitosan-based wound dressing	Materials	Tested bacteria	Ref.
Membrane	CS	*P. aeruginosa* *S. aureus*	[156]
	CS/BC	*E. coli* *S. aureus*	[157]
	CS/PP/NIPAAm/CG	*S. aureus*	[158]
	CS/SF	*E. coli* *S. aureus*	[159]
	CS/sericin	*E. coli* *B. subtilis*	[160]
	CS/CS-glucan	*E. coli* *K. pneumoniae* *B. subtilis* *S. aureus*	[161]
	CS/Aloe vera	*E. coli* *S. aureus*	[153]
Hydrogel	CS/Agarose	*E. coli* *S. aureus*	[162]
Sponge	CS/PCD	*S. aureus*	[163]
	CS/PVA	*E. coli*	[164]
Film	CS/PVP/ nanocellulose	*S. aureus* *P. aeruginosa*	[165]
	CS/Hyaluronan	*E. coli* *S. aureus*	[166]

Tegasorb® and KytoCel® [153].

Antunes et al. produced an electrospun membrane comprised by deacetylated/arginine modified chitosan (CS-A) to be used as a wound dressing. In this study, CS was modified with arginine to increase the number of positively charged groups available on material's surface, to enhance its electrostatic interaction with bacteria cell wall. The obtained results highlight the importance of coupling arginine residues to CS, since the modified CS exhibit a much higher antimicrobial activity [154]. Furthermore, Yuan et al. prepared a CS and polyethylene oxide (PEO) nanofibrous meshes for wound healing application. The electrospun mesh was able to significantly reduce the bacterial colonies attached to the membrane surface. In addition, those materials with a higher concentration of chitosan present a greater bactericidal effect [155]. Other studies where CS has also been used for the production of antimicrobial wound dressings are summarized in Table 4.

5. Concluding remarks and future prospects

Nowadays, nearly everyone has already suffered an open skin wound as a consequence of a cut, burn, diseases (e.g. diabetes) or surgical interventions. In some circumstances those wounds can easily be contaminated by different pathogens found in the surrounding environment, endogenous microbes living in the mucous membranes, or by the microflora available on the adjacent skin. Gram-positive bacteria, like *E. coli* and *P. aeruginosa*, and gram-negative bacteria, such as *S. aureus*, are the predominant pathogens responsible for skin contamination and subsequent infections. Wound dressings displaying antimicrobial activity started to be produced in order to surpass this health problem. Different strategies, comprising materials' surface functionalization with different groups or antimicrobial agents incorporation (antibiotics, nanoparticles and natural products), have been used to confer bactericidal activity to dressings. However, despite of developments attained so far, further improvements of these type of dressings is demanded. In a near future it is expected that the co-administration of antibacterial agents leads to an increased therapeutic outcome. Furthermore, the development of new NPs or the loading of antimicrobial agents into nanodevices may open new avenues to treat

infected wounds. In addition, dressings containing sensors and therapeutic molecules may also be produced in order to simultaneously perform the monitoring and treatment of an infected wound.

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References

[1] A.W.C. Chua, B.K. Tan, C.L. Foo, K.C. Tan, S.J. Chong, Y.C. Khoo, Skin tissue engineering advances in severe burns: review and therapeutic applications, Burns & Trauma 4 (2016) 3–17.
[2] D. Sundaramurthi, U.M. Krishnan, S. Sethuraman, Electrospun nanofibers as scaffolds for skin tissue engineering, Polym. Rev. 54 (2014) 348–376.
[3] W. Paul, C.P. Sharma, Advances in Wound Healing Materials: Science and Skin Engineering, Smithers Rapra Technology, 2015.
[4] M. Mühlstädt, C. Thomé, C. Kunte, Rapid wound healing of scalp wounds devoid of periosteum with milling of the outer table and split-thickness skin grafting, Br. J. Dermatol. 167 (2012) 343–347.
[5] F. Siedenbiedel, J.C. Tiller, Antimicrobial polymers in solution and on surfaces: overview and functional principles, Polymers 4 (2012) 46–71.
[6] J.P. Burnham, J.P. Kirby, M.H. Kollef, Diagnosis and management of skin and soft tissue infections in the intensive care unit: a review, Intensive Care Med. 42 (2016) 1899–1911.
[7] A.F. Cardona, S.E. Wilson, Skin and soft-tissue infections: a critical review and the role of telavancin in their treatment, Clin. Infect. Dis. 61 (2015) S69–S78.
[8] V. Ki, C. Rotstein, Bacterial skin and soft tissue infections in adults: a review of their epidemiology, pathogenesis, diagnosis, treatment and site of care, Can. J. Infect. Dis. Med. Microbiol. 19 (2008) 173–184.
[9] M. Andonova, V. Urumova, Immune surveillance mechanisms of the skin against the stealth infection strategy of Pseudomonas aeruginosa, Comp. Immunol., Microbiol. Infect. Dis. 36 (2013) 433–448.
[10] G. Han, R. Ceilley, Chronic wound healing: a review of current management and treatments, Adv. Ther. (2017) 1–12.
[11] A.R. Siddiqui, J.M. Bernstein, Chronic wound infection: facts and controversies, Clin. Dermatol. 28 (2010) 519–526.
[12] K. Vig, A. Chaudhari, S. Tripathi, S. Dixit, R. Sahu, S. Pillai, V.A. Dennis, S.R. Singh, Advances in skin regeneration using tissue engineering, Int. J. Mol. Sci. 18 (2017) 789.
[13] A.A. Chaudhari, K. Vig, D.R. Baganizi, R. Sahu, S. Dixit, V. Dennis, S.R. Singh, S.R. Pillai, Future prospects for scaffolding methods and biomaterials in skin tissue engineering: a review, Int. J. Mol. Sci. 17 (2016) 1974.
[14] S. Dhivya, V.V. Padma, E. Santhini, Wound dressings–a review, BioMedicine 5 (2015) 24–28.
[15] K. Järbrink, G. Ni, H. Sönnergren, A. Schmidtchen, C. Pang, R. Bajpai, J. Car, Prevalence and incidence of chronic wounds and related complications: a protocol for a systematic review, Syst. Rev. 5 (2016) 152–158.
[16] S.A. Eming, P. Martin, M. Tomic-Canic, Wound repair and regeneration: mechanisms, signaling, and translation, Sci. Translational Med. 6 (2014) 265sr266-265sr266..
[17] P.G. Bowler, Wound pathophysiology, infection and therapeutic options, Ann. Med. 34 (2002) 419–427.
[18] T. Velnar, T. Bailey, V. Smrkolj, The wound healing process: an overview of the cellular and molecular mechanisms, J. Int. Med. Res. 37 (2009) 1528–1542.
[19] P.I. Morgado, A. Aguiar-Ricardo, I.J. Correia, Asymmetric membranes as ideal wound dressings: An overview on production methods, structure, properties and performance relationship, J. Membr. Sci. 490 (2015) 139–151.
[20] F.M. Thiruvoth, D.P. Mohapatra, D. Sivakumar, R. Chittoria, V. Nandhagopal, Current concepts in the physiology of adult wound healing, Plastic Aesthet. Res. 2 (2015) 250–256.
[21] P. Agrawal, S. Soni, G. Mittal, A. Bhatnagar, Role of polymeric biomaterials as wound healing agents, Int. J. Lower Extremity Wounds 13 (2014) 180–190.
[22] L.I. Moura, A.M. Dias, E. Carvalho, H.C. de Sousa, Recent advances on the development of wound dressings for diabetic foot ulcer treatment—a review, Acta Biomaterialia 9 (2013) 7093–7114.
[23] M. Flanagan, The physiology of wound healing, J. Wound Care 9 (2000) 299–300.
[24] J. Lu, M. Yang, T. Xu, J. Yue, M. Zhan, X. Xuewen, Antibiotics for treating infected burn wounds, Cochrane Database Syst. Rev. (2016).
[25] S.A. Guo, L.A. DiPietro, Factors affecting wound healing, J. Dental Res. 89 (2010) 219–229.
[26] N.B. Menke, K.R. Ward, T.M. Witten, D.G. Bonchev, R.F. Diegelmann, Impaired wound healing, Clin. Dermatol. 25 (2007) 19–25.
[27] D. Church, S. Elsayed, O. Reid, B. Winston, R. Lindsay, Burn wound infections, Clin. Microbiol. Rev. 19 (2006) 403–434.
[28] R. Edwards, K.G. Harding, Bacteria and wound healing, Curr. Opin. Infect. Dis. 17 (2004) 91–96.
[29] K.B. Hobizal, D.K. Wukich, Diabetic foot infections: current concept review, Diabetic Foot Ankle 3 (2012) 18409.
[30] A. Gangawane, B. Bhatt, M. Sunmeet, Skin infections in diabetes: a review, J. Diabetes Metab. 7 (2016) 2.
[31] S.R. Shah, F.K. Kasper, A.G. Mikos, Perspectives on the prevention and treatment of infection for orthopedic tissue engineering applications, Chin. Sci. Bull. 58 (2013) 4342–4348.
[32] S.J. Templer, M.O. Brito, Bacterial skin and soft tissue infections, Hospital Phys. 26 (2009) 9–16.
[33] O. Sarheed, A. Ahmed, D. Shouqair, J. Boateng, Antimicrobial dressings for improving wound healing, Wound Healing-New insights into Ancient Challenges, InTech, 2016.
[34] N. Woodford, D.M. Livermore, Infections caused by Gram-positive bacteria: a review of the global challenge, J. Infect. 59 (2009) S4–S16.
[35] G.D. Winter, Formation of the scab and the rate of epithelization of superficial wounds in the skin of the young domestic pig, Nature 193 (1962) 293–294.
[36] S. Thomas, Wound and wound healing, Wound Management and Dressings, Pharmaceutical Press, London, 2004.
[37] M. Ramos-e-Silva, M.C.R. de Castro, New dressings, including tissue-engineered living skin, Clin. Dermatol. 20 (2002) 715–723.
[38] E. Caló, V.V. Khutoryanskiy, Biomedical applications of hydrogels: A review of patents and commercial products, Eur. Polym. J. 65 (2015) 252–267.
[39] E.M. Ahmed, Hydrogel: Preparation, characterization, and applications: A review, J. Adv. Res. 6 (2015) 105–121.
[40] E.A. Kamoun, E.-R.S. Kenawy, X. Chen, A review on polymeric hydrogel membranes for wound dressing applications: PVA-based hydrogel dressings, J. Adv. Res. 8 (2017) 217–233.
[41] F.S. Pott, M.J. Meier, J.G.D. Stocco, K. Crozeta, J.D. Ribas, The effectiveness of hydrocolloid dressings versus other dressings in the healing of pressure ulcers in adults and older adults: a systematic review and meta-analysis, Revista latino-americana de enfermagem 22 (2014) 511–520.
[42] S.R. Bhattarai, N. Bhattarai, H.K. Yi, P.H. Hwang, D.I. Cha, H.Y. Kim, Novel biodegradable electrospun membrane: scaffold for tissue engineering, Biomaterials 25 (2004) 2595–2602.
[43] P. Zahedi, I. Rezaeian, S.O. Ranaei-Siadat, S.H. Jafari, P. Supaphol, A review on wound dressings with an emphasis on electrospun nanofibrous polymeric bandages, Polym. Adv. Technol. 21 (2010) 77–95.
[44] M.T. Madigan, D.P. Clark, D. Stahl, J.M. Martinko, Brock Biology of Microorganisms, 13th ed., Benjamin Cummings, 2010.
[45] S. Hogg, Essential Microbiology, John Wiley & Sons, 2013.
[46] H. Pawar, J. Tetteh, J. Boateng, Preparation, optimisation and characterisation of novel wound healing film dressings loaded with streptomycin and diclofenac, Colloids Surf., B 102 (2013) 102–110.
[47] M. Sabitha, S. Rajiv, Preparation and characterization of ampicillin-incorporated electrospun polyurethane scaffolds for wound healing and infection control, Polym. Eng. Sci. 55 (2015) 541–548.
[48] T. Cerchiara, A. Abruzzo, R.A.Ñ. Palomino, B. Vitali, R. De Rose, G. Chidichimo, L. Ceseracciu, A. Athanassiou, B. Saladini, F. Dalena, Spanish Broom (Spartium junceum L.) fibers impregnated with vancomycin-loaded chitosan nanoparticles as new antibacterial wound dressing: Preparation, characterization and antibacterial activity, Eur. J. Pharm. Sci. 99 (2017) 105–112.
[49] J. Kurczewska, P. Pecyna, M. Ratajczak, M. Gajęcka, G. Schroeder, Halloysite nanotubes as carriers of vancomycin in alginate-based wound dressing, Saudi Pharm. J. (2017) 911–915.
[50] Y. Lan, W. Li, R. Guo, Y. Zhang, W. Xue, Y. Zhang, Preparation and characterisation of vancomycin-impregnated gelatin microspheres/silk fibroin scaffold, J. Biomater. Sci. Polym. Ed. 25 (2014) 75–87.
[51] N. Pásztor, E. Rédai, Z.-I. Szabó, E. Sipos, Preparation and characterization of levofloxacin-loaded nanofibers as potential wound dressings, Acta Medica Marisiensis 63 (2017) 66–69.
[52] M. Mohseni, A. Shamloo, Z. Aghababaei, M. Vossoughi, H. Moravvej, Antimicrobial wound dressing containing silver sulfadiazine with high biocompatibility: in vitro study, Artificial Organs 40 (2016) 765–773.
[53] W. Shao, H. Liu, X. Liu, S. Wang, J. Wu, R. Zhang, H. Min, M. Huang, Development of silver sulfadiazine loaded bacterial cellulose/sodium alginate composite films with enhanced antibacterial property, Carbohydr. Polym. 132 (2015) 351–358.
[54] N. Adhirajan, N. Shanmugasundaram, S. Shanmuganathan, M. Babu, Collagen-based wound dressing for doxycycline delivery: in-vivo evaluation in an infected excisional wound model in rats, J. Pharm. Pharmacol. 61 (2009) 1617–1623.
[55] W. Shao, H. Liu, S. Wang, J. Wu, M. Huang, H. Min, X. Liu, Controlled release and antibacterial activity of tetracycline hydrochloride-loaded bacterial cellulose composite membranes, Carbohydr. Polym. 145 (2016) 114–120.
[56] G.L. Patrick, An Introduction to Medicinal Chemistry, Oxford University Press, 2013.
[57] M.A. Kohanski, D.J. Dwyer, J.J. Collins, How antibiotics kill bacteria: from targets to networks, Nat. Rev. Microbiol. 8 (2010) 423–435.
[58] S.P. Denyer, N.A. Hodges, S.P. Gorman, Hugo and Russell's Pharmaceutical Microbiology, John Wiley & Sons, 2008.
[59] A. Bermingham, J.P. Derrick, The folic acid biosynthesis pathway in bacteria: evaluation of potential for antibacterial drug discovery, Bioessays 24 (2002) 637–648.

[60] E. Etebu, I. Arikekpar, Antibiotics: classification and mechanisms of action with emphasis on molecular perspectives, Int. J. Appl. Microbiol. Biotechnol. Res. (2016).
[61] W. Hong, J. Zeng, J. Xie, Antibiotic drugs targeting bacterial RNAs, Acta Pharm. Sin. B 4 (2014) 258–265.
[62] K.J. Aldred, R.J. Kerns, N. Osheroff, Mechanism of quinolone action and resistance, Biochemistry 53 (2014) 1565–1574.
[63] H. Chen, X. Xing, H. Tan, Y. Jia, T. Zhou, Y. Chen, Z. Ling, X. Hu, Covalently antibacterial alginate-chitosan hydrogel dressing integrated gelatin microspheres containing tetracycline hydrochloride for wound healing, Mater. Sci. Eng., C 70 (2017) 287–295.
[64] M. Contardi, J.A. Heredia-Guerrero, G. Perotto, P. Valentini, P.P. Pompa, R. Spanò, L. Goldoni, R. Bertorelli, A. Athanassiou, I.S. Bayer, Transparent ciprofloxacin-povidone antibiotic films and nanofiber mats as potential skin and wound care dressings, Eur. J. Pharm. Sci. 104 (2017) 133–144.
[65] A.R. Unnithan, N.A. Barakat, P.T. Pichiah, G. Gnanasekaran, R. Nirmala, Y.-S. Cha, C.-H. Jung, M. El-Newehy, H.Y. Kim, Wound-dressing materials with antibacterial activity from electrospun polyurethane–dextran nanofiber mats containing ciprofloxacin HCl, Carbohydr. Polym. 90 (2012) 1786–1793.
[66] N. Monteiro, M. Martins, A. Martins, N.A. Fonseca, J.N. Moreira, R.L. Reis, N.M. Neves, Antibacterial activity of chitosan nanofiber meshes with liposomes immobilized releasing gentamicin, Acta Biomaterialia 18 (2015) 196–205.
[67] W. Shao, J. Wu, S. Wang, M. Huang, X. Liu, R. Zhang, Construction of silver sulfadiazine loaded chitosan composite sponges as potential wound dressings, Carbohydr. Polym. 157 (2017) 1963–1970.
[68] M.C. García, A.A. Aldana, L.I. Tártara, F. Alovero, M.C. Strumia, R.H. Manzo, M. Martinelli, A.F. Jimenez-Kairuz, Bioadhesive and biocompatible films as wound dressing materials based on a novel dendronized chitosan loaded with ciprofloxacin, Carbohydr. Polym. 175 (2017) 75–86.
[69] H. Li, G.R. Williams, J. Wu, H. Wang, X. Sun, L.-M. Zhu, Poly (N-isopropylacrylamide)/poly (l-lactic acid-co-ε-caprolactone) fibers loaded with ciprofloxacin as wound dressing materials, Mater. Sci. Eng., C 79 (2017) 245–254.
[70] L.R. Peterson, A review of tigecycline—the first glycylcycline, Int. J. Antimicrob. Agents 32 (2008) S215–S222.
[71] P. Montravers, M. Bassetti, H. Dupont, C. Eckmann, W.R. Heizmann, X. Guirao, M.S. García, M.R. Capparella, D. Simoneau, K.F. Bodmann, Efficacy of tigecycline for the treatment of complicated skin and soft-tissue infections in real-life clinical practice from five European observational studies, J. Antimicrob. Chemother. 68 2013, pp. ii15–ii24.
[72] V. Dhanalakshmi, T. Nimal, M. Sabitha, R. Biswas, R. Jayakumar, Skin and muscle permeating antibacterial nanoparticles for treating Staphylococcus aureus infected wounds, J. Biomed. Mater. Res. B Appl. Biomater. 104 (2016) 797–807.
[73] T. Nimal, G. Baranwal, M. Bavya, R. Biswas, R. Jayakumar, Anti-staphylococcal activity of injectable nano tigecycline/chitosan-PRP composite hydrogel using drosophila melanogaster model for infectious wounds, ACS Appl. Mater. Interfaces 8 (2016) 22074–22083.
[74] A.R. Fajardo, L.C. Lopes, A.O. Caleare, E.A. Britta, C.V. Nakamura, A.F. Rubira, E.C. Muniz, Silver sulfadiazine loaded chitosan/chondroitin sulfate films for a potential wound dressing application, Mater. Sci. Eng., C 33 (2013) 588–595.
[75] M. Safdari, E. Shakiba, S.H. Kiaie, A. Fattahi, Preparation and characterization of Ceftazidime loaded electrospun silk fibroin/gelatin mat for wound dressing, Fibers Polym. 17 (2016) 744–750.
[76] P. Jana, T. Mitra, T.K.R. Selvaraj, A. Gnanamani, P. Kundu, Preparation of guar gum scaffold film grafted with ethylenediamine and fish scale collagen, cross-linked with ceftazidime for wound healing application, Carbohydr. Polym. 153 (2016) 573–581.
[77] H. Liu, K.K. Leonas, Y. Zhao, Antimicrobial properties and release profile of ampicillin from electrospun poly (ε-caprolactone) nanofiber yarns, J. Eng. Fiber Fabr. 5 (2010) 10–19.
[78] E.A. Kamoun, E.-R.S. Kenawy, T.M. Tamer, M.A. El-Meligy, M.S.M. Eldin, Poly (vinyl alcohol)-alginate physically crosslinked hydrogel membranes for wound dressing applications: characterization and bio-evaluation, Arabian J. Chem. 8 (2015) 38–47.
[79] G. Rath, T. Hussain, G. Chauhan, T. Garg, A.K. Goyal, Development and characterization of cefazolin loaded zinc oxide nanoparticles composite gelatin nanofiber mats for postoperative surgical wounds, Mater. Sci. Eng., C 58 (2016) 242–253.
[80] A.R. Unnithan, G. Gnanasekaran, Y. Sathishkumar, Y.S. Lee, C.S. Kim, Electrospun antibacterial polyurethane–cellulose acetate–zein composite mats for wound dressing, Carbohydr. Polym. 102 (2014) 884–892.
[81] A. Tandi, T. Kaur, P. Ebinesan, A. Thirugnanama, A. Mondal, Drug Loaded Poly (Vinyl Alcohol)-Cellulose Composite Hydrogels for Wound Dressings, 8th International Conference on Materials for Advanced Technologies of the Materials Research Society of Singapore & IUMRS & 16th International Conference in Asia (ICMAT2015 & IUMRS-ICA2015), 2015.
[82] T. Nitanan, P. Akkaramongkolporn, T. Rojanarata, T. Ngawhirunpat, P. Opanasopit, Neomycin-loaded poly (styrene sulfonic acid-co-maleic acid)(PSSA-MA)/polyvinyl alcohol (PVA) ion exchange nanofibers for wound dressing materials, Int. J. Pharm. 448 (2013) 71–78.
[83] P.I. Siafaka, A.P. Zisi, M.K. Exindari, I.D. Karantas, D.N. Bikiaris, Porous dressings of modified chitosan with poly (2-hydroxyethyl acrylate) for topical wound delivery of levofloxacin, Carbohydr. Polym. 143 (2016) 90–99.
[84] N.J.M. Sebri, K.A.M. Amin, Composite film of chitosan loaded norfloxacin with improved flexibility and antibacterial activity for wound dressing application, Orient. J. Chem. 33 (2017) 628–636.
[85] R. Fu, C. Li, C. Yu, H. Xie, S. Shi, Z. Li, Q. Wang, L. Lu, A novel electrospun membrane based on moxifloxacin hydrochloride/poly (vinyl alcohol)/sodium alginate for antibacterial wound dressings in practical application, Drug Delivery 23 (2016) 818–829.
[86] C. Ma, L. Liu, W. Hua, Y. Cai, J. Yao, Fabrication and characterization of absorbent and antibacterial alginate fibers loaded with sulfanilamide, Fibers Polym. 16 (2015) 1255–1261.
[87] B.N. Green, C.D. Johnson, J.T. Egan, M. Rosenthal, E.A. Griffith, M.W. Evans, Methicillin-resistant Staphylococcus aureus: an overview for manual therapists, J. Chiropractic Med. 11 (2012) 64–76.
[88] G.R. Rudramurthy, M.K. Swamy, U.R. Sinniah, A. Ghasemzadeh, Nanoparticles: alternatives against drug-resistant pathogenic microbes, Molecules 21 (2016) 836.
[89] S. Ranghar, P. Sirohi, P. Verma, V. Agarwal, Nanoparticle-based drug delivery systems: promising approaches against infections, Brazilian Arch. Biol. Technol. 57 (2014) 209–222.
[90] R. Singh, M. Smitha, S.P. Singh, The role of nanotechnology in combating multi-drug resistant bacteria, J. Nanosci. Nanotechnol. 14 (2014) 4745–4756.
[91] M. Berthet, Y. Gauthier, C. Lacroix, B. Verrier, C. Monge, Nanoparticle-based dressing: the future of wound treatment? Trends Biotechnol. 35 (2017) 770–784.
[92] M. Salouti, A. Ahangari, Nanoparticle based drug delivery systems for treatment of infectious diseases, Application of Nanotechnology in Drug Delivery, InTech, 2014.
[93] Y. Yang, Z. Qin, W. Zeng, T. Yang, Y. Cao, C. Mei, Y. Kuang, Toxicity assessment of nanoparticles in various systems and organs, Nanotechnol. Rev. 6 (2017) 279–289.
[94] C. Santos, A. Albuquerque, F. Sampaio, D. Keyson, Nanomaterials with antimicrobial properties: applications in health sciences, Microbial Pathogens and Strategies for Combating them: Science, Technology and Education 4 (2013) 2.
[95] V. Kandi, S. Kandi, Antimicrobial properties of nanomolecules: potential candidates as antibiotics in the era of multi-drug resistance, Epidemiol. Health 37 (2015).
[96] N. Sanvicens, M.P. Marco, Multifunctional nanoparticles–properties and prospects for their use in human medicine, Trends Biotechnol. 26 (2008) 425–433.
[97] L. Wang, C. Hu, L. Shao, The antimicrobial activity of nanoparticles: present situation and prospects for the future, Int. J. Nanomed. 12 (2017) 1227–1249.
[98] B. Zewde, A. Ambaye, J.S. III, D. Raghavan, A Review of Stabilized Silver Nanoparticles– Synthesis, Biological Properties, Characterization, and Potential Areas of Applications, JSM Nanotechnol. Nanomed. (2016).
[99] G. Nam, S. Rangasamy, B. Purushothaman, J.M. Song, The application of bactericidal silver nanoparticles in wound treatment, Nanomater. Nanotechnol. 5 (2015) 23–37.
[100] T. Mokhena, A. Luyt, Electrospun alginate nanofibres impregnated with silver nanoparticles: Preparation, morphology and antibacterial properties, Carbohydr. Polym. 165 (2017) 304–312.
[101] D.J. Leaper, Silver dressings: their role in wound management, Int. Wound J. 3 (2006) 282–294.
[102] J. Wu, Y. Zheng, W. Song, J. Luan, X. Wen, Z. Wu, X. Chen, Q. Wang, S. Guo, In situ synthesis of silver-nanoparticles/bacterial cellulose composites for slow-released antimicrobial wound dressing, Carbohydr. Polym. 102 (2014) 762–771.
[103] R. Augustine, N. Kalarikkal, S. Thomas, Electrospun PCL membranes incorporated with biosynthesized silver nanoparticles as antibacterial wound dressings, Appl. Nanosci. 6 (2016) 337–344.
[104] A. Mohandas, S. Deepthi, R. Biswas, R. Jayakumar, Chitosan based metallic nanocomposite scaffolds as antimicrobial wound dressings, Bioact. Mater. (2017).
[105] B. Anisha, R. Biswas, K. Chennazhi, R. Jayakumar, Chitosan–hyaluronic acid/nano silver composite sponges for drug resistant bacteria infected diabetic wounds, Int. J. Biol. Macromol. 62 (2013) 310–320.
[106] N. Cai, C. Li, C. Han, X. Luo, L. Shen, Y. Xue, F. Yu, Tailoring mechanical and antibacterial properties of chitosan/gelatin nanofiber membranes with Fe 3 O 4 nanoparticles for potential wound dressing application, Appl. Surf. Sci. 369 (2016) 492–500.
[107] D. Archana, B.K. Singh, J. Dutta, P. Dutta, In vivo evaluation of chitosan–PVP–titanium dioxide nanocomposite as wound dressing material, Carbohydr. Polym. 95 (2013) 530–539.
[108] C.H. Woo, Y.C. Choi, J.S. Choi, H.Y. Lee, Y.W. Cho, A bilayer composite composed of TiO2-incorporated electrospun chitosan membrane and human extracellular matrix sheet as a wound dressing, J. Biomater. Sci. Polym. Ed. 26 (2015) 841–854.
[109] M. El-Aassar, N.M. El-Deeb, H.S. Hassan, X. Mo, Electrospun polyvinyl alcohol/pluronic F127 blended nanofibers containing titanium dioxide for antibacterial wound dressing, Appl. Biochem. Biotechnol. 178 (2016) 1488–1502.
[110] R. Raguvaran, B.K. Manuja, M. Chopra, R. Thakur, T. Anand, A. Kalia, A. Manuja, Sodium alginate and gum acacia hydrogels of ZnO nanoparticles show wound healing effect on fibroblast cells, Int. J. Biol. Macromol. 96 (2017) 185–191.
[111] P. Sudheesh Kumar, V.-K. Lakshmanan, T. Anilkumar, C. Ramya, P. Reshmi, A. Unnikrishnan, S.V. Nair, R. Jayakumar, Flexible and microporous chitosan hydrogel/nano ZnO composite bandages for wound dressing: in vitro and in vivo evaluation, ACS Appl. Mater. Interfaces 4 (2012) 2618–2629.
[112] A. Khalid, R. Khan, M. Ul-Islam, T. Khan, F. Wahid, Bacterial cellulose-zinc oxide nanocomposites as a novel dressing system for burn wounds, Carbohydr. Polym. 164 (2017) 214–221.
[113] A. Mohandas, P. Sudheesh Kumar, B. Raja, V.-K. Lakshmanan, R. Jayakumar, Exploration of alginate hydrogel/nano zinc oxide composite bandages for infected wounds, Int. J. Nanomed. 10 (2015) 53.
[114] Z. Pei, Q. Sun, X. Sun, Y. Wang, P. Zhao, Preparation and characterization of silver nanoparticles on silk fibroin/carboxymethylchitosan composite sponge as antibacterial wound dressing, Bio-med. Mater. Eng. 26 (2015) S111–S118.
[115] B. Boonkaew, P.M. Barber, S. Rengpipat, P. Supaphol, M. Kempf, J. He, V.T. John, L. Cuttle, Development and characterization of a novel, antimicrobial, sterile

hydrogel dressing for burn wounds: single-step production with gamma irradiation creates silver nanoparticles and radical polymerization, J. Pharm. Sci. 103 (2014) 3244–3253.
[116] T. Khampieng, P. Brikshavana, P. Supaphol, Silver nanoparticle-embedded poly (vinyl pyrrolidone) hydrogel dressing: gamma-ray synthesis and biological evaluation, J. Biomater. Sci. Polym. Ed. 25 (2014) 826–842.
[117] H. Bahadar, F. Maqbool, K. Niaz, M. Abdollahi, Toxicity of nanoparticles and an overview of current experimental models, Iranian Biomed. J. 20 (2016) 1–11.
[118] C.S. Costa, J.V.V. Ronconi, J.F. Daufenbach, C.L. Gonçalves, G.T. Rezin, E.L. Streck, M.M. da Silva Paula, In vitro effects of silver nanoparticles on the mitochondrial respiratory chain, Mol. Cell. Biochem. 342 (2010) 51–56.
[119] M.C. Botelho, C. Costa, S. Silva, S. Costa, A. Dhawan, P.A. Oliveira, J.P. Teixeira, Effects of titanium dioxide nanoparticles in human gastric epithelial cells in vitro, Biomed. Pharmacother. 68 (2014) 59–64.
[120] C.S. Yah, G.S. Simate, Nanoparticles as potential new generation broad spectrum antimicrobial agents, DARU J. Pharm. Sci. 23 (2015) 43–57.
[121] M.M. Essa, A. Manickavasagan, E. Sukumar, Natural products and their active compounds on disease prevention, Nova Biomedical, 2012.
[122] M. Saleem, M. Nazir, M.S. Ali, H. Hussain, Y.S. Lee, N. Riaz, A. Jabbar, Antimicrobial natural products: an update on future antibiotic drug candidates, Nat. Prod. Rep. 27 (2010) 238–254.
[123] Z. Hadisi, J. Nourmohammadi, S.M. Nassiri, The antibacterial and anti-inflammatory investigation of Lawsonia Inermis-gelatin-starch nano-fibrous dressing in burn wound, Int. J. Biol. Macromol. (2017) in press.
[124] I. Yousefi, M. Pakravan, H. Rahimi, A. Bahador, Z. Farshadzadeh, I. Haririan, An investigation of electrospun Henna leaves extract-loaded chitosan based nanofibrous mats for skin tissue engineering, Mater. Sci. Eng., C 75 (2017) 433–444.
[125] S. Güneş, F. Tıhmınlıoğlu, Hypericum perforatum incorporated chitosan films as potential bioactive wound dressing material, Int. J. Biol. Macromol. 102 (2017) 933–943.
[126] F. Pourhojat, M. Sohrabi, S. Shariati, H. Mahdavi, L. Asadpour, Evaluation of poly ε-caprolactone electrospun nanofibers loaded with Hypericum perforatum extract as a wound dressing, Res. Chem. Intermed. 43 (2017) 297–320.
[127] G.D. Venkatasubbu, T. Anusuya, Investigation on Curcumin nanocomposite for wound dressing, Int. J. Biol. Macromol. 98 (2017) 366–378.
[128] P.B. Tsekova, M.G. Spasova, N.E. Manolova, N.D. Markova, I.B. Rashkov, Electrospun curcumin-loaded cellulose acetate/polyvinylpyrrolidone fibrous materials with complex architecture and antibacterial activity, Mater. Sci. Eng., C 73 (2017) 206–214.
[129] I. Garcia-Orue, G. Gainza, F.B. Gutierrez, J.J. Aguirre, C. Evora, J.L. Pedraz, R.M. Hernandez, A. Delgado, M. Igartua, Novel nanofibrous dressings containing rhEGF and Aloe vera for wound healing applications, Int. J. Pharm. 523 (2017) 556–566.
[130] Z. Karami, I. Rezaeian, P. Zahedi, M. Abdollahi, Preparation and performance evaluations of electrospun poly (ε-caprolactone), poly (lactic acid), and their hybrid (50/50) nanofibrous mats containing thymol as an herbal drug for effective wound healing, J. Appl. Polym. Sci. 129 (2013) 756–766.
[131] J.M. Packer, J. Irish, B.R. Herbert, C. Hill, M. Padula, S.E. Blair, D.A. Carter, E.J. Harry, Specific non-peroxide antibacterial effect of manuka honey on the Staphylococcus aureus proteome, Int. J. Antimicrob. Agents 40 (2012) 43–50.
[132] A.M. Scagnelli, Therapeutic review: Manuka honey, J. Exotic Pet Med. 25 (2016) 168–171.
[133] G. Bodeker, T. Ryan, C.-K. Ong, Traditional approaches to wound healing, Clin. Dermatol. 17 (1999) 93–98.
[134] S.C. Davis, R. Perez, Cosmeceuticals and natural products: wound healing, Clin. Dermatol. 27 (2009) 502–506.
[135] P.H. Kwakman, A.A. te Velde, L. de Boer, D. Speijer, C.M. Vandenbroucke-Grauls, S.A. Zaat, How honey kills bacteria, FASEB J. 24 (2010) 2576–2582.
[136] T. Sato, G. Miyata, The nutraceutical benefit, part III: honey, Nutrition 16 (2000) 468–469.
[137] K.F. Cutting, Honey and contemporary wound care: an overview, Ostomy Wound Manage. 53 (2007) 49–54.
[138] G.B. Ryan, G. Majno, Acute inflammation. A review, Am. J. Pathol. 86 (1977) 183.
[139] P.C. Molan, The role of honey in the management of wounds, J. Wound Care (1999).
[140] P.C. Molan, The evidence supporting the use of honey as a wound dressing, Int. J. Lower Extremity Wounds 5 (2006) 40–54.
[141] P.C. Molan, The antibacterial activity of honey: 1. The nature of the antibacterial activity, Bee World 73 (1992) 5–28.
[142] A. Simon, K. Traynor, K. Santos, G. Blaser, U. Bode, P. Molan, Medical honey for wound care—still the 'latest resort'? Evidence-based Complementary Altern. Med. 6 (2009) 165–173.
[143] S.E. Bulman, G. Tronci, P. Goswami, C. Carr, S.J. Russell, Antibacterial properties of nonwoven wound dressings coated with Manuka honey or methylglyoxal, Materials 10 (2017) 954–968.
[144] S.E. Bulman, P. Goswami, G. Tronci, S.J. Russell, C. Carr, Investigation into the potential use of poly (vinyl alcohol)/methylglyoxal fibres as antibacterial wound dressing components, J. Biomater. Appl. 29 (2015) 1193–1200.
[145] X. Yang, L. Fan, L. Ma, Y. Wang, S. Lin, F. Yu, X. Pan, G. Luo, D. Zhang, H. Wang, Green electrospun Manuka honey/silk fibroin fibrous matrices as potential wound dressing, Mater. Des. 119 (2017) 76–84.
[146] Y.X. Seow, C.R. Yeo, H.L. Chung, H.-G. Yuk, Plant essential oils as active antimicrobial agents, Crit. Rev. Food Sci. Nutr. 54 (2014) 625–644.
[147] D. Altiok, E. Altiok, F. Tihminlioglu, Physical, antibacterial and antioxidant properties of chitosan films incorporated with thyme oil for potential wound healing applications, J. Mater. Sci. - Mater. Med. 21 (2010) 2227–2236.
[148] I. Liakos, L. Rizzello, H. Hajiali, V. Brunetti, R. Carzino, P. Pompa, A. Athanassiou, E. Mele, Fibrous wound dressings encapsulating essential oils as natural antimicrobial agents, J. Mater. Chem. B 3 (2015) 1583–1589.
[149] I. Liakos, L. Rizzello, D.J. Scurr, P.P. Pompa, I.S. Bayer, A. Athanassiou, All-natural composite wound dressing films of essential oils encapsulated in sodium alginate with antimicrobial properties, Int. J. Pharm. 463 (2014) 137–145.
[150] R.C. Goy, S.T. Morais, O.B. Assis, Evaluation of the antimicrobial activity of chitosan and its quaternized derivative on E. coli and S. aureus growth, Revista Brasileira de Farmacognosia 26 (2016) 122–127.
[151] R.C. Goy, D.D. Britto, O.B. Assis, A review of the antimicrobial activity of chitosan, Polímeros 19 (2009) 241–247.
[152] M. Arkoun, F. Daigle, M.-C. Heuzey, A. Ajji, Mechanism of action of electrospun chitosan-based nanofibers against meat spoilage and pathogenic bacteria, Molecules 22 (2017) 585–602.
[153] S.P. Miguel, M.P. Ribeiro, P. Coutinho, I.J. Correia, Electrospun polycaprolactone/aloe vera_chitosan nanofibrous asymmetric membranes aimed for wound healing applications, Polymers 9 (2017) 183–207.
[154] B. Antunes, A. Moreira, V. Gaspar, I. Correia, Chitosan/arginine–chitosan polymer blends for assembly of nanofibrous membranes for wound regeneration, Carbohydr. Polym. 130 (2015) 104–112.
[155] T.T. Yuan, P.M. Jenkins, A.M. DiGeorge Foushee, A.R. Jockheck-Clark, J.M. Stahl, Electrospun chitosan/polyethylene oxide nanofibrous scaffolds with potential antibacterial wound dressing applications, J. Nanomater. 2016 (2016) 25–35.
[156] F.-L. Mi, S.-S. Shyu, Y.-B. Wu, S.-T. Lee, J.-Y. Shyong, R.-N. Huang, Fabrication and characterization of a sponge-like asymmetric chitosan membrane as a wound dressing, Biomaterials 22 (2001) 165–173.
[157] W.-C. Lin, C.-C. Lien, H.-J. Yeh, C.-M. Yu, S.-H. Hsu, Bacterial cellulose and bacterial cellulose–chitosan membranes for wound dressing applications, Carbohydr. Polym. 94 (2013) 603–611.
[158] C.C. Wang, C.H. Su, C.C. Chen, Water absorbing and antibacterial properties of N-isopropyl acrylamide grafted and collagen/chitosan immobilized polypropylene nonwoven fabric and its application on wound healing enhancement, J. Biomed. Mater. Res. Part A 84 (2008) 1006–1017.
[159] Z.-X. Cai, X.-M. Mo, K.-H. Zhang, L.-P. Fan, A.-L. Yin, C.-L. He, H.-S. Wang, Fabrication of chitosan/silk fibroin composite nanofibers for wound-dressing applications, Int. J. Mol. Sci. 11 (2010) 3529–3539.
[160] R. Zhao, X. Li, B. Sun, Y. Zhang, D. Zhang, Z. Tang, X. Chen, C. Wang, Electrospun chitosan/sericin composite nanofibers with antibacterial property as potential wound dressings, Int. J. Biol. Macromol. 68 (2014) 92–97.
[161] A. Abdel-Mohsen, J. Jancar, D. Massoud, Z. Fohlerova, H. Elhadidy, Z. Spotz, A. Hebeish, Novel chitin/chitosan-glucan wound dressing: Isolation, characterization, antibacterial activity and wound healing properties, Int. J. Pharm. 510 (2016) 86–99.
[162] S.P. Miguel, M.P. Ribeiro, H. Brancal, P. Coutinho, I.J. Correia, Thermoresponsive chitosan–agarose hydrogel for skin regeneration, Carbohydr. Polym. 111 (2014) 366–373.
[163] C. Flores, M. Lopez, N. Tabary, C. Neut, F. Chai, D. Betbeder, C. Herkt, F. Cazaux, V. Gaucher, B. Martel, Preparation and characterization of novel chitosan and β-cyclodextrin polymer sponges for wound dressing applications, Carbohydr. Polym. (2017) 535–546.
[164] C. Chen, L. Liu, T. Huang, Q. Wang, Y.e. Fang, Bubble template fabrication of chitosan/poly (vinyl alcohol) sponges for wound dressing applications, Int. J. Biol. Macromol. 62 (2013) 188–193.
[165] R. Poonguzhali, S.K. Basha, V.S. Kumari, Synthesis and characterization of chitosan-PVP-nanocellulose composites for in-vitro wound dressing application, Int. J. Biol. Macromol. 105 (2017) 111–120.
[166] R.M. Abdel-Rahman, A. Abdel-Mohsen, R. Hrdina, L. Burgert, Z. Fohlerova, D. Pavliňák, O. Sayed, J. Jancar, Wound dressing based on chitosan/hyaluronan/nonwoven fabrics: Preparation, characterization and medical applications, Int. J. Biol. Macromol. 89 (2016) 725–736.