# Advanced Therapeutic Dressings for Effective Wound Healing—A Review

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**ABSTRACT:** Advanced therapeutic dressings that take active part in wound healing to achieve rapid and complete healing of chronic wounds is of current research interest. There is a desire for novel strategies to achieve expeditious wound healing because of the enormous financial burden worldwide. This paper reviews the current state of wound healing and wound management products, with emphasis on the demand for more advanced forms of wound therapy and some of the current challenges and driving forces behind this demand. The paper reviews information mainly from peer-reviewed literature and other publicly available sources such as the US FDA. A major focus is the treatment of chronic wounds including amputations, diabetic and leg ulcers, pressure sores, and surgical and traumatic wounds (e.g., accidents and burns) where patient immunity is low and the risk of infections and complications are high. The main dressings include medicated moist dressings, tissue-engineered substitutes, biomaterials-based biological dressings, biological and naturally derived dressings, medicated sutures, and various combinations of the above classes. Finally, the review briefly discusses possible prospects of advanced wound healing including some of the emerging physical approaches such as hyperbaric oxygen, negative pressure wound therapy and laser wound healing, in routine clinical care.  J Pharm Sci 104:3653–3680, 2015

**Keywords:** natural products; wound healing; polymeric biomaterials; macromolecular drug delivery; tissue engineering

## INTRODUCTION

### Overview

Wound healing is a global medical concern with several challenges including the increasing incidence of obesity and type II diabetes, an ageing population (especially in developed countries with low birth rates) and the requirement for more effective but also cost-effective dressings.[1] Wound healing is a complex process involving several inter-related biological and molecular activities for achieving tissue regeneration. The main physiological events include coagulation, inflammation, and removal of damaged matrix components, followed by cellular proliferation and migration, angiogenesis, matrix synthesis and deposition, re-epithelization, and remodeling.[2] These are generally classified into five major phases, known as hemostasis, inflammation, proliferation, migration, and remodeling/maturation.[1] Wound healing and the different phases involved have been extensively discussed in several reviews and textbooks and the reader is referred to these for detailed exposition on the molecular and physiological basis of the different stages of wound healing.[1–9]

### Wounds

A wound can be defined as an injury or disruption to anatomical structure and function resulting from simple or severe break in structure of an organ such as the skin and can extend to other tissues and structures such as subcutaneous tissue, muscles, tendons, nerves, vessels, and even to the bone.[1,9,10] Of all the body tissues, the skin is definitely the most exposed to damage and easily prone to injury, abrasions, and burns because of trauma or surgery. The rapid restoration of homeostatic physiological conditions is a prerequisite for complete lesion repair, because a slow and incorrect repair can cause serious damages including the loss of skin, hair and glands, onset of infection, occurrence of skin diseases, injuries to the circulatory system, and, in severe cases, death of the tissue.

On the basis of the nature of the repair process, wounds can be classified as acute or chronic. Acute wounds are usually tissue injuries that heal completely, with minimal scarring and within the expected time frame, usually 8–12 weeks.[11] The primary causes of acute wounds include mechanical injuries because of external factors such as abrasions and tears, which are caused by frictional contact between the skin and hard surfaces. Mechanical injuries also include penetrating wounds caused by knives and gunshots and surgical wounds caused by incisions, for example, to remove tumors. Another category of acute wounds includes burns and chemical injuries, which arise from a variety of sources such as radiation, electricity, corrosive chemicals, and thermal sources. Chronic wounds, on the contrary, arise from tissue injuries that heal slowly (normally do not heal within 12 weeks) and often reoccur.[5] Chronic wounds are often heavily contaminated and usually involve significant tissue loss that can affect vital structures such as bones, joints, and nerves. Such wounds fail to heal because of repeated trauma to the injured area or underlying physiological conditions such as diabetes, persistent infections, poor primary treatment, and other patient-related factors.[12] These result in a disruption of the orderly sequence of events during the wound healing process.[5,13,14] Furthermore, impaired wound healing can lead to an excessive production of exudates that can cause maceration of healthy skin tissue around the wound.[15]

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**Table 1.** Local and Systemic Factors That Slow Down Wound Healing[7]

| Local Factors | Systemic Factors |
|---|---|
| Inadequate blood supply | Shock |
| Wound dehiscence | Chronic renal and hepatic failure |
| Infection | Advancing physiological age |
| Excess local mobility, such as over a joint | Obesity |
| Poor surgical apposition or technique | Smoking |
| Increased skin tension | Chemotherapy and radiotherapy |
| Topical medicines | Diabetes mellitus |
| Poor venous drainage | Systemic malignancy |
| Presence of foreign body or foreign body reactions | Immunosuppressants, anticoagulants, cortico steroids |
| Hematoma | Vitamin and trace elements deficiency |

Wounds are also characterized based on the number of skin layers and area of skin affected.[16] Injury that affects the epidermal skin surface alone is referred to as a superficial wound, whereas injury involving both the epidermis and the deeper dermal layers, including blood vessels, sweat glands, and hair follicles is referred to as partial thickness wound. Full thickness wounds occur when the underlying subcutaneous fat or deeper tissues are damaged in addition to the epidermis and dermal layers. Ferreira et al.[17] have described both acute and chronic wounds that are difficult to heal as "complex wounds" with unique characteristics that can be summarized as extensive loss of the integument that comprises skin, hair, and associated glands; infection (e.g., Fournier's gangrene) that may result in tissue loss; tissue death or signs of circulation impairment and the presence of underlying pathology.

Nawaz and Bentley,[7] have described some of the factors that contribute toward retardation in wound healing (chronic wounds) that are summarized in Table 1. Common chronic skin and soft tissue wounds can be divided into three major groups because of similarities in their pathogenesis. These are leg ulcers (of venous, ischemic, or of traumatic origin), diabetic foot ulcers, and pressure ulcers.[18] It also includes other hard-to-heal acute wounds such as wounds caused by cancer, pyoderma gangrenosum, immunologic and hematologic wounds,[19] amputations, abdominal wounds, burns, and skin grafts.[20] In recent years, other more serious forms of chronic wounds such as buruli ulcer, caused by bacterial infection that involves significant skin tissue loss, have been reported.[21,22]

Venous leg ulcers are triggered by malfunction of venous valves causing venous hypertension in the crural veins (veins supplying the leg), which increases the pressure in capillaries and results in edema. Venous pressure exceeding 45 mmHg certainly leads to development of a venous leg ulcer. Diabetic foot ulcer is triggered by monotonous load on the neuropathic and often ischemic foot, whereas pressure ulcers are caused by sustained or repetitive load on often vulnerable areas such as the sciatic (spinal nerve roots), tuberculum, sacral area, heels, and shoulders in the immobilized patient.[23] Patients with chronic ulcers usually present with underlying complicated factors caused by immunological defects, dysfunction in diabetic fibroblasts, and the effect of local infection or critical colonization and disruptive effects of bacteria. The resultant effect is increased cytokine cascades that prolong the inflammatory phase by continuous influx of polymorphonuclear neutrophils that release cytotoxic enzymes, free oxygen radicals, and inflammatory mediators. These factors are responsible for cellular dysfunction and damage to the host tissue,[24] which cause delays or stop completely, the wound healing process.[25] The physiological basis of chronic wound evolution is complex. Continuous migration of neutrophils into the wound area causes raised levels of the destructive proteins called matrix metallo-proteinases (MMPs)[26–28] including MMP-8 and neutrophil-derived elastase. This is in contrast to normal healing wounds in which excess levels of MMPs are inhibited through the non-specific proteinase inhibitor, α2-macroglobulin, and the more specific tissue inhibitors of MMPs (TIMMP).[29] In chronic wounds, the ratio of the harmful MMP to the protective TIMMP is raised, resulting in the degradation of extracellular matrix (ECM),[30–32] changes in the cytokine profile, and reduced levels of proliferative factors required for effective healing.[33,34] Table 2 summarizes the different types of chronic wounds commonly encountered in clinical management, whereas Figure 1 shows photographic representation of the four most common chronic wounds reported.

### The Need for Advanced Dressings

Wound dressings are traditionally used to protect the wound from contamination,[36] but they can be exploited as platforms to deliver bioactive molecules to wound sites. The use of topical bioactive agents in the form of solutions, creams, and ointments for drug delivery to the wound is not very effective as they rapidly absorb fluid and in the process lose their rheological characteristics and become mobile.[1] For this reason, the use of solid wound dressings is preferred in the case of exudative wounds as they provide better exudate management and prolonged residence at the wound site. Unlike traditional dressings such as gauze and cotton wool that take no active part in the wound healing process, advanced dressings are designed to have biological activity either on its own or the release of bioactive constituents (drugs) incorporated within the dressing.[1] The incorporated drugs can play an active role in the wound healing process either directly as cleansing or debriding agents for removing necrotic tissue, or indirectly as antimicrobial drugs, which prevent or treat infection or growth agents (growth factors) to aid tissue regeneration. In chronic wound management, where patients usually undergo long treatments and frequent dressing changes, a system that delivers drugs to a wound site in a controlled fashion can improve patient compliance and therapeutic outcomes. Bioadhesive, polymeric (synthetic, semisynthetic, or naturally derived) dressings are potentially useful in the treatment of local infections where it may be beneficial to achieve increased local concentrations of antibiotics while avoiding high-systemic doses, thus reducing patient exposure to an excess of drug beyond that required at the wound site.[37]

Composite dressings comprising both synthetic and naturally occurring polymers have also been reported for controlled drug delivery to wound sites.[1] By controlling the degree of swelling, cross-linking density, and degradation rate, delivery kinetics can be tailored according to the desired drug release schedule.[38] Drug release from polymeric formulations is controlled by one or more physical processes including (1) hydration of the polymer by fluids, (2) swelling to form a gel, (3) diffusion of drug through the polymer matrix, and (4) eventual degradation/erosion of the polymeric system.[37,39,40] Upon

**Table 2.** The Major Chronic Wounds Commonly Encountered in Clinical Wound Therapy

| Type of Ulcer | Description | Risks Factors | Symptoms |
|---|---|---|---|
| Diabetic ulcers | Diabetic foot ulcers (also known as neuropathic ulcers) are a major complication of diabetes mellitus. The most common cause is uncontrolled blood glucose (sugars) over a prolonged period of time. Two other disorders, diabetic neuropathy and peripheral vascular disease, can also contribute to ulcer formation. | •Uncontrolled blood sugars<br>•Diabetic peripheral neuropathy<br>•Peripheral vascular disease | Diabetic ulcers usually present on the foot at an area of trauma or a weight-bearing surface. The wound bed is commonly dry and may have necrotic tissue or a foul odor. This kind of ulcer may be a small wound area on the outside but can hide an underlying abscess. The skin around the wound commonly has hyperkeratosis. These ulcers are generally painless because of altered sensation or neuropathy. |
| Pressure ulcers | Pressure ulcers, also known as decubitus ulcers or bed sores, occur in people with conditions that limit or inhibit movement of body parts that are commonly subjected to pressure, such as the sacrum and heels. A pressure ulcer is an area of skin that deteriorates when the skin is exposed to prolonged pressure. This prolonged and unrelieved pressure restricts blood flow into the area and tissue damage or tissue death results. | •Patients confined to wheelchair or bed<br>•Increased age<br>•Mental or physical deficits that affect their ability to move<br>•Chronic conditions that prevent areas of the body from receiving proper blood flow<br>•Fragile skin (patient under steroidal therapy), urinary or fecal incontinence<br>•Malnutrition | A pressure ulcer generally starts as reddened area on the skin and, if the contributing pressure is unrelieved, the ulcer progresses to a blister, then an open sore, and finally a deep crater. This deterioration may occur rapidly. The most common places for pressure ulcers to form are over bones close to the skin, such as the sacrum, heels, elbows, hips, ankles, shoulders, back, and back of the head. Pressures sores are categorized from stage I (earliest signs) to stage IV (worst) according to severity and the treatments depend on the wound stage. Two additional stages can be used in case of severe wounds. They are “unstageable” and “suspected deep tissue injury.” |
| Venous ulcers | Venous ulcers, also known as vascular or stasis ulcers, develop as a consequence of venous insufficiency. The damaged valves allow blood to pool in the vein, and as the vein overfills, blood may leak out into the surrounding tissue leading to a breakdown of the tissue and development of a skin ulcer. Venous ulcers commonly occur on the sides of the leg, above the ankle and below the knee. | •Deep vein thrombosis<br>•Obesity or poor nutrition<br>•Pregnancies<br>•A family history of varicose veins<br>•Smoking and excessive alcohol use<br>•The lack of physical activity<br>•Aging<br>•Work that requires prolonged standing more | The first sign of a venous skin ulcer is skin that turns dark red or purple over the area where the blood is leaking out of the vein. The wound bed is often beefy red and may bleed easily. The ulcer may be painful. Necrotic tissue, slough (yellow, tan, grey, green, or brown) and/or eschar (tan, brown, or black), may also be present. The skin may also become thick, dry, and itchy. Venous ulcers are commonly slow to heal and often require lifetime modifications to prevent re-development. |
| Arterial ulcers | Arterial ulcers result from a complete or partial blockage in the arteries. They are almost always caused by atherosclerosis. In this pathology, cholesterol or other fatty plaques settle in the arteries causing obstructions that result in poor blood circulation. This poor circulation leads to tissue death and ulcer formation. | •Trauma<br>•Limited joint mobility<br>•Increased age<br>•Diabetes mellitus<br>•High blood pressure<br>•Arteriosclerosis<br>•Peripheral vascular disease | Wounds commonly have minimal drainage and are often very painful. Pain is often relieved by dangling legs and increased when legs are elevated. |

contact of a dry polymeric dressing with a moist wound surface, wound exudate penetrates into the polymer matrix. This causes hydration and eventually swelling of the dressing to form a release system over the wound surface (Fig. 2). In certain wound dressings, the mechanism for drug release has been explained by the hydrolytic activity of enzymes present in the wound exudates[41] or from bacteria in the case of infected wounds.[42]

## Dressing Materials

Polymeric materials employed in the formulation of wound dressings can be broadly divided into natural inert, natural


**Figure 1.** (a) Arterial ulcer at the cross malleolus of the leg with sharp margins and a punched out appearance. (b) Venous stasis ulcer with irregular border and shallow base. (c) Diabetic foot ulcer with surrounding callus, severe ulcer caused by diabetic neuropathy and bony deformity. (d) Pressure ulcer in a paraplegic (impairment of motor or sensory function in the lower extremities) patient, causing full-thickness skin loss. Adapted from Fonder et al.[35] with permission from Elsevier Inc.

bioactive, and synthetic polymers. A brief overview of these categories of polymers used in wound healing and associated references are summarized in Table 3 and briefly discussed below. However, for a detailed description about the use of these materials in wound healing, the reader is referred to the recent review article by Mogosanu et al.[43]

**Table 3.** Summary of the Different Type of Polymers Used in Commonly Used Dressings

| Natural | Carboxymethylcellulose[69–71] |
|---|---|
| | Bacterial cellulose[44,72–74] |
| | Silk fibroin[75–77] |
| | Pectin[78,79] |
| | Carrageenan[80–82] |
| Synthetic | Poly(ethylene oxide)[80–83] |
| | Poly(vinyl alcohol)[84–87] |
| | Poly-L-lactic acid[88–90] |
| | Poly(ethylene glycol)[61,91,92] |
| | Polyurethane[60,93,94] |
| Bioactive | Collagen[95,96] |
| | Gelatin[97,98] |
| | Hyaluronic acid[53,54,99,100] |
| | Chitosan[101–104] |
| | Sodium alginate[105–108] |

### *Natural Inert Polymers*

Natural polymers can be obtained from plant, bacterial, fungal, or animal sources and are commonly used because of their biocompatibility and biodegradability. Bacterial cellulose is a pure natural exopolysaccharide produced by specific microbial genera. The good biocompatibility, hemocompatibility, mechanical strength, microporosity, and biodegradability make this material one of the most trending natural polymeric materials used for wound care.[44] Bacterial cellulose is used especially as a healing scaffold/matrix for chronic wound dressings because it possesses many of the characteristics of an ideal wound dressing. It is known to promote autolytic debridement, reduce pain, and accelerate granulation, ensuring effective wound healing.[45] Furthermore, therapeutically active wound

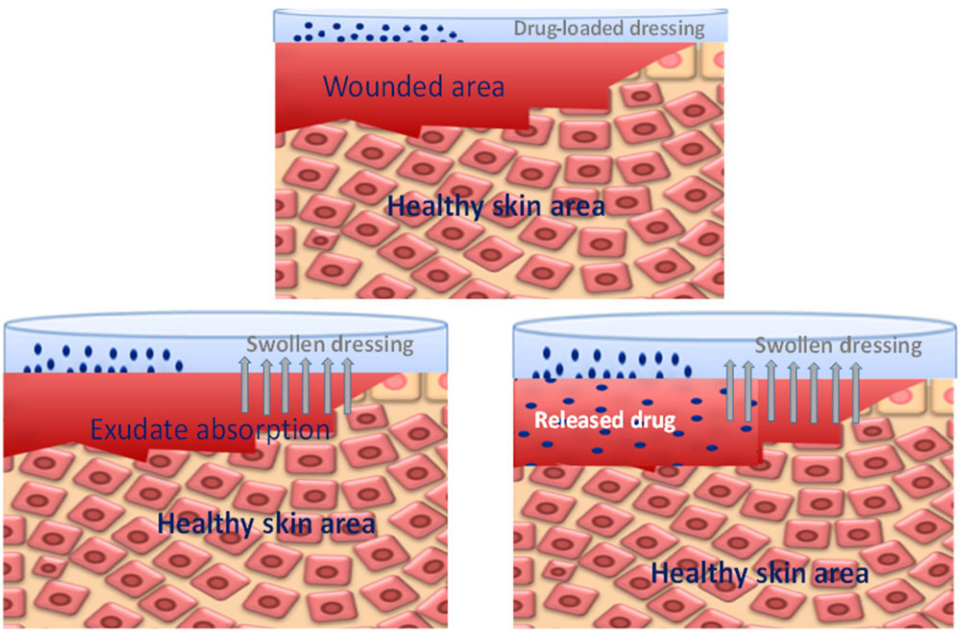


**Figure 2.** Schematic diagrams illustrating the movement of exudate into and drug release from swollen bioactive dressings during wound healing.

dressings with modified cellulose can be prepared by coimmobilization with different active molecules such as enzymes, antioxidants, hormones, vitamins, and antimicrobial drugs.[44] Silk fibroin is another natural biopolymer with a highly repetitive amino acid sequence, which leads to the formation of a biomaterial with remarkable mechanical and biological characteristics. The unique properties of biocompatibility, biodegradability, flexibility, adherence, and absorption of exudates with minimal inflammatory reaction make silk a very promising material for wound dressings.[46] Other examples of natural polymers employed in wound dressings include carrageenan, carboxymethylcellulose, and pectin.

### *Natural Bioactive Polymers*

Bioactive polymers are also commonly used because of their biocompatibility and biodegradability, but more importantly, they have an active therapeutic effect on one or more stages of wound healing. Most of them form part of the natural body matrix or contain components that possess physiological activity as part of the natural wound healing process. The most common bioactive polymer dressing materials include collagen (and gelatin), hyaluronic acid, chitosan, and sodium alginate.

Sodium alginate probably has the largest number of applications in biomedical science and bioengineering because of its biocompatibility, bioresorption, and ease of gelation. Alginate is typically used in the form of a hydrogel in biomedicine, including wound healing, drug delivery, and tissue engineering applications.[38]

The most common method to prepare hydrogels from an aqueous alginate solution is to combine with an ionic cross-linking agent such as divalent cations (e.g., $Ca^{2+}$). The interaction occurs between guluronic acid (G)-rich regions of adjacent polymer chains resulting in the formation of a bulk structure in the shape of an "egg-box."[47] The composition in the guluronic segments (molecular weight and mannuronic/guluronic – M/G ratio) and the extent of cross-linking will largely affect the quality of the matrices formed. When hydrogels are made from alginate rich in guluronic acid residues, the resulting gels tend to be rigid, whereas more elastic gels are produced from alginates with low α-l-guluronic acid content.[48] The ability of calcium ions ($Ca^{2+}$) to form cross-links with alginate makes calcium alginate dressings ideal materials as scaffolds for tissue engineering.[49]

Alginate-based absorbent wound dressings may be used on multiple wound types, including pressure, diabetic, and venous ulcers as well as cavity and some bleeding wounds. Indeed, the high water absorption limits wound secretions and minimizes bacterial contamination.[50] The wide acceptance of alginates in wound healing is also related to the positive clinical advantages shown in various studies. For example, a randomized, controlled trial involving patients with full-thickness pressure ulcers reported better clinical outcomes using alginate wound dressing when compared with topical treatment with a dextranomer paste.[51]

Hyaluronic acid is one of the principal components of the human connective tissues and has become recognized as an active participant in tissue repair processes, including wound healing.[52] It is already used in some commercially available advanced dressings such as Hyalofill® (Anika Therapeutics, Bedford Massachusetts), Hyalomatrix® (Anika Therapeutics), and Hyiodine® (Contipro Pharma, Dolni Dobrouc Czech Republic), which have demonstrated that the application of exogenous hyaluronic acid on wounds can exert positive effects on the wound-healing process and pain management.[53] Hyaluronic acid can be easily included within gauze, foams, or creams for topical use and has a high capacity to retain water and provides a moist environment to protect the wounded tissue surface from dryness and promotes wound healing.[54]

Collagen gives the skin its tensile strength and like hyaluronic acid, forms part of the natural tissue matrix, is biodegradable, and plays an active part in normal physiological wound healing and new tissue formation, which makes it an attractive choice from a tissue biocompatibility and a toxicological point of view.[55–57] Chitosan has ideal wound healing properties including hemostasis and antibacterial activity.[58,59] It is reported to be able to stimulate formation of granulation tissue followed by angiogenesis and deposition of collagen fibers to further improve repair of dermal and epidermal wounds.

### *Synthetic Polymers*

Synthetic polymers commonly employed in wound dressings include polyvinylalcohol, polyethylene oxide (PEO), and polyurethane. Their hydrophilic nature imparts important functional wound healing characteristics such as moisture absorption capacity and water vapor transmission, which allow maintenance of a moist wound environment while avoiding collection of excess exudate. In addition, they are generally adhesive, which allows prolonged residence as well as being biocompatible and possessing higher mechanical strength than the natural ones described above. Synthetic polymer dressings can be produced using various techniques, such as electrospinning and hydrogel synthesis.[43] Often, synthetic materials are used in combination with natural or bioactive polymers to improve the mechanical properties of the final wound dressing, as in the case of electrospinned polyurethane-dextran nanofiber mats[60] or poly(ethylene glycol)/chitosan,[61] both of which are dressings with antibacterial activity because of the presence of ciprofloxacin hydrochloride.

### *Hydrogels*

Hydrogels have been widely reported in the peer-reviewed literature and in patents, whereas several products are commercially available.[62] A hydrogel can be described as a three-dimensional network of hydrophilic polymers.[63] They can be prepared from various water-soluble polymers with a wide range of chemical and physical properties. Hydrogels are capable of absorbing large volumes of water because of the presence of hydrophilic chains, which allow them to swell extensively without changing their gelatinous nature. This property enables hydrogels to function as moist absorbent wound dressings.[64] They can be used on dry, sloughy, or necrotic wounds but usually need a secondary dressing to hold it close against the wound bed.[65] These dressings are conventional for unusual shapes of wounds because of their jelly-like nature. Hydrogels are nonparticulate, nontoxic, and nonadherent.[66] They also assist in providing a moist environment to dehydrated tissue to prevent them from desiccation and absorb exudates from wounds. Gamma radiation cross-linking was employed by Rosiak and Olejniczak[67] and Rosiak[68] to obtain sterile hydrogels used in wound care. The materials used included natural polymers such as gelatin and agar and synthetic polymers such as polyvinyl pyrrolidone and polyvinyl alcohol. Some of the most common hydrogel dressings currently available commercially include Intrasite™, Nu-gel™, Kikgel, Aqua-gel, and Aquaform™.

## TRADITIONAL AND IMPREGNATED DRESSINGS

Majority of dressings currently on the market only take a passive part in the wound healing process. Traditional dressings include cotton, wool, natural or synthetic bandages, and gauzes and may be used as primary or secondary dressings, or form part of a composite of several layers with each performing a specific function.[1] These were used commonly in the past, and though now less widely used, they are still of some benefit in certain clinical settings for wound treatment. Traditional wound dressings have been largely replaced for chronic wounds and burns by the more recent and advanced dressings because they do not provide a moist environment for wound healing. However, sometimes, moist dressings showed no clinical advantages over treatment with traditional dressing (as in the case of treatment of split-thickness skin graft donor sites[109]) that can be preferred because of ease of use, ready accessibility in most clinics and surgical centers, lower treatment costs, and better patient acceptance.

Traditional dressings can provide some bacterial protection, but this is lost when the outer surface of the dressing becomes moistened either by wound exudate or external fluids.[110] Further, traditional dressings provide only little occlusion and allow evaporation of moisture, resulting in a dehydrated wound bed, and they tend to become more adherent to wounds as fluid production diminishes and are painful to remove. An improvement of the properties of these dressings can be achieved by impregnating them with other materials or compounds to obtain a functional dressing. For example, paraffin (petrolatum)-impregnated dressings prevent sticking of the dressing to dry wound surface, are more occlusive and easier to remove from the skin, and therefore avoid causing trauma and bleeding during dressing change. Gauze and bandage can also be functionalized with topical antimicrobials, which can prevent or reduce bacterial bioburden or reinfection especially during dressing changes. Commonly used topical antiseptic agents include iodine-releasing agents [e.g., povidone iodine (PVP-I)], chlorine-releasing solutions (e.g., Dakin's and sodium hypochlorite solutions), hydrogen peroxide, chlorhexidine, silver-releasing agents, and acetic acid. These compounds can be used to either kill or control the growth of micro-organisms in wounds[111,112] and are generally classified as antiseptics or antibiotics and characterized by low specificity to treat wound infection. Antiseptics, which are disinfectants that are used on intact skin and some open wounds to kill or inhibit micro-organisms, tend to have multiple microbial targets, a broad antimicrobial spectrum, and residual anti-infective activity. However, they can be harmful to healthy tissues and cell components essential for effective wound healing such as fibroblasts, keratinocytes, and possibly leukocytes.[113] Antibiotics are potent antimicrobial agents or chemicals with high specificity, which in dilute concentrations, inhibit or kill micro-organisms. They usually act on one specific cell target and are relatively nontoxic; however, they are more susceptible to loss of activity because of the development of bacterial resistance.[113] These are discussed in further detail under the *Antimicrobial Dressings* section below. In terms of efficacy, acetic acid (1%) has limited activity but has been used with great success in the management of wounds heavily colonized with *Pseudomonas aeruginosa*.[114,115]

## DRUG-CONTAINING (DELIVERY) DRESSINGS

### Wound Drug Delivery

Different wound types require different dressing materials possessing different characteristics including fluid absorption, residence time on the wound, and mechanical strength. A relatively new approach to wound healing involves the use of polymeric wound dressings to deliver various pharmacological agents that can take active part in one or more stages of the wound healing process. The activities of these compounds together with the physical characteristics of the dressing can enhance the wound healing rate, while eliminating some of the factors that can impair wound healing. Hydrogels, hydrocolloids, foams, films, and wafers can be used to deliver a variety of compounds such as antimicrobials, anti-inflammatory agents, analgesics, growth factors (GFs), proteins, and supplements directly to the wound site, thus increasing the efficiency of the therapy.

### Antimicrobial Dressings

Many new wound dressings loaded with antimicrobial drugs have been developed in the past 20 years, taking advantage of the properties of advanced dressing to actively kill bacteria and/or fungi present in infected wounds, reduce bacteria bio-burden, and prevent reinfection during healing, wound inspection, surgical procedures, or dressing change.

#### *Wound Infection*

Infection occurs in wounds when one or more micro-organisms (mainly bacteria and sometimes fungi) compete with the host natural immune system. Most open injuries are contaminated with different microbes; however, this usually has no clinical significance as they express no evidence of infection and heal as expected. Pathogenic bacteria, such as *Staphylococcus aureus, Pseudomonas, aeruginosa, Streptococcus pyogenes,* and some *Proteus*, *Clostridium,* and *Coliform* species are the most common causes of infection and most frequently cited as the reason for delayed wound healing.[114,116–119] Inadequate control measures in the management of infected wounds can lead to cellulitis and ultimately bacteremia and septicemia, both of which can be fatal. Wound colonization describes the presence of multiplying micro-organisms on the surface of a wound, but with no immune response from the host,[120] and with no associated clinical signs and symptoms. The invasion of viable tissue by these micro-organisms provokes a series of local and systemic host responses such as purulent discharge, painful spreading erythema, or symptomatic cellulitis around a wound that can lead to soft tissue destruction.[111,112] As reported by several authors, high microbial load has severe implications in delaying wound healing and the formation of bacterial biofilms is one of the critical mediators of chronic wounds.[114,121,122] It has been reported that approximately 75% of wounds caused by burns have a risk of infection through contamination by micro-organisms from the sweat glands and hair follicles, gastrointestinal and upper respiratory tracts and the presence of *Pseudomonas aeruginosa and Staphylococcus aureus* significantly reduced skin graft healing.[114,123–125] Chronic wounds are prone to infection because of the formation of high microbial bioburden and

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**Table 4.** Different Antibiotics and the Type of Dressings Used to Deliver Them to Infected Wounds

| Delivery System | Drug | Reference |
|---|---|---|
| Chitosan films | Minocycline | Aoyagi et al.[138] |
| Chitosan sponges | Vancomycin | Stinner et al.[139] |
| Polyox composite film | Streptomycin | Pawar et al.[82] |
| Polyox/carrageenan composite film | Streptomycin | Boateng et al.[80] |
| Polyox/carrageenan and polyox/sodium alginate wafers | Streptomycin | Pawar et al.[81] |
| Wafers | Neomycin | Labovitiadi et al.[140] |
| Polysaccharide wafers | Chlorhexidine digluconate | Labovitiadi et al.[141,142] |
| Electrospun polyurethane-dextran nanofiber mats | Ciprofloxacin | Unnithan et al.[60] |
| Poly(ethylene glycol)/chitosan scaffold | Ciprofloxacin | Sinha et al.[61] |

inability of leukocytes to deal with impaired migration, phagocytosis, and intracellular killing of micro-organisms.[126] Local tissue necrosis, hypoxia, ischemia, and some immune deficiencies such as the one caused by human immunodeficiency virus or chemotherapy are factors that promote wound infection.[114]

### *Antibiotic Drugs*

The use of antibiotic drugs for local wound application is gradually becoming popular, at least in the scientific literature, because of many factors, the most common being the lower amounts required when applied directly at the wound sites compared with systemic administration via injections or the gastrointestinal route. Different classes of antibiotics have been used in wound dressings for delivery to wound sites and a selection of these are summarized in Table 4. Treatment of wound infection requires a decrease in exogenous microbial bioburden that can be achieved using various approaches including topical and systemic broad-spectrum antimicrobial agents, debridement of devitalized tissue, appropriate dressing, maximization of immune resistance, and provision of adequate nutrition.[114,128,129] Combinations of antibiotics can be used to cover multidrug-resistant micro-organisms; however, clinical data supporting this strategy are limited.[127]

The persistent emergence of antibiotic-resistant strains of pathogens, together with the reduced rate of new antibiotics coming through the drug discovery pipeline has resulted in the need for alternative treatments to manage wound infections more effectively. To overcome this problem, novel dressings containing nonantibiotic compounds (e.g., silver and plants) are continually developed and their use can enhance the antimicrobial activities of dressings, limiting the occurrence of antimicrobial resistance.[130–137]

### *Silver*

Silver and the newer silver nanoparticles (AgNPs) have been recognized as optimal candidates for overcoming pathologies previously treated with conventional antibiotics, because of their strong and broad-spectrum antimicrobial characteristics.

Various mechanisms have been proposed for silver's antibacterial action. The first proposed mechanism involves bacterial cell membrane enzyme protein deactivation by binding to thiol groups. These proteins are known to take part in membrane energy production and ion transport.[143] Davies and Etris[144] reported that silver is involved in catalytic oxidation reactions resulting in disulfide bond formation by catalyzing reactions between oxygen present in the cell and hydrogen from thiol groups, ultimately inhibiting cell function because of changes in protein structure. Other authors have reported the binding of silver to the 30S ribosomal subunit, thereby preventing protein translation.[145] Another mechanism reported involves the entry of positively charged silver ions into the cell and denaturing DNA by "locking" itself between purine and pyrimidine base pairs,[143] though this has not been proved conclusively. For silver to exhibit antibacterial activity, it needs to be in the ionized form, and therefore unionized silver metal is nonactive and only becomes active in the presence of moisture (exudate in the case of wounds).[146,147]

New wound dressings have been developed that release silver to help prevent wound infections caused by both Gram-positive and Gram-negative bacteria both *in vitro* and *in vivo*.[148] In the past, the use of silver had been severely limited by the toxicity of its ions to humans; however, the development of nanotechnology has facilitated the production of nanostructured silver particles with a high surface area (and therefore a higher area-to-volume ratio) that demonstrates greater efficacy against bacteria and more importantly less toxicity to humans.[131]

A novel composite scaffold dressing comprising β-chitin and AgNPs for wound healing showed bactericidal activity against *Escherichia coli* and *Staphylococcus aureus* in addition to good blood-clotting ability because of chitin.[149] In a related study, Pant et al.[150] reported on nylon nanofibers incorporating AgNPs by an electrospinning method for wound healing. Their results showed that the composite system exhibited antibacterial activity against Gram-negative *Escherichia coli* and Gram-positive *Staphylococcus aureus*. Silver-loaded dressings have also been reported as effective against nonbacterial targets, including fungi.[151]In a recent study, silver-containing activated carbon fibers compared with commercial silver dressings were investigated to determine the effects of different silver concentrations on the dressing efficacies.[152] It was shown that the "various silver-containing activated carbon fibers exhibited good antibacterial effects and biocompatibility in terms of cell viability and that silver concentration showed a minor influence on cell growth," The authors concluded that silver-containing activated carbon fiber and other commercial silver dressings aided wound healing by promoting granulation and collagen deposition. Chitosan and polyvinyl pyrolidone-based film dressing containing silver oxide has been functionally evaluated for potential wound healing properties, compared with cotton, pure chitosan, and other chitosan-based dressing.[153] The results showed better performance of the composite chitosan-PVP-silver oxide dressing compared with the other materials.

Commercially, there are many dressings that are just upgrades of existing polymer-based moist wound dressings, loaded with silver either in pure form, as salts or as nanoparticles for treating and/or preventing infection in various wound types. The different silver-loaded dressings currently available on the market are summarized in Table 5 below. Most of these have been reported in the peer-reviewed scientific literature

**Table 5.** Commercially Available Wound Care Products Containing Silver[158]

| Formulation | Product Name | Manufacturer | Silver Form |
|---|---|---|---|
| Fibrous/cloths, others | Silverseal | Derma Sciences, Princeton New Jersey | Silver oxide |
| | Tegaderm Ag Mesh Dressing with Silver | 3M, Bracknell UK | Silver sulfate |
| | Urgotul SSD | Laboratoies Urgo, Chenôve France | Silver sulfadiazine |
| | Vliwaktiv Ag, Absorbent Activated Charcoal | Lohmann and Rauscher, Rengsdorf Germany | Silver |
| | Vliwaktiv Ag, Activated Charcoal Rope with Silver | Lohmann and Rauscher | Silver |
| Films/meshes | Acticoat 7 | Smith and Nephew, Hull UK | Elemental silver |
| | Arglaes film | Medline Industries Inc, Mundelein Illinois | Silver |
| | Restore Contact Layer with Silver | Hollister Wound Care LLC, Libertyville Illinois | Silver chloride |
| Foams | Acticoat Moisture Control | Smith and Nephew | Elemental silver |
| | Allevyn Ag | Smith and Nephew | Silver sulfadiazine |
| | Biatain Ag | Coloplast, Denmark | Silver |
| | Mepilex Ag | Molnlycke Healthcare Ltd, Dunstable UK | Silver |
| | Optifoam Ag Adhesive | Medline Industries Inc | Ionic silver |
| | Optifoam Ag Nonadhesive | Medline Industries Inc | Ionic silver |
| | PolyMem Silver Island | Ferris Mfg. Corporation, Fort Worth Texas | Elemental silver |
| | PolyWic Silver | Ferris Mfg. Corporation | Elemental silver |
| | Restore nonadherent foam with silver | Hollister Wound Care LLC | Silver |
| | Silverlon Negative Pressure | Argentum Medical LLC, Geneva Illinois | Ionic silver |
| | SilverSite | Centurion Medical Products, Williamston Michigan | Silver alginate |
| | UrgoCell Silver/Cellosorb Ag | Urgo Medical, Loughborough UK | Silver salts |
| | V.A.C GranuFoam Silver | KCI, Gatwick UK | Silver |
| Gauze | Urgotul SSD/S.Ag | Urgo Medical | Silver sulfadiazine |
| Hydrocolloid | Contreet Hydrocolloid | Coloplast | Silver |
| | SILVERSEAL Hydrocolloid | Derma Sciences | Silver |
| | SureSkin | EuroMed, Orangeburg New York | Silver zeolite |
| Hydrofiber | Aquacel Ag | ConvaTec, Deeside UK | Ionic silver |
| Hydrogel | Elta Silvergel | Elta, Carrollton Texas | Silver |
| | ExcelGinate Ag | MPM Medical Inc, Irving Texas | Silver |
| | Gentell Ag Hydrogel Wound Dressing | Gentell, Bristol Pensylvania | Silver sulfadiazine |
| | Silvasorb Gel | Medline | Ionic silver |
| | SilverMed Antimicrobial Silver | MPM Medical Inc, | Silver |
| | SILVERSEAL | Derma Sciences | Silver oxide |
| | Silver-Sept Antimicrobial Gel | Anacapa Tech Inc, San Dirmas California | Silver salt |
| Powder | Arglaes Powder | Medline | Silver |
| Wash | SilverMed Antimicrobial Wound Cleanser | MPM | Silver microparticles |

and shown in most cases to have antibacterial activity both *in vitro* [154,155] and *in vivo*.[156,157]

### *Antimicrobial Peptides and Bacteriolytic Enzymes*

Infections caused by multidrug-resistant organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Staphylococcus aureus* (VRSA), extended spectrum beta-lactamase (ESBL), vancomycin-resistant *Enterococcus* (VRE), and multidrug-resistant *Acinetobacter baumannii* can lead to increased patient morbidity and mortality and increase the cost of treatment because of prolonged hospitalization. Antimicrobial peptides (AMPs) are recognized as promising candidates to overcome infections caused by resistant bacteria. These therapeutic agents are widely synthesized in nature by micro-organisms, plants, and animals (both invertebrates and vertebrates) as components of their natural defenses against invading pathogens. AMPs are active against a broad spectrum of micro-organisms, including multidrug-resistant strains such as MRSA, VRSA, ESBL, VRE, and multidrug-resistant *Acinetobacter baumannii* because of the fact that they have a low propensity for developing microbial-resistance making them very efficient at treating infection.[140,159] This activity is attributed to a rapid mechanism of action and the ability to discriminate between host and microbial cells (cell selectivity) making them promising candidates for clinical applications and potential alternatives to conventional antibiotics. More than 2000 AMPs have been reported with differences in their sequence and structure, and they are all generally low molecular weight (10–50 amino acids) peptides and have at least two positive charges.[160]

Antimicrobial peptides are widely used to functionalize biomaterial surfaces that impart antibiofilm properties and their immobilization within wound dressings is just one of the applications in the biomedical field.[161] Chemical and physically cross-linked natural and synthetic hydrogels are probably the most versatile platforms for the delivery of drugs and peptides to mitigate biofilm formation. In particular, when hydrogels are used to simultaneously codeliver antimicrobial polymers/peptides and conventional antimicrobial agents, a strong synergistic effect can be achieved.[162] Biodegradable antimicrobial polymers or peptide-loaded gels are more attractive than gels loaded with antibiotics or metal (e.g., silver) nanoparticles as bacteria easily develop resistance to antibiotics and the nondegradability of metal nanoparticles can result in toxicity. Good results were also obtained when AMPs were included in freeze-dried wafers, polyelectrolyte multilayers, or cotton gauzes.[163,164]

The use of bacteriolytic enzymes can be another promising strategy for the treatment and prevention of drug-resistant organisms and biofilm establishment. The biopolymers involved in cell attachment are the main target of such enzymes, leading to an inhibition of biofilm formation or promoting detachment of established biofilms. Several enzymes have been shown to exhibit this antibiofilm activity and are currently extensively studied for preventing bacterial colonization on surfaces if incorporated into antibiofilm coatings.[161] Recently, Miao et al.[165] proposed the use of these molecules to produce a functional wound dressing with antimicrobial activity against a drug-resistant bacterial strain. Lysostaphin, a cell lytic endopeptidase derived from bacteriophages, was immobilized onto biocompatible polymeric fibers generated by electrospinning to obtain an anti-infective bandage. The resulting dressing was tested in an *in vitro* skin model, and showed good activity against *Staphylococcus aureus* and a low toxicity toward keratinocytes, suggesting a possible application of these materials as antimicrobial wound dressings. Other hydrolytic enzymes derived from bacteriophages have been proposed as promising and potent antibacterial therapeutic agents even against MRSA and VRSA strains. As a result, they can become an interesting future therapeutic tool as first-line antibiotics in the battle against resistant bacteria strains.[166]

#### *Poly(Hexamethylene) Biguanide Hydrochloride*

Poly(hexamethylene) biguanide hydrochloride (PHMB) is a low molecular weight polymer with structure (Fig. 3) related to chlorhexidine. It is an antimicrobial agent with broad spectrum activity against several Gram-positive and Gram-negative bacteria, fungi, and yeast and reported to be particularly active against the difficult to control *Pseudomonas* species. Because of its water solubility, it is used in water-based products, which are most susceptible to microbial growth. As a preservative, PHMB is used in cosmetics, personal care products, fabric softeners, contact lens solutions, and hand washes. Moreover,

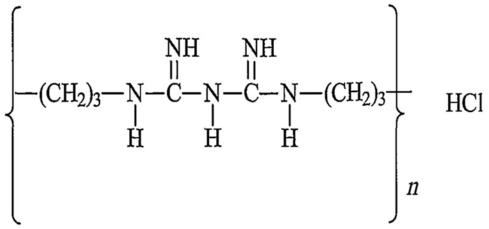

**Figure 3.** Chemical structure of PHMB.

PHMB has also been used to prevent microbial contamination in wound irrigation and sterile dressings and has been reported for use in reducing bloodstream infection caused by catheter use.[167]

In a study comparing electrospinned polylactide (PLA) nanofibers loaded with either PHMB or chlorhexidine, it was shown that the nanofibers became smoother and their diameter smaller with increasing amount of PHMB with a resultant increase in surface roughness and hydrophobicity of the scaffold.[137] The PHMB-loaded PLA scaffolds showed antibacterial properties by inhibiting adhesion and bacterial growth and at the same time exhibited biocompatible characteristics that allowed cell adhesion and proliferation of fibroblasts and epithelial cells *in vitro*.[137] In a randomized clinical trial, comparing the effectiveness of bio-cellulose dressing containing PHMB with silver sulfadiazine cream, in partial thickness burns, the former showed faster and better reduction in pain compared with the silver sulfadiazine cream. This suggests that PHMB reduced the duration of inflammation by controlling infection.[168] Dilamian et al.[169] prepared composite electrospinned membranes using chitosan and PEO incorporating PHMB to impart antimicrobial properties for use as a medical biomaterial. The effect of PHMB on the electrospinnability and antimicrobial properties of chitosan/PEO nanofibers were studied together with viscosity of the solutions and nanofiber morphology. The results showed that PHMB in chitosan/PEO solutions resulted in decreased zero-shear rate viscosity up to 20%, whereas increasing PHMB from 0.5 to 1 mM led to formation of thinner fibers. The drug-loaded fibers showed activity against *Escherichia coli* and *Staphylococcus aureus* with a burst release of PHMB from the materials in the first hour.[169]

### Anti-Inflammatory and Analgesic Dressings

Wound healing begins with an acute inflammatory phase within a few hours after injury with release of exudate rich in proteins. This causes vasodilation through the release of histamine and serotonin, which allows phagocytes to enter the wound and engulf dead cells. As a result of this inflammatory phase, a wound clot is formed, to stop bleeding and give strength and support to the injured tissue. However, this inflammatory phase is also characterized by swelling and pain, which can be severe in certain wound types. In chronic wounds, the wound is stuck in a continuous cycle of inflammation and patients can be in constant pain, which can be very debilitating. Pain also occurs either because of repeated tissue insults caused by physical trauma, but the most common cause of wound pain is probably because of dressing change, especially in the case of dry wounds, debriding, and wound cleansing. In addition, wound infection can contribute to wound pain by triggering a continuous inflammatory response. The response against the infecting micro-organisms causes the release of inflammatory mediators and stimulates the production of enzymes and free radicals, which can cause tissue damage.[170] Furthermore, the pain-related stress reduces the immune response to infection and stimulates proinflammatory cytokine production in wounds.[171] For these reasons, the treatment of pain and infection should be prioritized on an equal basis.

Wound pain can be classified into two types: nociceptive and neuropathic pain. Nociceptive pain is an appropriate physiological response to a painful stimulus and occurs as a result of tissue damage. This type of pain is usually time limited, but when the wounds are slow to heal, the prolonged inflammatory response may cause heightened sensitivity in both the wound (primary hyperalgesia) and in the surrounding skin (secondary hyperalgesia).[171] Neuropathic pain is an inappropriate response caused by a primary lesion or dysfunction in the nervous system. Nerve damage is the commonest cause of the primary lesion, which may be because of trauma, infection, metabolic disorder, or cancer. Neuropathic pain is a major factor in the development of chronic pain.[172] Reduction of pain is the highest treatment priority from the patient's perspective, especially in the case of a chronic wound. An appropriate wound management can significantly improve a patient's quality of life and may indirectly promote healing by improving appetite and sleep.[173] In skin transplants to help wound regeneration, the wound created is extremely painful as the layer of skin harvested touches the painful nerve endings and therefore requires pain management at the secondary wound site.

Topical treatment using pharmacological agents is an effective and safe approach to manage wound pain. Medicated dressings can perform the two essential functions: (1) the treatment of the cause (e.g., wound infection) and (2) the management of the actual wound pain. The treatment of wound infection, by reducing bacterial load and thereby reducing the inflammatory stimulus to the nervous system, should result in a reduction in pain. Antimicrobial drugs, however, may take some days to have a significant effect on pain. Therefore, to obtain rapid pain relief, dressings loaded with drugs, such as local anesthetics (e.g., lidocaine), or NSAIDs can be very useful to reduce wound pain during wear time and dressing change. In particular, ibuprofen has excellent local effects on superficial wounds, without detectable systemic levels[174] and provide clinically relevant pain relief for patients with exuding, painful venous ulcers.[175–178] In a multicenter randomized controlled trial, Arapoglou et al.[175] examined the analgesic effect (over 5 days) of foam dressings loaded with ibuprofen (112.5 mg) compared with local best practice wound management in various wound types (arterial, venous and mixed arterial-venous ulcers, vasculitis and traumatic ulcers). They showed that the ibuprofen releasing foam dressing produced a significantly higher analgesic effect than the local best practice group based on patient scores. They concluded that local pain relief by ibuprofen is possible in the most common painful exuding, chronic, and acute wounds, and therefore a safer alternative to systemic drug administration.[175] Romanelli et al.[178] showed that commercial ibuprofen containing foam dressing (Biatain Ibu, Coloplast, Denmark) provided better pain relief for painful exuding wounds compared with patients treated with local best practice wound management.

Another option to induce efficient analgesia in patients with severe skin wounds is the topical application of opioids. Opioid receptors are upregulated during inflammation and in addition to its analgesic functions; they can also directly modulate the inflammatory process and wound healing.[179,180] Topical opioid treatment can therefore be used to achieve local analgesia and enhance wound healing, thus reducing the severe adverse effects of systemic administration. Furthermore, wound dressings can be properly designed to ensure a slow release, increasing the safety and extending the interval between regular dressing changes.[181]

## ADVANCED DRESSINGS CONTAINING BIOLOGICAL AGENTS

### Growth Factors

The use of GFs to promote wound healing has always been considered one of the possible therapeutic approaches to overcome the problem of chronic wounds. GFs are a class of biomacromolecules locally secreted by the ECM, capable of regulating biological processes by transferring signals between cells and their local environment, regulating proliferation, migration, and differentiation of cells.[182,183] Interactions among the ECM, GFs, and cells are fundamental to all phases of wound healing and abnormalities in those interactions usually lead to chronic wounds.[184] In an exhaustive review, Barrientos et al.[185] summarized the action and therapeutic effects of various GFs in the clinical management of nonhealing wounds. Four GFs have shown the greatest potential for wound healing in randomized controlled trials: granulocyte-macrophage colony-stimulating factor, platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), and vascular endothelial growth factor (VEGF).[186] The local application of the GFs on the wound site is essential to exert a therapeutic action on wounds, but the need for continuous local injection makes this formulation difficult to use in clinical practice. The formulation of GFs in the form of a topical delivery system (e.g., cream, gel, or ointment) directly administered to the wound surface could facilitate their therapeutic application in the clinical management of chronic wounds. However, to date, only REGRANEX® Gel (Becaplermin 0.01%; Smith and Nephew, UK) has been approved by the FDA for the treatment of diabetic foot ulcers.[187,188] Despite the ability of Becaplermin to accelerate wound closure and significantly reduce amputations,[189–192] its use is expensive, requires frequent dressing changes, and is associated with an increased risk of cancer.[188]

Polymeric wound dressings were successfully developed for incorporation of free GFs using biocompatible biomaterials such as gelatin,[193,194] dextran,[195] collagen,[196] or chitosan.[197] Microencapsulation and nanoencapsulation are often necessary to protect GFs during the formulation and production phases and to achieve a long-term exposure, a characteristic required for the delivery of GFs to chronic wounds. Furthermore, as reported by Ulubayram et al.,[194] incorporating GFs into a wound dressing either in free form or loaded within microspheres, (to provide sustained release) have shown greater effects in wound healing than only free GFs. Electrospinned nanofibers is another very popular approach to develop novel multifunctional platforms by integrating controlled-release strategies within scaffolding materials, which are able to control and regulate the wound healing process.[198] Different fabrication techniques have been used for the development of GFs-loaded electrospinned fibers. GFs can be incorporated into the nanofibers[199] or conjugated onto the fibers surface,[200] and different release characteristics are obtained, depending on the loading method. An interesting hybrid approach was proposed by Kulkarni et al.,[201] which used a layer-by-layer assembly technique, to obtain a dressing able to preserve the bioactivity of encapsulated epidermal growth factor (EGF) while allowing the tuning of EGF release for an extended period, depending upon the number of layers deposited onto the surface.

Wound healing is one of the most complex mechanisms in the human body where multiple cellular pathways are simultaneously activated by different molecules. For this reason, the delivery of a single GF might be insufficient and a combined action of different GFs was shown to improve the reparative processes in the wounded skin of diabetic mice better than single-agent treatment.[202] Furthermore, the local concentration and the spatio-temporal gradients can be crucial for a successful treatment and combining different preparation techniques provides the possibility of simulating the natural conditions involved in the wound healing process. Using a combination of encapsulated and free GFs, it is possible to design a multiple release system with a controlled, sequential release of GFs mimicking the physiological action sequence and providing the most effective outcome. Multiple GFs including bFGF, EGF, VEGF, and PDGF were encapsulated in collagen and hyaluronic acid-based electrospinned nanofibers loaded with gelatin nanocapsules by Lai et al.[196] for sequential release of the GFs onto the wound site. GFs encapsulated either in nanofibers or in nanoparticles are released over 1 month by gradual degradation of nanofibers/nanoparticles simulating the temporal release of regulatory factors in the normal wound healing process. The initial delivery of bFGF and EGF biomimics the early stage of the wound healing process, whereas slow controlled release of VEGF and PDGF imitates the late stage of skin reconstruction promoting re-epithelialization, dermal reconstruction, and formation of mature vasculature as confirmed by *in vivo* studies on streptozotocin-induced diabetic rats.[196]

Platelets can constitute a natural potential source of multiple GFs and proteins involved in tissue regeneration. For this reason, topical treatments with platelet derivatives have increasingly been described as capable of accelerating wound healing and to aid in tissue repair.[203] Platelet lysate (PL) is a hemo-derivative obtained through platelet destruction by freeze–thawing and was shown to have activities of different cell types involved in wound healing.[204] The possibility to use allogeneic PL, which minimizes individual variability, represents an advantage compared with patient derivatives such as platelet-rich plasma or platelet-rich fibrin. Different controlled-release systems have been developed to provide sustained delivery of PL to the wound, including sponge-like dressings,[205] mucoadhesive gels,[206] and eye drops.[207] Recently, a powdered alginate formulation was proposed for the combined delivery of PL and vancomycin hydrochloride in chronic skin ulcers.[208] The alginate particles released the active drugs and also absorbed wound exudates to form a gel and at the same time enhance fibroblast proliferation.[208]

### Nucleic Acids

The local delivery of GFs presents some challenges and there has been limited success in clinical trials. The combined effects of physical inhibition and biological degradation cause significant loss of drug activity that minimizes their therapeutic efficacy. The introduction and expression of exogenous DNA into a host cell to achieve a permanent insertion (known as gene therapy) or transient transformation (gene medicine) has great potential in the treatment of wounds, stimulating the cells themselves to produce the GFs directly onto the wound site.[209] Such an approach could avoid the degradation of GFs on the wound site and achieve a temporary expression of these factors until wound closure. One of the first attempts to use a plasmid DNA (pDNA) coding for interleukin 8 genes in wound healing was by Hengge et al.[210] by injecting naked genes into the skin that resulted in a significant recruitment of dermal neutrophils. However, naked DNA constructs injected into the skin has been shown to have a low transfection efficiency because of their fragility in the extracellular environment, large size, and electrical charge. The transfection efficiency can be enhanced using a gene-activated matrix, which allows better control over the duration of transgene expression and promotes new tissue formation in a more effective way. A controlled release from a matrix can maintain the right level of the vector over time, providing repeated opportunities for transfection/transduction and extending transgene expression. For this reason, the design parameters of gene-loaded scaffolds (e.g., material, architecture, vector incorporation, biochemical cue presentation) are very important and directly affect the transgene expression and tissue repair.[211] Biodegradable carriers loaded with adenoviral vectors have been investigated for gene transfer in different animal wound healing models showing an increased granulation tissue formation, vascularization, and re-epithelialization compared with controls treated with carriers alone or carriers containing a reporter gene vector.[212–214] However, the limited loading capacity, the high costs of production, and the safety risk restrict their application range. Synthetic DNA delivery systems, known as nonviral vectors, have the advantage to deliver genes to target cells without the potential for recombination with wild-type viruses and possible cellular damage because of repeated exposure to the viral vectors.[215] Typically, these nonviral vectors are complexes of naked pDNA with cationic polymers (polyplex), lipid (lipoplex), or inorganic particles. These synthetic constructs have a lower risk of toxicity and offer the possibility of using a wider range of DNAs with different sizes, but at the expense of lower transfection efficiency compared with viral vectors. The transfection rate and the consequent success of the therapy depend on the degradation rate of biomaterials and the cellular infiltration into the scaffolds. The control of these two parameters allows a modulation of the therapeutic action over a long period of time, making this system very attractive for wound dressing application. Hydrogels containing pDNA coding for transforming growth factor-beta 1[216] and VEGF[217] have already been shown to promote wound healing in mouse wound models. Electrospinned nanofibers can be easily engineered to obtain scaffolds for delivery of nucleic acids because of their high surface area, high porosity and interconnected pores, beneficial for cell adhesion/proliferation, and oxygen/nutrient transfer.[198] The blending of DNA with an electrospinning solution did not give satisfactory results because of improper encapsulation and transfection efficiency,[132] but the development of other techniques, such as the incorporation of DNA-loaded particles into nanofibers, core–shell nanofibers, or surface modification, helped to overcome the low transfection efficiency of naked DNA-loaded nanofibers.[198] Saraf et al. formulated a fiber mesh scaffold containing a nonviral gene delivery vector polyethyleneimine–hyaluronic acid complex and pDNA within the sheath and core of the fiber, respectively.[218] They showed that the release rate and the transfection efficiency could be tuned by changing parameters such as concentration of pDNA and molecular weight of the core polymer.

Small interfering RNAs (siRNA) are tiny pieces of double-stranded mRNA that can inhibit gene expression and prevent the production of specific proteins.[219] The use of siRNA in wound healing could provide a gene-specific silencing of inflammatory or other specific proteins directly involved in chronic wounds. However, for an effective siRNA wound therapy, it is necessary to protect and deliver the nucleic acid directly into the cytoplasm, a process complicated by the very short half-life *in vivo* and by the difficult cellular internalization.[219] Research in this field is very attractive and many biomaterials and nanoparticles are constantly developed and optimized to create efficient delivery systems for siRNA.[220] Biodegradable scaffold injected or implanted directly at the wound site has already been investigated, and demonstrated the ability to achieve a high level of gene silencing efficiency and tunability *in vivo*.[221] However, despite the enormous potential of these technologies in wound healing, only few attempts[222,223] have been made to develop dressings or medical implants for localized and sustained siRNA delivery to the wound.

### Stem Cells

In recent years, there has been increasing evidence showing that the paracrine effect of stem cells can play an important role in wound healing, in particular regulating the levels of cytokines and GFs around the wound site.[224–226] Compared with many differentiated cell phenotypes, stem cells are potentially permanent residents of the wound site and naturally modulate the healing response in acute and chronic wounds, synthesizing and delivering multiple GFs. The use of biomaterial scaffolds loaded with stem cells can provide a local delivery of GFs, and at the same time, strengthen the action of the stem cells that create a favorable environment to promote cell adhesion, proliferation, migration, and differentiation. Different cell types and methods can be employed in the stem cell therapy for wound healing and Branski et al.[227] have provided a detailed outline of these technologies. Bone marrow-derived stem cells (BMSCs) are probably the most studied marrow-derived stem cells (MSCs), and several clinical studies have demonstrated their usefulness in wound healing.[228,229] However, bone marrow harvesting is an invasive and painful procedure and some pathologic conditions (e.g., severe burn trauma, sepsis, silver sulfadiazine toxicity, or old age) can reduce the BMSCs availability.[227]

Adipose-derived stem cells (ADSCs) are considered an interesting alternative to BMSCs for wound healing application because they express a similar array of cytokines and GFs and can be easily isolated from sections of whole fat (biopsy) or lipoaspirate, which means a less aggressive and painful harvesting procedure. The biggest challenge in the use of MSCs is to keep the cells in contact with the wound bed and keep them viable in the hostile wound microenvironment. *In situ*-forming injectable hydrogel dressings have been successfully applied for the delivery of large volumes of cells or biomolecules as they allow the retention of the cells at the injection site, therefore increasing efficiency. Furthermore, the relative ease of loading living cells into those systems and the conformability to complex tissue or implant shapes make hydrogels a very popular scaffold for cell encapsulation.[230] BMSCs-loaded[231] and ADSCs-loaded[232] thermoresponsive hydrogels have already been tested in wound models and showed potential as a bioactive wound dressing. A new interesting application of ADSCs is as filler in biodegradable sutures to provide a local proregenerative effect at the injured site. The simultaneous release of key molecules involved in the different phases of wound healing in association with mechanical wound fixation represents a promising tool to promote wound healing.

## DRESSINGS CONTAINING NATURALLY DERIVED AGENTS

### Naturally Occurring Plant Compounds

The development of new wound management products based on traditional or alternative medicine has become very popular in recent years. Before the advent of modern medicine, people of all continents used medicines from natural sources and nowadays the perception toward traditional medicine has also changed. Natural products, including the β-glucans, aloe, honey, cocoa, essential oils, and oak bark extracts are already being used in wound healing.[233] However, the lack of standard methods to evaluate their composition has made it more difficult to determine the true efficacy of these products for wound healing.

#### *Aloe Vera*

Aloe vera (*Aloe barbadensis*) preparations have been used for centuries to treat wounds and burns and its wound healing properties have always attracted the interest of the scientific community. Aloe vera gel is an extremely complicated mixture of natural products, but the biological activity is principally attributed to polysaccharides and glycoproteins (e.g., lectins) present in the leaf pulp.[234] Acemannan, the main polysaccharide present in aloe vera gel, seems to play an important role in the wound healing process by inhibiting bacterial growth and stimulating macrophage activity.[235] Furthermore, the antiseptic and antimicrobial activity are also related to the presence of natural antiseptic agents such as lupeol, salicylic acid, urea nitrogen, cinnamonic acid, phenols, and sulfur, which have inhibitory activity against fungi, bacteria, and viruses.[236] Several authors have already proposed the use of aloe vera as an alternative to synthetic drugs to develop active wound dressing materials useful for wound healing applications.[237–239]

#### *Other Plant Extracts*

Table 6 summarizes the use of other herbal medicines useful in wound care. Plant extracts from *Chamomilla recutita*,[240] *Hamamelis virginiana*,[241] *Polisiphonia lanosa* seaweed,[242] *Acacia arabica*, and *Moringa oleifera*,[243] are already being employed in the development of advanced wound dressings. Recently, a collagen sponge containing an extract of *Macrotyloma uniflorum*, generally utilized as cattle feed, was developed by Muthukumar et al.[244] The plant extract imparts antimicrobial activities to the sponge and at the same time increased the tensile strength and the stability of the sponge against collagenase enzyme.

Essential oils are the volatile products of secondary metabolism of plants and can be obtained from plant flowers, seeds, leaves, fruits, and roots most commonly via distillation, expression, or solvent extraction. Approximately 3000 essential oils are known, of which around 300 are commercially important.[136] Some of these, such as thyme oil, oregano, bay, lavender, peppermint, cinnamon, tea tree, rosemary, eucalyptus, and lemongrass, have been found to exhibit antimicrobial properties, but only lemongrass, oregano, and bay essential oil showed antimicrobial activity at concentrations less than 2% (v/v).[246] Liakos et al.[247] tested the antimicrobial

**Table 6.** Extracts from Different Plants Useful in Wound Healing

| Herbal Medicine | Properties |
|---|---|
| *Aspilia Africana* | Hemostatic properties on wounds, inhibits the growth of microbial organism, accelerates wound healing, treatment of rheumatic pain, bee, and scorpions stings, removes corneal opacity and foreign bodies from the eyes |
| *Bridelia ferrugunea, Parkia biglobosa Jacq* | Increased the proliferation of dermal fibroblast |
| *Elaeis Guineensis* leaf extract | Improve tissue regeneration |
| *Cedrus libani, Abies cilicica subsp cilicica* | Improved wound healing and anti-inflammatories properties |
| *Carapa Guineensis* leaves | Increased rate of wound contraction, skin breaking straight, and hydroxyproline content |
| Combination of *Yasha Bhasma, shoea robusta*, and *flax seed oil* | Increased wound contraction, higher collagen content, and better skin breaking straight |
| *Hippophae rhamniodes L* | Improve wound healing |
| *Carica papaya latex* | Increased wound contraction and epithelialization rate |
| Methanol extract of *Heliotropium indicum Linn.* leaves | Improve wound healing |
| *Rafflesia hasselti,* buds, and flower extract | Improve wound healing rate and wound contraction |
| *Melaleuca alternifolia* | Antimicrobial, antiseptic, antiviral, antifungal, and anti-inflammatory properties |

Adapted from Dorai et al.[244,245]

and antifungal properties of nine different essential oils incorporated in a sodium alginate-based film at three different concentrations. The loaded films showed the capacity of inhibiting bacterial and fungal growth depending on the essential oil type and concentration and can be suitable to use as novel antimicrobial wound dressing. Several other studies have been conducted on the antimicrobial activity of essential oils in wound dressing systems. Thyme oil was successfully incorporated into chitosan films to obtain antibacterial and permeable films for wound healing applications.[249] Thyme oil showed good antimicrobial effects on both Gram-negative and Gram-positive micro-organisms, and its efficacy as safe and effective source of natural antioxidant and antimicrobial agents was confirmed also by their incorporation into gelatin films[250] and N-carboxybutylchitosan/agarose foam using supercritical carbon dioxide.[251] Eugenol and limonene were doped in nanofluid-based magnetite and used to fabricate modified wound dressings with antimicrobial properties.[252] *Garcinia mangostana* extracts were incorporated into electrospinned chitosan-based nanofiber mats that showed the ability to inhibit the growth of *Staphylococcus aureus* and *Escherichia coli*.[253] However, essential oils, because of their hydrophobicity, tend to have a poor dispersion, and eventual phase separation can occur either in solution or in the final dried film. To avoid these phenomena and improve the dispersion and the stability of the essential oils, the use of surfactants is often required. A different approach was used by Catanzano et al.[248] who proposed a microemulsion as carrier to obtain a homogeneous distribution of tea tree oil in an alginate hydrogel.

## Honey

Over centuries, honey, produced from nectar by industrious honeybees (*Apis mellifera*), has been valued for its biomedical activity in treating various types of wounds including burns, diabetic ulcers, pressure ulcers, and leg ulcers.[254] Different ancient Sumerian and Greek manuscripts mentioned the use of honey as a drug against wounds such as ulcers.[255] Even as far back as World War I, Russian soldiers used honey to prevent wound infection as well as to accelerate healing of their wounds. The Germans also used honey in combination with cod liver oil to treat ulcers, burns, fistulas, and boils.[256] A broad spectrum of wounds are reported to be responsive to honey, including scratches, boils, amputation, leg ulcers, burns, chill blains, burst abdominal wounds, cracked nipples, fistulas, diabetic, malignant, leprosy, traumatic, cervical, varicose and sickle cell ulcers, septic wounds, surgical wounds, or wounds of abdominal wall and perineum.[238,257] The pharmacological activities of honey[258,259] relevant for wound healing include antimicrobial, deodorizing, debriding, osmotic, anti-inflammatory, and antioxidant actions that are known to enhance the rate of wound healing.[260] Various studies have demonstrated the antimicrobial effectiveness of honey in killing challenging wound-infecting bacteria[261] with significant increase in randomized clinical trials using honey to treat wounds.[259] In its natural state, honey contains major and minor ingredients that account for its biomedical actions in the treatment of various wounds including burns and ulcers,[254] and these ingredients vary in their physicochemical properties depending on the plant species on which the bees feed as well as the climatic and variations in general vegetation.[262] The main ingredients in honey are sugars mainly glucose and fructose, sucrose, disaccharides, so trisaccharides and other higher saccharrides. These sugars form during a chain of enzymatic reactions occurring during the ripening of honey or by chemical action in the concentrated honey.[263] Honey also contains various organic acids, such as gluconic acid, which makes up just 0.5% of the total solids with pH ranging from 3 to 4.5. Other acids in honey include formic, acetic, butyric, lactic, oxalic, succinic, and tartaric acids.[263] Another group of important constituents of honey are polyphenols that account for the natural antioxidants properties. Among these polyphenols, catechin, quercetin, and taxifolin have been reported to have the highest antioxidation effects.[264]

### *Antimicrobial Activity*

The antibacterial activity of honey is reported against over 60 bacteria species including aerobes and anaerobes, Gram-negative, Gram-positive, and some fungi. These include *Pseudomonas aeruginosa, Staphyloccocus aureus, Candida albicans* and *Escherichia coli*, coagulase-negative *Staphylococci, Acinetobacter baumannii Stenotrophomonas maltophilia,* MRSA, and VRE.[238–240,257–259] Furthermore, honey plays an important role in preventing biofilm formation.[265] The high sugar content of honey was previously considered as the main antibacterial agent because of the osmotic action of sugars that deprive bacterial cells of water vital for growth.[266] However, dilution in water increased the antimicrobial efficiency of honey and further research later identified hydrogen peroxide as an important antimicrobial agent.[267] The antimicrobial properties of honey is attributed to the cumulative action of high sugar content, acidity (low pH),[266] hydrogen peroxide,[268,269] and some phytochemicals, including flavonoids and phenolic acids. The flavonoid, pinocembrin has been identified as a potential antimicrobial factor,[270] possibly resulting from the ability of flavonoids to form complexes with soluble proteins and cell walls of bacteria. Phenolic acids such as methyl syringate are reported to possess antibacterial activity; however, they only account for about 4% of the nonperoxide antibacterial activity of diluted honey.[271] Furthermore, freshly extracted honey from the comb is known to have high levels of lysozyme that possesses antimicrobial action.[272] Other important chemical factors such as volatiles, organic acids, beeswax, nectar, pollen, and propolis are reported to be important for the antibacterial properties of honey.[273] It should, however, be noted that the specific mechanism by which honey inhibits bacterial growth and results in bacterial death is still not conclusive and further work is required in this area.

Though there is no conclusive evidence of benefit in medical use of honey,[274] honey dressings, gels, and the pure liquid have been gaining in popularity, fueled by scientific reports on their medical benefits. The largely low quality of the evidence and the heterogeneous nature of the patient populations make it difficult to draw overall conclusions about the effects of honey as a topical treatment for wounds. However, from data collected in a recent Cochrane review, honey appears to heal partial thickness burns more quickly than conventional (polyurethane film, paraffin gauze, tobramycin-impregnated gauze, sterile linen) treatment, whereas infected postoperative wounds healed more quickly than antiseptics and gauze.[274] Honey dressings are available in various commercial preparations such as honey gel ointment, honey-impregnated tulle dressings, honey-impregnated calcium alginate dressings, and honey-based sheet hydrogel dressings (Table 7).[130,258,275,276]

Manuka honey is probably the most widely known honey used as a wound dressing. It is a monofloral honey produced in New Zealand and Australia from the nectar of the mānuka tree (*Leptospermum scoparium*), plant that is endemic in parts of Australia and New Zealand. Manuka honey has been reported to exhibit antibacterial activity against a broad spectrum of bacteria including *Staphylococcus aureus* (including MRSA), *Pseudomonas aeruginosa*, and VRE.[277] The antibacterial properties of Manuka honey are principally, but not exclusively, because of methylglyoxal.[278] Medihoney® dressing (Derma Sciences) was the first wound dressings based on active Manuka honey to receive FDA approval for clinical use. According to the FDA, Medihoney® dressings are indicated for the management of light to moderately exuding wounds such as diabetic foot ulcers, venous or arterial leg ulcers, partial or full thickness pressure ulcers/sores, first and second partial thickness burns, and traumatic and surgical wounds.

A high-standardized synthetic antibacterial honey was developed by H&R Healthcare using a proprietary manufacturing process to produce precise levels of antimicrobial potency through steady delivery of oxygen-free radicals. Surgihoney® is a licensed sterile product based on natural, organic honey from a variety of sources, which has been developed for wound care and as a prophylactic dressing for wounds. The antimicrobial activities mediated by hydrogen peroxide[279] make Surgihoney® active against both Gram-positive and Gram-negative bacterial at very low concentration.[280]

Because of their natural origin and the high purity, honey dressings have few contraindications; however, they should be avoided in patients with a known history of allergy to either honey or bee venom. It was also reported that patients with diabetes should have their blood sugar monitored as they may be at higher risk of hyperglycemia because of the high sugar content of honey.[275]

Propolis (honeybee glue) is another natural substance produced by honeybee useful in wound healing.[281] It is a resinous mixture of botanical balsams and resins with digestive enzymes of bees used principally as a sealant in the hive. In traditional medicine, propolis is widely used for the treatment of various ailments including ulcer and wound healing. The presence of biologically active ingredients such as flavonoids, phenolic acids, terpenes, benzoic acids, amino acids, and vitamins imparts to propolis an antioxidant, antimicrobial, and immune-modulatory action with a resultant acceleration of wound healing.[281,282] Collagen-based films containing hydroalcoholic extracts of two different varieties of propolis were studied by de Almeida et al.[283] on dermal burn healing in a rodent model. These films significantly decreased the inflammatory severity, improving the biological events associated with burn healing and seems to be a promising new dressing for wound occlusion and tissue repair.[283]

## MEDICATED SUTURES

Sutures are biomaterial devices (natural or synthetic), usually used for mechanical wound closure to hold tissues together following surgery or trauma. Suturing in one of the most ancient wound healing techniques and although other methods for mechanical wound closure, such as staples, tape, and adhesive, have been developed over the years, sutures are still the most widely used materials.[284] Sutures are generally categorized according to the type of material (natural or synthetic), the lifetime of the material in the body (absorbable or nonabsorbable), and the form in which they were made (braided, twisted, and monofilament). Each type of suture has different characteristics, properties, and surgical application, as reported by Pillai and Sharma.[284] Despite the differences in materials and performance, the main goal of suturing is the approximation of the epithelial portion of the wound, maintaining the tensile strength across the wound until tissue tensile strength is adequate. To exert this action, sutures are in direct contact with the wound, and for this reason, can represent a useful scaffold for local delivery of active molecules to the wound.

Despite the significant advances in aseptic principles of surgery and the ongoing improvement of minimal invasive surgery, surgical site infections (SSIs) are still the major source of prolonged illness and death in surgical patients.[285] SSIs occur when pathogenic organisms (usually members of the *Staphylococci* family) proliferate in surgical wounds, resulting in the impeding of wound healing, separation of the wound edges (dehiscence), and increase in the risk of abscess in deeper wound tissues. At least 5% of patients undergoing surgery develop SSIs, which increase the duration of hospitalization by 20-fold and result in a greater risk of readmission and higher healthcare costs.[286] Sutures can be a source of surgical wound contamination because of their nonshedding surface to which bacteria can adhere, form biofilms, and potentiate SSIs. The presence of foreign materials in a wound enhances the susceptibility

**Table 7.** Commercially Available Honey Products Used in Wound Healing

| Commercial Name | Company | Forms | Honey Type |
|---|---|---|---|
| MGO™ Manuka Honey | Manuka Health, New Zealand Ltd. | Pure honey | Manuka honey |
| Manuka Fill® | Links Medical, Irvine California | Sterile Manuka honey | Manuka honey |
| Manuka IG® | Links Medical | Honey-impregnated gauze | Manuka honey |
| Surgihoney™ | H&R Healthcare, Hull UK | Pure honey | Bioengineered honey |
| TheraHoney® | Medline | Sheets, ribbon, gel | Manuka honey |
| Medihoney® | Derma Sciences | Hydrogel colloidal sheet, honey colloid dressing, calcium alginate dressings, gel, and paste | Manuka honey |
| Activon® | Advancis Medical, Kirkby UK | Knitted viscose mesh dressing, pure honey | Manuka honey |
| Algivon® | Advancis Medical | Alginate ribbon and dressing | Manuka honey |
| Actilite® | Advancis Medical | Composite foam/silicone dressings, nonadherent viscose net dressing | Manuka honey |

of surrounding tissues to infection and in the presence of sutures only 100 colony-forming units (CFU)/mg are necessary to produce infection.[287] Bacteria can also contaminate the suture itself making local mechanisms of wound decontamination become ineffective.

To reduce bacterial adherence and colonization of suture materials, sutures impregnated or coated with antibacterial agents have been developed. Suture materials, especially braided or twisted sutures, are frequently coated to facilitate their handling properties, and the incorporation of antibiotic drugs or silver ions is one of the approaches adopted to impart antimicrobial activity. Ideally, an antimicrobial-impregnated suture should prevent bacterial adhesion and biofilms formation using antiseptic drugs with a rapid, potent, and broad microbiocidal spectrum, long-lasting effects, and no risk of developing antimicrobial resistance. Furthermore, they should be biocompatible with medical products, not impair healing processes, and be well tolerated in wounds with no toxicity or systemic absorption. Even though the development of an antibacterial surgical suture has been under consideration since the early 1980s, the first commercial antimicrobial suture, Polyglactin 910 suture loaded with triclosan (Vicryl Plus®), was only approved for clinical use by the FDA in 2002. Different polymeric triclosan-coated sutures are actually on the market, but clinical studies are still unclear about the real effectiveness of these antibacterial sutures.[286] The main disadvantage of triclosan is that its widespread use in nonmedical products such as cosmetics, soaps, and detergents has resulted in a rise in triclosan-resistant bacteria.

The enormous market potential of this device makes research into antimicrobial surgical sutures very attractive, and as a result, new potential alternatives to triclosan are currently under investigation. A suitable alternative to overcome triclosan bacterial resistance is chlorhexidine, a broad spectrum antimicrobial agent principally used as oral antiseptics. Chlorhexidine-coated sutures were recently successfully developed using different fatty acids as coating material to achieve a high antimicrobial efficacy and biocompatibility.[288] In addition, silver[289] and AgNPs[290] have been proposed for suture coating, showing anti-inflammatory and antimicrobial activities suitable for potential clinical application.

This new generation of suture materials, when used to deliver GFs, enzymes, or other biomacromolecules directly to the wound site, can result in significant improvement beyond the currently employed surgical procedures. Several studies have demonstrated the possibility of incorporating GFs into polymeric bioadsorbable coating materials. Bigalke et al.[291] investigated a poly(L-lactide) coating on a commercially available suture for the delivery of VEGF. The authors obtained a well-tuned VEGF release from the suture wire, which resulted in an increased vascularization and consequent wound healing enhancement. Other GFs, such as insulin-like growth factor 1 or growth differentiation factor-5, have been investigated and observed to promote healing in rat models of anastomoses[292] and tendon repair,[293] respectively. An innovative approach for GFs release from a suture wire was proposed by Reckhenrich et al.[294] who prepared a surgical suture filled with ADSCs to provide pro-regenerative features and allowed the treatment and the fixation of the wound in one single step. The incorporation of ADSCs into the inner core of the suture did not affect their viability and the cells remained attached to the suture materials after implantation, constantly releasing cytokine and GFs. However, the low mechanical properties of this ADSC-loaded suture (because of the filling procedure) restrict their use only to elastic tissues.

Tissue degradation is a problem that often occurs at the repair site, resulting in increased risk of postoperative leakage. Implantation of a foreign material into the tissues invariably evokes a reaction, characterized by an elevated production of MMPs, an enzyme that degrades the ECM, allowing the suture to cut through the tissue and thus contributes to repair site elongation and gap formation. Medicated sutures coated with doxycycline, an MMP inhibitor, were used to improve the suture-holding capacity in tendon repair procedure during early repair of collagenous tissues.[295]

Though coating has been shown to be an easy procedure to prepare drug-loaded sutures, such fabrication procedures can have negative effects on the suture's mechanical strength, especially at the site of the knot, which is essential for effective wound closure. Moreover, it has been shown that suture coatings can lead to physical disruption of the bioactive reagent during the mechanically bearing suturing process.[296] To overcome these limitations, new strategies have been developed. For example, Lee et al.[297] prepared a composite surgical dressing by assembling together a drug-loaded biocompatible polymeric sheet with a surgical suture material, which enabled controlled delivery of an analgesic drug and is already in clinical use. The drug-loaded suture showed good biocompatibility and mechanical properties comparable to those of the original surgical suture, and by modifying only the polymeric sheet, it is possible to tune the drug release for up to 6 days, effectively relieving the pain at the surgical site during the period of wound healing. Drug-eluting electrospinned fibers have been proposed for the local delivery of antibiotics[298] and local anesthetics,[299] but their weak mechanical properties and the difficulty of scaling up make these sutures difficult to be applied in clinical settings.

Extrusion processes are usually employed for the large-scale synthetic production of sutures because they allow a precise and controlled manufacturing process resulting in uniform and reproducible properties. However, the high temperature required to melt the polymers can degrade the bioactive molecules, limiting the application of this process in the biomedical field. To protect the drugs from degradation, inclusion of active drugs into an organic or inorganic microstructure that can be dispersed in the polymeric matrix during the extrusion phase has been proposed.[300] Medicated sutures containing an anti-inflammatory agent loaded into an inorganic-layered material has already been developed, showing the potential of this approach.[301]

## TISSUE-ENGINEERED SKIN SUBSTITUTES

For wounds where there has been excessive skin loss or damage, in which both epidermal and dermal skin layers are lost, wound healing using only dressing materials or delivery of active agents alone is not viable. Therefore, alternative solutions using either artificial or bioengineered skin substitutes are required to allow the necessary regeneration and replacement of lost tissue. According to Mansbridge, tissue-engineered skin substitutes, function effectively largely because of the ability of fibroblasts and keratinocytes to spontaneously form three-dimensional structures similar to skin, though other cell types have been included that allow a wide range of properties naturally displayed by normal intact skin.[302] Limova[303] in 2010 made the following poignant summary about these highly advanced wound healing products: “extensive skin loss and chronic wounds present a significant challenge to the clinician. With increased understanding of wound healing, cell biology and cell culture techniques, various synthetic dressings and bioengineered skin substitutes have been developed. These materials can protect the wound, increase healing, provide overall wound coverage and improve patient care. The ideal skin substitute may soon become a reality,” Since this observation, several advances have been made in this field and skin substitutes represent a significant improvement over modern moist dressings and advanced drug delivery (medicated) dressings. In addition, they also provide a more convenient alternative to the harvesting and use of skin grafts from healthy areas of the body as these are very painful and self-defeating because of the need to create a wound elsewhere in the body.

Unlike dressing or direct regenerative approaches, tissue-engineered skin substitutes comprise fabricated biomaterial polymer matrix (such as collagen) that acts as scaffolds for engineered skin substrates, which grow to actively replace lost tissue. The scaffolds possess mechanical and anatomic characteristics ideally approaching that of the tissue (normal dermis) that they are to replace.[304] The scaffold materials gradually degrade within the body, leaving behind a matrix of connective tissue with the appropriate structural and mechanical properties. Hartmann-Fritsch et al.[305] have reported on reinforced collagen hydrogels as dermal-epidermal skin substitutes in rats. Their results showed that the skin substitutes developed into a homogeneous and well-stratified epidermis over the entire surface of the grafts, with a continuous basement membrane and dermo-epidermal junction. An antibacterial scaffold was prepared by electrospinning of a solution comprising dextran, polyurethane, and ciprofloxacin hydrochloride.[306] The results showed favorable interaction between fibroblast cells and the scaffolds, in particular the ciprofloxacin-loaded matrices.[306] Jin et al.[307] also showed the potential of electrospinned nanofibers containing polycaprolactone and the plant extract of *Memecylon edule* as substrates for skin tissue engineering in burn wounds.

Several tissue-engineered skin substitutes are available on the market but these have been previously reviewed,[1] and the reader is referred to this for relevant references and more detailed discussion. However, there has been several published literature on the subject including newer models and advanced characterization of these wound healing systems, most driven by recent advances in tissue regeneration approaches including plastic surgery.

Michael et al.[308] proposed a mouse model for the functional characterization and testing of skin substitutes using the dorsal skin fold chamber of mice. They inserted commercial dermal construct (Matriderm®; MedSkin Solutions Dr. Suwelack AG, Billerbeck Germany) covered with collagen gel, into full thickness wounds in the skin fold chambers and showed good integration into the nearby healthy skin and wound epitheliazation within 11 days. They suggested that such a model could be useful in situations where a lack of sufficient areas for obtaining split thickness skin grafts becomes an issue.[308] Morissette Martin et al.[309] investigated the effect of tissue-engineered biological dressing matrices loaded with human *in vitro*-differentiated adipocytes and ADSCs by evaluating re-epithelization, granulation tissue formation, and neovascularization of full-thickness cutaneous wounds in fluorescent epidermis of a mouse model.[309] It was demonstrated that the tissue-engineered treated wounds showed significantly faster wound closure than control wounds without the dressing application over an 18-day period. They also showed by noninvasive imaging of green fluorescent protein-expressing keratinocytes that the rate at which the wounds re-epithelized was similar for both groups with the treated wounds exhibiting thicker collagen-enriched granulation tissues. It was concluded from their study that composite engineered substitutes comprising both adipocytes and ADSCs have potential to stimulate cutaneous wound healing when applied as temporary dressings. Table 8 summarizes other reported uses of tissue-engineered skin substitutes for treating various types of wounds including chronic wounds.

## ADVANCED WOUND HEALING THERAPIES

### Oxygen-Associated Therapies

A significant number of recent research studies have demonstrated the importance of oxygen in the field of chronic wound healing.[316,317] Oxygen plays an essential role in support of cellular processes and infection control, and it is commonly accepted that inadequate cellular oxygenation and perfusion leads to impaired wound healing, triggering wound maceration, and delayed healing.[318] Chronic wounds, in particular diabetic ulcers, usually have a compromised circulation because of a disruption

**Table 8.** Selected Tissue-Engineered Substitutes Reported in the Literature for Application to Different Wound Types Including Chronic Wounds

| Matrix | Construct Source | References |
|---|---|---|
| Collagen | Human dermis | Netchiporouk et al.[310] |
| Collagen-elastin | Human subcutaneous adipose tissue | Keck et al.[311] |
| Synthetic electrospun polylactide | Finely minced split thickness human skin | Sharma et al.[312] |
| Collagen | Living skin substitute | Wahab et al.[313] |
| EGF incorporated gelatin microspheres | Bone-marrow-derived mesenchymal stem cells (BM-MSCs) | Huang et al.[314] |
| 3D fibrin/collagen type 1-hydrogels | Human dermo-epidermal skin substitutes | Klar et al.[315] |

of the blood flow or edema, which decreases or prevents oxygen delivery to healing cells.

Hyperbaric oxygen therapy was originally designed for use in decompression illness in deep sea divers and has been used as an adjunct in wound healing for 40 years.[319] This treatment involves placing the patient in a sealed chamber where 100% oxygen is pressurized to between 1.5 and 3 atmospheres absolute for 60–120 min over a course of multiple treatments. Hyperbaric oxygen significantly increases the oxygen saturation of plasma, raising the partial pressure ($PaO_2$) available to tissues, which in turn causes vasoconstriction. This vasoconstriction on the arterial end reduces capillary pressure, which promotes fluid absorption into the venous system, thereby reducing edema as well as causing an increase in hyperoxygenated plasma to the tissues. Tissue repair processes such as collagen elongation and deposition and bacterial killing by macrophages are dependent upon oxygen; therefore, increased levels in wound areas that already have impaired perfusion serve to facilitate wound healing. The application of hyperbaric oxygen is particularly advantageous in patients with diabetic foot ulcers where it is associated with significantly higher rates of wound healing and could significantly reduce the risk of major amputation.[316,320,321] In addition to immediate assistance in healing, hyperbaric oxygen also has a role in long-term wound improvement, perhaps because of the realization of the full effects of neovascularization.[322]

Topical wound oxygen therapy is an alternative method of administering oxygen to a wound, where 100% humidified, pressurized oxygen is directly applied to the surface of an open, ischemic wound in order to increase the local oxygen levels in the tissue. This route of administration involves injecting pure oxygen into a portable inflatable bag, which encases the wound area. Topical oxygen therapy, used as an adjunct to other therapies, has been shown to be effective for wound healing,[323,324] and the low costs, greater portability, and reduced risks of oxygen toxicity make this approach more beneficial than hyperbaric oxygen.[316] However, both these therapeutic approaches are time-consuming and inconvenient for the patient because of the required immobility during treatment.

The use of a therapeutic wound dressing to deliver oxygen directly to the cells may be an interesting strategy as it is more cost-effective, portable, and presents the possibility of promoting more rapid wound healing. Topically delivered dissolved oxygen has no deleterious effects and stimulates beneficial effects even on intact, nonwounded skin.[325] Furthermore, these dressings maintain some of the properties of an ideal[1] wound dressing providing all the desirable useful features to promote effective wound healing. Different approaches have been proposed to obtain local oxygen release from wound dressings. Oxygen can be stored inside the dressing between an occlusive upper layer and a lower permeable film, which allows the dressing to supersaturate the wound fluid with regenerative oxygen for days. These "oxygen reservoir dressings" are foam-based systems containing oxygen microbubbles that begin to "dissolve" when the foam is moistened with exudate, and once dissolved, oxygen can easily travel according to the oxygen gradient across poorly perfused tissue. Transcutaneous-dissolved oxygen was demonstrated to promote wound healing and limit necrosis, thus decreasing the healing time and the pain at donor sites.[326,327]

Table 9 shows some of the commercially available topically delivered dissolved oxygen dressings. Oxyzyme® dressing (Crawford Healthcare Ltd) is an enzyme-activated hydrogel dressing developed to support the wound healing process by releasing oxygen and also impeding microbial growth because of the release of iodine. The dressing is a two component advanced hydrogel containing glucose oxidase to generate hydrogen peroxide and a halide iodide to generate hypoiodite that leads to iodine production. When the dressing is removed from its airtight package and the two layers are brought into contact with each other, the oxidase enzyme within the top layer is ready to start its reaction with oxygen. The enzyme activation generates a flow of hydrogen peroxide in the dressing. When applied on the wound, the hydrogen peroxide is converted to water and dissolved oxygen by serum catalase in the wound.[328] The wound bed becomes rich in locally available oxygen, with all of its associated benefits, to work in harmony with the antimicrobial effects of the iodine and various other optimizing effects of the dressing. A similar product (Iodozyme®; Crawford Healthcare Ltd.) has been developed for patients with chronic infection or bacterial bioburden using the same principle and differs only in the amount of iodine produced. Both dressings have lower levels of iodine if compared with other iodine-based dressings, but have similar antimicrobial properties.[328]

## Negative Pressure Wound Therapy

Negative pressure wound therapy (NPWT), also known as topical negative pressure therapy or vacuum-assisted closure, has become an integral part of modern wound care practice and is used routinely in hospitals throughout the world, where it is estimated that 300 million acute wounds are treated globally each year.[329–331] Morykwas and coworkers[332,333] first reported on this NPWT using an open-cell foam dressing with the application of a controlled subatmospheric pressure for the treatment of acute and chronic wounds. NPWT promotes wound healing by applying a vacuum through a special sealed dressing. The continued vacuum draws out fluid from the wound and increases blood flow to the area.

**Table 9.** Commercially Available Topically Delivered Dissolved Oxygen Dressing

| Commercial Name | Company | Form | Oxygen delivery System | References |
|---|---|---|---|---|
| Oxyzyme® | Crawford Healthcare Ltd, Knutsford UK | Two-part sterile hydrogel dressing | Enzyme-activated *in situ* oxygen production | Moffatt et al.[328] |
| OxyBand® | OxyBand Technologies Inc, St Louis Missouri. | Self-contained multiple layers hydrocolloid dressing. The top layer is a waterproof barrier film | Oxygen prefilled wound dressing | Lairet et al.[326] |
| Oxygenesys® | Halyard Health Inc, Alpharreta Georgia. | Adsorbent foam dressing | Oxygen prefilled wound dressing | Kellar et al.[325] and Zellner et al.[327] |

Preclinical and clinical studies have confirmed that NPWT provides a moist wound healing environment, drains exudate, reduces tissue edema, contracts wound edges, mechanically stimulates the wound bed, alters blood flow in and around the wound edges, and stimulates angiogenesis and the formation of granulation tissue.[332–334] The beneficial effects of NPWT on wounds are mediated by multiple mechanisms, which together contribute to the observed clinical effects. However, little is known about the influence of different NPWT settings on their biological activity in the wound.

The dressings used for the technique include open-cell foam dressings and gauze with a pore range of 400–600 μm cut to fit the wound surface and sealed with an occlusive dressing intended to contain the vacuum at the wound site. The open-cell polyurethane foam dressing enables equal distribution of the negative pressure over the entire wound bed and also allows exudate to flow freely for collection and removal in the canister. The foam can be used to pack open cavity wounds and can also be cut to size to fill underlying areas. The pore size of the NPWT foam dressings are larger than other foam dressings to maximize tissue growth.[332] The first device for NPWT introduced on the market was the V.A.C.® Therapy System (KCI) and was the only commercially available system until 2003. With the acceptance of the method, different devices were introduced with the main difference between them being the type of dressing used to fill the wound (foam or gauze).

Negative pressure wound therapy can be used to achieve a variety of treatment goals, but cannot replace surgical procedures. The therapeutic efficacy depends on the patient and the characteristics of the wound[329] and usually may allow a wound to progress to the point at which a less invasive procedure is possible.[335] NPWT can also be used in cases of infected wounds, as an adjuvant to an appropriate systemic antibiotic therapy. The application of negative pressure creates a hypoxic environment at the wound bed–dressing interface reducing the bacterial count at the wound bed up to 1000 times after 4 days of treatment.[336] As its mode of action is not selective, NPWT is effective against difficult infections such as MRSA and drug-resistant bacterial strains. Commercially, a foam dressing coated with silver (GranuFoam™; KCI) was developed to impart additional antimicrobial properties.[337]

## Physical Therapies in Wound Healing

### *Electrical Stimulation*

Electrical stimulation (ES) is believed to aid in wound healing for the treatment of both acute and chronic wounds by imitating the natural electrical current that occurs in injured skin. The body naturally creates and uses electrical energy that aids in the recruitment of cells necessary for healing through a process called galvanotaxis or electrotaxis.[338] The undamaged skin contains an electropotential of 30–100 mV between the *stratum corneum* and the dermis; however, when the epithelial cells break down because of injury, this difference in potential is lost. This loss in potential is the earliest indicator stimulus signal to initiate cell migration, and re-epithelization and many epithelial cells including human keratinocytes have the ability to detect electric fields and respond with directed migration.[339] In addition, other cell types such as neutrophils, macrophages, and fibroblasts seem to be sensitive to ES, increasing the migration rate.[340] Some experiments have indicated that when the electric field is removed, the wound healing rate is 25% slower.[338]

The clinical evidence for the application of different types of ES to enhance cutaneous wound healing has recently been summarized by Ud-Din and Bayat.[341] ES has been shown to have beneficial effects on the different phases of cutaneous wound healing in both chronic and acute wounds, concluding that the application of an electric potential on the wounded skin results in a significant improvement in wound area reduction or accelerated wound healing compared with the standard methods of care as well as improved local perfusion.[341] Additionally, ES has action against bacterial infection, a major cause of impaired wound healing.[342] Usually, the ES is applied using an external device by placing the electrodes on the skin and often directly onto the wound. Many different modalities of ES have been described for each wound type with varying voltages, currents, electrical waveforms, modes, and length of time of application, and no device-related complications or adverse effects have been reported in the existing literature, indicating that the therapy is safe and easy to use.[341]

Bioelectric dressings (BED) are emerging as a useful method of delivering ES to the wound site. This device combines the beneficial wound repair characteristics of both an occlusive dressing and an electrical gradient and simultaneously utilizes two separate mechanisms that have been shown to aid wound healing. One of the first BEDs introduced on the market was PosiFect® RD (Biofisica UK Ltd, Basingstoke UK), which contains a miniature electrical circuit that delivers a microcurrent derived from two lithium nonrechargeable coin cell batteries to the wound bed for a minimum of 48 h. This device has been demonstrated to have potentially multiple positive effects on all phases of wound healing, in particular in treating chronic wounds that have previously been nonresponsive to treatment.[343] A new bioelectric bandage based on the PROSIT™ technology was approved by the FDA to treat partial and full-thickness wounds. Its dressing form, Procellera®

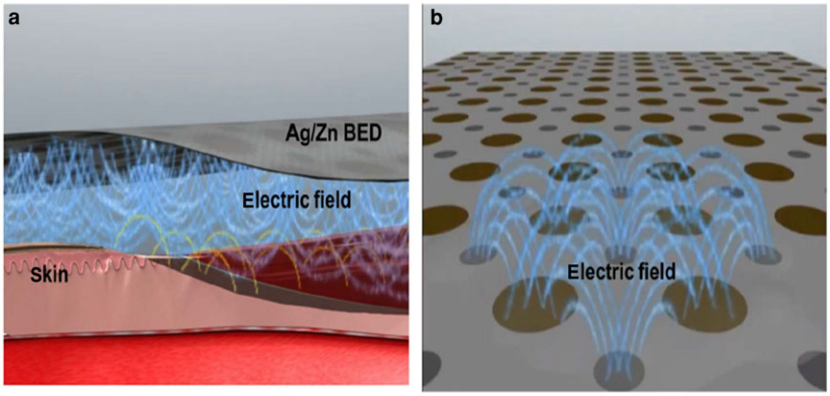


**Figure 4.** Schematic diagram of the design, application (a), and electric fields (b) generated by Procellera® bioelectric dressing.[344]

(Vomaris Wound Care Inc, Tempe Arizona.) is a woven metallic BED (Fig. 4a) activated by wound exudate, thereby generating a sustained electric stimulation of 2–10 mV produced by microbatteries of silver (Ag) and zinc (Zn) metals, which are inside a woven material (Fig. 4b). After its application, the wound is covered with an overlying dressing to keep the wound moist and the dressing active for up to 30 days. The application of an electric field generated by Ag/Zn BED increases keratinocyte migration, a critical event in wound re-epithelization, via redox-dependent processes,[344] resulting in faster wound epithelization and improved scar appearance.[345,346] In addition, it showed antimicrobial properties against antibiotic-sensitive strains and multiple antibiotic-resistant strains of wound pathogens,[347] even when these bacterial strains formed a polymicrobial biofilm.[348] Procellera® can be easily cut to the size of the wound and conforms to irregular surfaces and to wound edges. The main advantage of these devices is that they are wireless with no need for an external power source and can be applied and changed easily without the requirement for someone specially trained in ES.

### *Pulsed Electromagnetic Therapy*

The use of pulsed radio frequency electromagnetic field (PEMF) therapy has shown notable success in healing of chronic wounds. PEMF is a nonionizing energy at the shortwave radio frequency band of the electromagnetic spectrum, commonly at a frequency of 27.12 MHz and widely used in the field of orthopedics. This therapy is noninvasive and can also be applied to the wound area through wound dressings to aid healing of chronic wounds such as venous leg ulcers.[349] Furthermore, it has been reported that PEMF can also provide analgesic benefit to patients following surgery or other soft tissue trauma, with few reports of side effects.[350]PEMF devices such as Provant® (Regenesis Biomedical Inc, Scottsdale Arizona) are already being used for the treatment of chronic ulcers and postoperative pain, and a new wearable PEMF device was successfully used for the treatment and healing of four patients with nonhealing wounds.[351] However, though the application of electromagnetic fields to the wound area significantly improved both diabetic and normal wound healing in mice,[352] there is no clinically relevant evidence to show that electromagnetic therapy increases the rate of healing of venous leg ulcers in patients and further research is therefore needed.[349,353]

### *Low-Level Laser Therapy*

Low-level laser therapy (LLLT) is a medical procedure that uses red and near-infrared monochromatic light (600–1000 nm) to enhance the body's natural healing processes. When the light source is placed in contact with the skin, the light energy (photons) penetrates into the tissue, where it alters the healing process at a cellular level. It is not exactly clear how LLLT works, but some reports[354] suggest that photons are absorbed by the mitochondria and stimulate more ATP production and low levels of reactive oxygen species. These then activate transcription factors such as NF-κB, to induce many gene transcript products that provide the beneficial effects.[354] The way light interacts with the biological tissues will depend on the characteristics and parameters of light devices, but there is evidence that coherent (laser) and noncoherent (LED) lights produce similar healing effects on tissues.[355] LLLT has been reported to promote osteogenesis,[356] wound healing, and the eradication of bacterial biofilms.[335] Currently, a large number of basic studies have reported biostimulative effects of LLLT on different types of chronic wounds both in animal models and in humans, but until now, there is insufficient evidence to establish the usefulness of LLLT as an effective tool in wound care management.[357–360] Further work is therefore required to confirm its clinical effectiveness in a conclusive way including randomized clinical trials.

## CONCLUDING REMARKS

Chronic wounds and other difficult-to-heal wounds have significant health, social, and economic burdens on both patients and society in general and therefore of current topical interest worldwide.

In this review, we have covered the current state of the art in chronic wound healing technologies involving the active treatment of these wounds, with emphasis on advanced therapeutically active systems and methods for healing of chronic and other difficult-to-heal wounds. The driving forces for the development of advanced dressings as improvements over currently used traditional and modern moist dressings, the evolution of the different advanced wound dressings reported in the literature and available commercially, have also been discussed. The major driving forces include the rise in an aging population and therefore increased incidence of pressure and venous leg ulcers, increase in obesity, and associated type II diabetes, linked to diabetic chronic ulcers as well as the rise of super antibiotic resistant microorganisms (mainly bacteria). All of the above increase the risk of delayed wound healing and potential morbidity (including amputations) and in severe cases, mortality. Other driving forces include the need to reduce cost to National Health Providers, by reducing hospital stays and nursing staff time spent with chronic wound patients.

The review has covered many advanced wound dressings, including biological dressings from natural biomaterial polymers (e.g., chitosan, collagen, and hyaluronic acid), medicated modern dressings using agents such as antimicrobials (antibiotics, silver, PHMB, AMPs), biological-based dressings (comprising mainly GFs, stem cells, nucleic acids, and other genetic materials), tissue-engineered skin substitutes, dressings containing naturally derived wound agents such as aloe and honey, as well as more recent advances in NPWT, oxygen-related dressings, ES, and laser therapy. Several challenges still remain in tackling the problems associated with chronic wounds, and it is clear that even single advanced dressings and other advanced physical wound healing procedures do not always address the problems encountered in chronic wounds for every single patient and therefore a combination of the above-mentioned advanced systems will be required.

It is plausible that this will be the way forward in future developments for an ideal advanced dressing that will tackle the problems of chronic wounds including pain and inflammation, odor, infection caused by resistant bacteria, delayed healing, and associated costs to health systems and populations worldwide. This is important given the many phases of wound healing and differences in complications observed in different patients. Therefore, a multitargeted approach appears to be the best way forward and it is hoped that this review has contributed toward identifying the critical factors that need to be tackled to make this a reality in the near to medium term future.

## DECLARATION OF INTEREST

The authors declare no potential conflict of interests with respect to the authorship, and/or publication of this article.

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