

Review

Modifications of Wound Dressings with Bioactive Agents to Achieve Improved Pro-Healing Properties

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Abstract: The great variety of wounds and the lack of an effective universal treatment method has resulted in high demand for modern treatment strategies. Traditional approaches are often ineffective on a variety of chronic wounds, such as venous ulcers or the diabetic foot ulcer. There is strong evidence that naturally derived bioactive compounds have pro-healing properties, raising a great interest in their potential use for wound healing. Plant-derived compounds, such as curcumin and essential oils, are widely used to modify materials applied as wound dressings. Moreover, dressing materials are more often enriched with vitamins (e.g., L-ascorbic acid, tocopherol) and drugs (e.g., antibiotics, inhibitors of proteases) to improve the skin healing rate. Biomaterials loaded with the above-mentioned molecules show better biocompatibility and are basically characterized by better biological properties, ensuring faster tissue repair process. The main emphasis of the presented review is put on the novel findings concerning modern pro-healing wound dressings that have contributed to the development of regenerative medicine. The article briefly describes the synthesis and modifications of biomaterials with bioactive compounds (including curcumin, essential oils, vitamins) to improve their pro-healing properties. The paper also summarizes biological effects of the novel wound dressings on the enhancement of skin regeneration. The current review was prepared based on the scientific contributions in the PubMed database (supported with Google Scholar searching) over the past 5 years using relevant keywords. Scientific reports on the modification of biomaterials using curcumin, vitamins, and essential oils were mainly considered.

Keywords: biomaterials; bioactive dressings; skin regeneration; curcumin; essential oils; vitamins; chronic wounds



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1. The Healing of Acute and Chronic Wounds

Chronic wounds occur as the result of delayed and prolonged healing of the acute wounds [1–3]. The differences between acute and chronic wounds mainly lie in the biochemical environment present in the wound bed [4]. The wound healing process is controlled by: resident skin cells, blood mononuclear cells, cytokines, chemokines, extracellular matrix, growth factors, and other regulatory molecules. In the case of the acute wound, the appropriate concentration and activity of the listed compounds leads to the controlled healing process that occurs in three main overlapping and sequential steps: the inflammatory phase, the proliferative phase, and the remodeling phase [5]. Chronic wounds are often associated with bacterial infections, which hinder the formation of new blood vessels. It leads to an imbalance between regulatory molecules involved in healing, impairs the entire process, and stops the tissue repair in one of the mentioned stages [6–8]. Most often, it is the prolonged inflammatory phase that is responsible for the chronic wound formation [9–11]. Impaired angiogenesis occurring in the chronic wounds also results in chronic hypoxia and inadequate micronutrient delivery. The mentioned phenomenon was identified in ischemic ulcers, venous insufficiency ulcers, and diabetic ulcers [12,13]. Apart from a higher concentration of matrix metalloproteinases (MMPs), chronic wounds are characterized by excessive levels of proinflammatory cytokines; deficiency of stem

cells; high levels of reactive oxygen species (ROS); and decreased levels of various growth factors, including fibroblast growth factor (FGF), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), and transforming growth factor- β (TGF- β) [7,9]. Importantly, acute and chronic wounds differ with respect to local pH level. Acute wounds have a slightly acidic environment, whereas a chronic wound bed is characterized by an alkaline pH [14]. A schematic comparison of the biochemical environment and the content of individual compounds in the wound bed is presented in Figure 1.

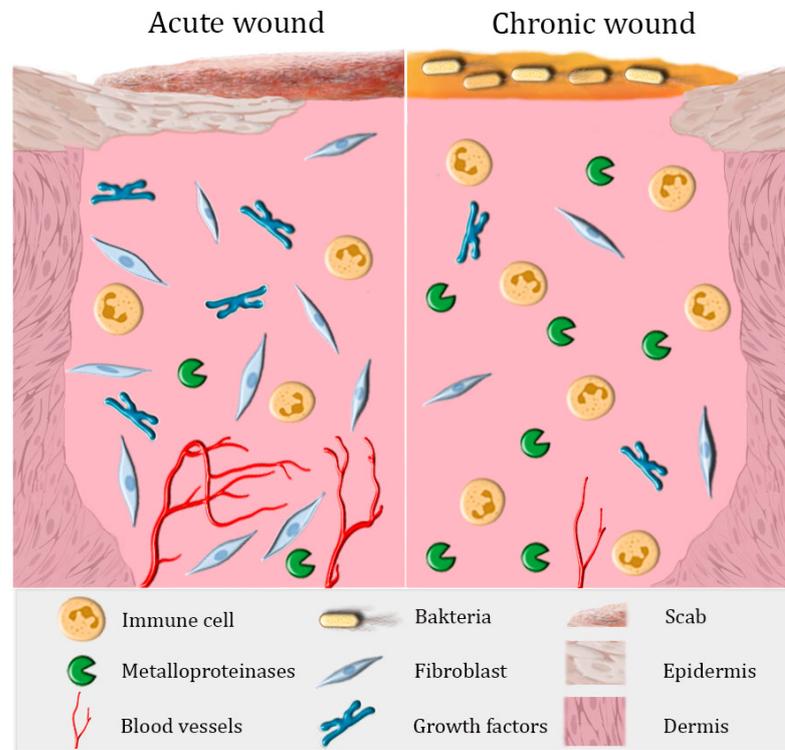


Figure 1. Schematic comparison of chronic and acute wound microenvironment.

2. Current Concepts in Wound Dressings

Accurate wound valuation—including estimation of the wound size, color, type, location, and exudate level—determines the most suitable type of the wound dressing to be used [15]. In contrast to the conventional approaches using gauze and cotton bandages in order to cover the wound, there is a broad range of polymer-based materials in the world market (e.g., gels, foams, and films) that can ensure a faster and more effective wound healing process by facilitating the function of the wound (not just covering it) [1,16]. An ideal wound dressing should: (1) absorb excessive exudates; (2) control the moisture in the wound bed; (3) possess good mechanical stability; (4) have great gases transmission; (5) protect from microorganism colonization and infections; (6) be non-toxic, biocompatible, and biodegradable; (7) ensure easy and non-painful removal after completed skin regeneration; and (8) be available at an acceptable cost [4,16–19]. The above-mentioned features are summarized in Figure 2.

A great challenge for scientists is to create an ideal dressing material that would have all the aforementioned features, providing optimal conditions for the most effective regeneration process. With the development of science, materials used in the production of the wound dressings have changed to provide better conditions for wound healing [20]. Since a moist environment is crucial for accelerated wound healing, modern hydrogel dressings containing 70–90% water have recently attracted a lot of attention. This type of dressing provides an easy application and removal without any tissue damage and can be used for burns, chronic and necrotic wounds, and pressure ulcers [1]. The most common method for hydrogel production involves polymerization of a monomer within

a cross-linked hydrogel network, whereby a second cross-linked network or a polymer is formed [21]. Conventional hydrogels are prone to breakages due to their reduced mechanical strength, limiting their clinical applications. To improve their mechanical strength, hybridization-based techniques using different polymers and strong physical and chemical interactions are used [22].

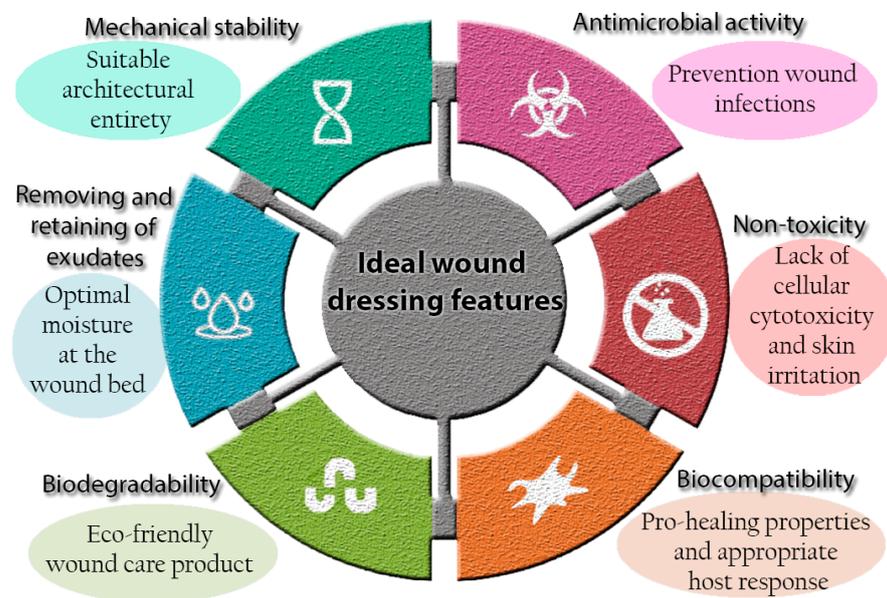


Figure 2. The features of the ideal wound dressing.

Hydrocolloid dressings are usually made of pectin, a cross-linked gelatin matrix, or carboxymethyl cellulose. This type of dressing forms a soft gel by absorbing wound fluid. They are useful for low-exuding or shallow wounds, and similarly to hydrogels they have the ability to maintain the moist environment at the wound bed [23]. Since hydrocolloids are semi-permeable to water and oxygen, it is not recommended to use mentioned dressings in strongly infected wounds due to the risk of hypoxia and increased infections [24,25]. In the case of moderately to heavily exuding wounds, it is recommended to use hydrofiber dressings, which combine the features of hydrocolloids and alginate dressings [26].

Alginate is a natural, readily available, non-toxic, and biocompatible biopolymer obtained from seaweed. It is particularly attractive in wound dressing production and application due to its high ability to maintain a moist environment and to reduce bacterial infections [27]. The most common method for alginate dressing preparation is cross-linking of the sodium alginate solution with divalent ions (calcium, barium, cadmium, magnesium, zinc, cobalt, strontium) in order to obtain a gel, which can be additionally processed to obtain a foam-like or fibrous dressing [28,29]. The absorption capacity of the cross-linked calcium alginate dressing is excellent because it is able to absorb fivefold–sevenfold more fluid compared to traditional gauze. Due to its specific features (homeostasis ability), it is recommended for the management of bleeding and highly exuding wounds [30].

Films and foams are two other large groups of dressings widely used in skin regeneration. Films protect wounds against bacterial infections, enhance regeneration, and provide optimal oxygenation and moisture at the wound bed due to their good permeability to oxygen and water vapor. The main restriction in their use is their low absorption capacity, which excludes these biomaterials from the list of suitable dressings for exuding wounds [27]. In contrast, foams have high absorption capacity due to their highly porous structure and are dedicated to highly exuding wounds. The structure of the foam dressing is usually multi-layered, made of a porous polymeric (most often polyurethane) inset with an outer germ-resistant, waterproof, and anti-adhesive layer [31]. This type of wound

dressing is also recommended for granulating wounds or lower leg ulcers, but it is not suitable for dry and eschar wounds [15,31].

A great variety of wound dressings are produced using a natural polysaccharide called chitosan. It can be processed into functional dressings, such as films, fibers, sponges, and hydrogels [3]. In view of important biological properties of the chitosan, such as biodegradability, biocompatibility [32,33], antioxidant [34–36] and antimicrobial [37,38] properties, non-toxicity [39,40], and anti-cancer properties [41,42], it is not surprising that chitosan is a frequently used compound for the production of various modern dressing materials. Nevertheless, its low solubility is a limiting factor that contributes to a growing interest when it comes to chemical modifications of this molecule [43]. Except chitosan, collagen is also frequently used in the production of wound dressings [44]. However, although it promotes wound healing, collagen-based materials are often permeable to external pathogens, limiting their clinical applications [20]. Cellulose has attracted considerable interest related to biomaterial production due to its suitable mechanical and physical properties. Moreover, it is characterized by biodegradability and low production cost, making it widely used for the fabrication of dressing materials [45].

Biomaterials for wound healing applications can be enriched with different bioactive compounds that can speed up the regeneration process. Bioactive dressings are aimed at delivering active substances (antibiotics, peptides, drugs, vitamins, growth factors etc.) to the wound environment to enhance the process of wound healing [46]. Interactive dressings directly interact with the wound bed promoting regeneration process. These interactions include removal of excessive exudate, providing a moist environment in the wound bed, and prevention of infections [47]. Importantly, interactive dressings are favorable for the re-epithelialization process due to better oxygen concentration and pH control [48]. All mentioned features of the dressings optimize the skin regeneration process. A short classification of the wound dressings is presented in Figure 3.

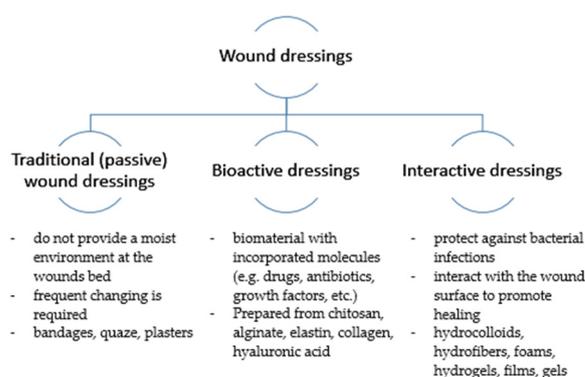


Figure 3. Classification of the currently used wound dressings.

Current review work was conducted using mainly a PubMed electronic database (supported with sporadic use of Google Scholar). The search of the available scientific contributions was limited to the last five years. The following keywords during collecting scientific reports were used: biomaterials, bioactive dressings, wound dressings, skin regeneration, curcumin, essential oils, vitamins, and chronic wounds.

3. Pro-Healing Wound Dressings

3.1. The Effect of Natural Compounds on Skin Regeneration

Plants play a significant role in conventional wound treatments. Widely used medical plants are rich in bioactive natural compounds with immunomodulatory properties. As a consequence, naturally derived active agents may control the inflammatory response and promote re-epithelialization and wound contraction [49]. According to the available literature, there are a number of natural compounds with proven favorable effects on the wound healing process. Many bioactive molecules, which can be potentially incorporated

within the structure of dressing materials, have been demonstrated to possess great effectiveness in the acceleration of wound healing process [50]. Therefore, production of biomaterial through the combination of natural or synthetic polymers with the medical plant compounds appears to be a promising strategy to create wound dressings with improved pro-healing properties. These plant-derived active agents ensure desirable properties of the biomaterial, supporting wound re-epithelialization and its angiogenesis [51]. This section focuses on the recent findings related to the production of novel dressing materials by incorporation of naturally derived bioactive compounds with pro-healing and immunomodulatory properties.

3.1.1. Curcumin-Loaded Biomaterials

Curcumin is a phytochemical belonging to polyphenolic group, occurring in a herb called *Curcuma longa*. It is one of the most active components of herbal turmeric. Due to its antioxidant, hypoglycemic, anti-inflammatory, anti-rheumatic, and antibacterial activity, this natural compound has been studied over the years [52,53]. Moreover, it is non-toxic and reveals superb biocompatibility, attracting wide interest in many biomedical research fields. However, its poor bioavailability and water solubility have contributed to its limited clinical applications. Nevertheless, curcumin is frequently used in the biomaterial production process, where it is combined with natural or synthetic polymers [54]. Currently, there are many reports in the literature on dressing materials loaded with curcumin. The latest studies concerning the evaluation of the biological properties of curcumin-enriched biomaterials are summarized in Table 1.

Table 1. Curcumin-loaded biomaterials for wound healing applications.

Type of Biomaterial	Composition of the Biomaterial	Experimental Model	Biological Properties and Advantages	Limitations	Ref.
Hydrogel	Curcumin, bacterial cellulose	In vitro (A549—human lung adenocarcinoma, MSTO—human mesothelioma, PANC1—human pancreatic ductal adenocarcinoma, U251MG—human glioblastoma, horse blood cells)	Non-cytotoxicity, antibacterial (<i>S. aureus</i>) and antioxidant properties	Not provided	[55]
Nanofiber	Curcumin, poly(3-hydroxybutyric acid-co-3-hydroxyvaleric acid) (PHBV)	In vitro (L929—mouse fibroblast cell line)	Enhanced cell adhesion and proliferation	Low mechanical properties related to high curcumin concentration	[56]
Fiber mat	Curcumin, pure poly-L-lactic acid (PLLA)	In vitro (HDFa—human adult dermal fibroblasts)	Enhanced cell adhesion and proliferation, antioxidant properties	Not provided	[57]
Membrane	Curcumin, chitosan, polyvinyl alcohol (PVA)	In vivo (rabbit model)	Biodegradability, low production cost, antibacterial (<i>P. multocida</i> , <i>S. aureus</i> , <i>E. coli</i> , <i>B. subtilis</i>) and antioxidant properties	Dedicated mainly to burn wounds	[52]
Nanofiber	Curcumin, polylactic acid (PLA), polycaprolactone (PCL)	In vitro (L929—mouse fibroblast cell line)	Antibacterial (<i>E. coli</i> , <i>S. aureus</i>) activity, hydrophobic behavior	Slight toxicity	[58]

Table 1. Cont.

Type of Biomaterial	Composition of the Biomaterial	Experimental Model	Biological Properties and Advantages	Limitations	Ref.
Film	Curcumin, chitosan, β -cyclodextrin	In vitro (NHDF—normal human dermal fibroblast cell line, NCTC clone 929 cells—mouse subcutaneous fibroblast cell line)	Enhanced mechanical properties, antioxidant activity	Slight reduction in water swelling	[59]
Hydrogel	Curcumin, PVA, TEMPO-oxidized cellulose nanofiber (TOCN)	In vitro (L929—mouse fibroblast cell line), In vivo (rat model)	Enhanced collagen organization, supported wound contraction	Not provided	[60]
Nanocomposite (gauze)	Curcumin, cotton	Not provided	Enhanced water absorption and drying time	Not provided	[61]
Hydrogel	Curcumin, cellulose–halloysite nanotube	In vitro (MC3T3-E1—mouse calvarial preosteoblasts, MCF-7—human breast cancer cell line)	Anticancer properties	Reduced cell proliferation	[62]
Nanocomposite	Curcumin, PCL, quaternary ammonium salt-modified montmorillonite (MMT)	In vitro (L929—mouse fibroblast cell line)	Enhanced antibacterial activity (<i>E.coli</i> , <i>S. aureus</i>)	Initial burst release of curcumin	[53]

Gupta et al. [55] prepared bacterial cellulose hydrogels with incorporated curcumin (that was entrapped in cyclodextrins) for potential wound treatment. The biomaterial had the antioxidant potential confirmed by DPPH test, and antibacterial activity was shown against *S. aureus*, associated with its interaction with prokaryotic cell proteins. The hydrogel showed also high water content, which was related to its porous structure, characterized mainly by nanopores (27 nm) and a few large superficial pores (<10 μ m). Multu et al. [56] developed curcumin-loaded nanofiber for wound-healing applications. Biomaterials with different curcumin content (0.1%, 0.3%, and 0.5% *w/v*) were produced and tested. It was shown that the reduction in the fiber's diameter (519–207 nm) was directly correlated with the curcumin concentration. Importantly, the highest concentration (0.5% *w/v*) of the compound increased cell proliferation and attachment. Nevertheless, high content of the curcumin resulted in decreased mechanical properties due to reduction of the fiber diameter. In another study, different curcumin concentrations (0.2, 0.5, and 1.0% *w/w*) were loaded to produce fiber mats. The researchers demonstrated that the average fiber diameter increased along with the increasing curcumin content in the composition of the biomaterial. Cell proliferation and attachment were also improved as a result of increased curcumin concentration. Furthermore, the initial release of the compound was faster for biomaterials with higher curcumin content [57]. In turn, Abbas et al. [52] produced a chitosan/polyvinyl alcohol/curcumin membrane with desirable wound healing properties by varying the content of curcumin and chitosan. The greatest reduction in a wound size (52.33% on the 7th day in a rabbit model) was obtained for the biomaterial containing the highest concentration of curcumin (30 mg). The produced biomaterial also possessed antibacterial (*P. multocida*, *S. aureus*, *E. coli*, and *B. subtilis*) and antioxidant activity. Saeed et al. [58] showed a production method of novel wound dressing using an electrospinning technique. The biomaterial was made of curcumin and polymeric mixture (PLA/PCL). The dressing material with 16% content of curcumin had strong antibacterial activity against *E. coli* and *S. aureus*, however it decreased cell viability to 60% compared to the control sample.

Kaolaor et al. [59] performed studies on the modification of curcumin-loaded biomaterial by quaternization of chitosan. As a result of the introduced changes, the water solubility of the biomaterial increased. Modified film revealed better mechanical properties and a higher curcumin release profile (higher antioxidant activity). However, it also contributed to lower biomaterial swelling properties. Shefa et al. [60] developed biomaterial through the incorporation of curcumin within a hydrogel system. The TEMPO-oxidized cellulose nanofiber–PVA–Cur hydrogel supported wound contraction and provided faster wound closure in a rat model compared to the control group. Furthermore, it was revealed that tested biomaterials loaded with curcumin enhanced collagen accumulation. Venkatasubbu et al. [61] demonstrated that curcumin coating on the cotton gauze improved the properties of the resultant wound dressing. A spin-coating technique was used to prepare curcumin nanocomposite on a cotton cloth. The introduced modification improved the average drying time and absorption capacity of the produced nanocomposite. In turn, Sadeghianmaryan et al. [53] showed enhanced antibacterial activity (*E. coli* and *S. aureus*) of the curcumin-loaded nanocomposite. Obtained PCL/quaternary ammonium salt-modified montmorillonite/curcumin nanocomposites exhibited low cytotoxicity and showed great potential for infected wound management. Interestingly, curcumin was also demonstrated to have promising anticancer activity. Huang et al. [62] proved a high inhibitory effect of the curcumin-loaded cellulose-halloysite nanotube hydrogel on human breast cancer cells (MCF-7 cell line) in vitro. Thus, it may be assumed that curcumin-loaded biomaterials may be potentially promising wound dressings for the management of the wound after skin cancer excision.

Based on presented scientific reports, it can be concluded that numerous of the biomaterial key features may be improved by the incorporation of curcumin component. Importantly, addition of curcumin not only may provide antibacterial properties of the dressing but also it can improve cell proliferation and growth or could even be used for anticancer treatment [55,59,63,64]. Moreover, curcumin-loaded biomaterials may reveal improved mechanical and physicochemical properties. Nevertheless, the concentration and composition of the biomaterial must be chosen reasonably to overcome the limitations that can appear after dressing productions (e.g., too fragile structure).

3.1.2. Essential-Oil-Loaded Biomaterials

Essential oils (EOs) are plant secondary metabolites that are characterized by antioxidant, anti-inflammatory, and antibacterial properties. Thus, EOs possess features that are useful in the chronic wound management [63]. According to the literature, EOs have also anti-tumor, anti-diabetic, analgesic, and antiviral properties [64]. Modifications of biomaterials with different EOs are presented in Table 2.

Table 2. Essential-oil-loaded biomaterials for wound healing applications.

Type of Biomaterial	Composition of the Biomaterial	Experimental Model	Biological Properties and Advantages	Limitations	Ref.
Hydrogel	Thymol, bacterial cellulose	In vitro (NIH 3T3—mouse fibroblast cell line) In vivo (rat model)	Enhanced antibacterial activity (<i>E. coli</i> , <i>S. aureus</i> , <i>P. aeruginosa</i> , <i>K. pneumoniae</i>) and wound closure speed	Decreased water vapor transmission rate	[65]
Nanofiber	Thymol, tyrosol, PCL	In vitro (J774A.1—macrophage cell line)	Anti-inflammatory activity	Not provided	[66]
Fibrous membrane	Thymol, cellulose	In vitro (L929—mouse fibroblast cell line)	Enhanced antibacterial activity (<i>E. coli</i> , <i>S. aureus</i>)	Decreased wettability	[67]
Nanofiber mat	<i>Zataria multiflora</i> essential oil, chitosan, PVA, gelatin	In vitro (L929—mouse fibroblast cell line)	Enhanced antimicrobial activity (<i>C. albicans</i> , <i>S. aureus</i> , <i>P. aeruginosa</i>)	Decreased swelling degree	[68]
Film	<i>Eugenia caryophyllata</i> essential oil, <i>Melaleuca alternifolia</i> essential oil, chitosan	Not provided	Enhanced biomaterial elasticity and flexibility	Decreased mechanical strength	[64]

Table 2. Cont.

Type of Biomaterial	Composition of the Biomaterial	Experimental Model	Biological Properties and Advantages	Limitations	Ref.
Nanofiber membrane	<i>Cymbopogon martini</i> essential oil, <i>Chamaecyparis obtusa</i> essential oil, PVA	Not provided	Enhanced antimicrobial activity (<i>S. aureus</i> , <i>C. albicans</i>) and aqueous stability	Not provided	[69]
Hydrogel	Clove essential oil, tea tree essential oil, oregano essential oil, PVA, starch	Not provided	Enhanced antibacterial activity (<i>E.coli</i> , <i>S. aureus</i>)	Decreased mechanical strength	[70]

Jiji et al. [65] incorporated thymol (which is primarily isolated from *Thymus vulgaris* EO) into bacterial cellulose hydrogel in order to improve biological properties of the biomaterial. The introduced modification not only increased the antibacterial activity against *E. coli*, *S. aureus*, *P. aeruginosa*, and *K. pneumoniae*, but also promoted faster wound closure in the in vivo rat animal model. Nevertheless, the conducted tests showed that the biomaterial with the addition of thymol had reduced water vapor permeability compared to the control sample. Similarly, Chen et al. [67] evaluated the effect of thymol addition to the cellulose fibrous membranes on their antibacterial properties. It was shown that porous biomaterial with the highest content of thymol (15%) revealed the best antibacterial properties (bacteria survival rate equal to 0.07% for *S. aureus* and 0.09% for *E. coli*). However, the water contact angle of the sample surfaces increased with the increased content of thymol in biomaterials. In turn, García-Salinas et al. [66] investigated the impact of EO-derived compounds on the biomedical properties of electrospun PCL nanofibers. The biomaterial produced by incorporation of thymol revealed anti-inflammatory activity and showed the ability to reduce size of inflamed cells. In another study, Ardekani et al. [68] focused on the modification of nanofiber mats with an essential oil obtained from *Zataria multiflora*. The study revealed a decreasing degree of biomaterial swelling with increasing content of the essential oil that may be related to its hydrophobic nature. Moreover, enhanced antimicrobial activity (*C. albicans*, *S. aureus*, and *P. aeruginosa*) of produced EO-loaded biomaterial was observed without cytotoxic effect on mouse fibroblast cell lines. Pereira dos Santos et al. [64] produced chitosan films with the addition of various content of EOs obtained from *Eugenia caryophyllata* and *Melaleuca alternifolia*. Obtained results showed that EOs did not affect the hydrophilicity of the tested films. However, the maximum tensile strength value recorded for pure chitosan biomaterial was higher than value estimated for EO-loaded samples, indicating reduced mechanical strength of the modified films. Nevertheless, the addition of the EOs improved elasticity and flexibility of the films. In turn, Lee et al. [69] modified biomaterial with EOs from palmarosa grasses and hinoki cypresses. Membranes containing palmarosa oil revealed better antimicrobial activity against *S. aureus* and *C. albicans* compared to phytoncide oil. It was also confirmed that the biomaterial's aqueous stability was enhanced by the heat treatment method. To provide better antibacterial activity, Altaf et al. [70] used different EOs (clove oil, tea tree oil, and oregano oil) in the production of potential wound dressings. It was revealed that pore generation and mass immiscibility were significantly affected by increasing oil concentrations. Among all tested natural compounds, the strongest inhibition of bacterial growth (*E.coli* and *S. aureus*) was obtained with clove-oil-loaded biomaterial.

The use of EO-derived compounds for the production of biomaterials mainly contributed to the increase of their antimicrobial activity and wound regeneration speed. Side effects and limitations related to the addition of EOs to the biomaterial were basically associated with a reduction in physicochemical and mechanical properties, decreasing mechanical strength, swelling degree, water vapor transmission rate, and material wettability [67–73]. Nevertheless, the rationality of using plant compounds is strictly dependent on the type of wound and treatment strategy, where giving preference to chosen properties requires some consideration.

3.2. The Effect of Vitamins on Skin Regeneration

Unique polymer-based biomaterials can be used as novel drug delivery systems, providing a new treatment strategy of non-healing chronic wounds. A high range of medicinal substances, such as antibiotics, vitamins, growth factors, anti-inflammatory agents, anesthetics, etc., are used in the fabrication of wound dressings in order to alleviate the inflammatory response and support the healing process [71]. Nevertheless, bioactive dressings are most often loaded with antibiotics to fight bacterial invasion or vitamins to support cell proliferation and stimulate wound healing mediators, accelerating the regeneration process. Moreover, vitamin-enriched dressings may reveal antioxidant properties, which are desired in the management of chronic wounds characterized by excessive ROS generation [72,73].

Vitamins are widely used in various cosmetic products and creams due to their leading significance in wound healing and skincare. Nevertheless, their low bioavailability due to the fast oxidation process results in the high demand for good drug delivery systems. Biomaterial-based drug carriers should be characterized by gradual compound release to overcome the problem of its low bioavailability [74]. Among many vitamins, tocopherol (vitamin E), L-ascorbic acid (vitamin C), and retinol (vitamin A)—which possess anti-inflammatory and anti-oxidant effects—have attracted the greatest attention in the context of wound dressing fabrication. Deficiencies in L-ascorbic acid result in decreased collagen synthesis, impaired angiogenesis, and reduced fibroblast proliferation. Its deficiency is also associated with increased susceptibility to the wound infections because of impaired host immune response [75–78]. It was proven that vitamin A significantly improves the wound healing process. Retinoic acid formed by the metabolism of retinol increases fibroblast proliferation, however with simultaneous reduction in collagen synthesis [79]. Vitamin E facilitates wound protection against numerous infection and supports wound healing due to its antioxidant properties, stabilization of granulation tissue, and stimulation of re-epithelialization [80,81].

Bioactive Dressings Enriched with Vitamins

It is well known that vitamin C is crucial for the wound healing process. In our previous study, it was confirmed that the addition of vitamin C to a chitosan/agarose foam-like dressing supported fibroblast viability and proliferation. Furthermore, biomaterial with incorporated L-ascorbic acid supported PDGF-BB synthesis and had the ability to reduce MMP-2 production by skin fibroblasts [73]. Importantly, Voss et al. [82] described a synergistic effect on the wound closure in a mouse model after application of the dressing material produced by combination of vitamin C and propolis. Cellulose/PVA film with the addition of propolis and vitamin C also revealed higher absorption capacity, antibacterial activity against *E. coli* and *S. aureus*, and controlled vitamin release. Similarly, Madni et al. [83] used vitamin C for the modification of the chitosan-based membrane to achieve accelerated wound healing. The developed biomaterial, which was also loaded with lactic acid, exhibited excellent biocompatibility under in vitro conditions (mouse fibroblast cell line), however vitamin addition negatively affected biomaterial mechanical properties by inducing its fragility. Farzanfar et al. [74] demonstrated positive impact of the vitamin B12 on wound closure in a rat model by application of nanofibrous PCL/gelatin biomaterial as a delivery system. The wound size was reduced by 92.27% in the case of vitamin B12-enriched biomaterial and by only 64.62% when scaffold without vitamin B12 was applied. Moreover, the developed nanofibrous dressing loaded with vitamin B12 had the ability to speed up re-epithelialization process. In turn, Ehterami et al. [84] investigated the effect of vitamin D3 on the repair process of skin tissue. The research showed the positive effect of the tested vitamin on the wound closure rate. Produced alginate hydrogels loaded with vitamin D3 enhanced cell proliferation compared to the control sample and vitamin-free biomaterial. The same research team also investigated the impact of different α -tocopherol (vitamin E) concentrations on wound healing in a rat model. The dose of 400 units turned out to be the most effective dose of vitamin E, which

significantly increased the rate of wound closure. Chitosan/alginate hydrogel loaded with the same dose of α -tocopherol was characterized by the best re-epithelialization among all tested samples [80]. In another study, vitamin E was used to improve antioxidant and antibacterial activities of the resultant biomaterial. Obtained data confirmed that biomaterials loaded with vitamin E significantly decreased intracellular ROS level after cell treatment with 100 μ M tertiary-butyl hydroperoxide (t-BuOOH). Nevertheless, the addition of vitamin E did not contribute to the improvement of the antibacterial properties of the tested biomaterials [85]. In turn, Li et al. [86] incorporated vitamins A and E into gelatin nanofiber using an electrospinning technique to gain better wound healing performance. A potent antibacterial property (*E. coli*, *S. aureus*) was observed in the case of the biomaterial containing only vitamin E. Cell growth investigation revealed the greatest amount of cells for biomaterial loaded with both vitamins. A positive effect of vitamin E on the wound healing process was also observed by Kheradvar et al. [87], who proved enhanced antioxidant activity of silk fibroin–PVA–*Aloe vera*/vitamin E nanofibrous dressing. It was also shown that a combination of vitamin E and *Aloe vera* gel had a positive impact on cell–matrix interaction and cellular viability.

The studies presenting a positive impact of biomaterials loaded with vitamins on wound healing process are summarized in Table 3.

Table 3. Vitamin-enriched biomaterials for wound healing applications.

Type of Biomaterial	Composition of the Biomaterial	Experimental Model	Biological Properties and Advantages	Limitations	Ref.
Foam-like, hydrocolloid type	Vitamin C, agarose, chitosan	In vitro (BJ—normal human skin fibroblast cell line)	Enhanced fibroblasts viability and proliferation, supported platelet-derived growth factor (PDGF-BB) synthesis	Initial burst release of vitamin C	[73]
Film	Vitamin C, Brazilian propolis, cellulose, PVA	In vivo (mouse model)	Enhanced absorptive capacity, accelerated wound closure rate	Not provided	[82]
Membrane	Vitamin C, chitosan, polyethylene glycol (PEG), glycerol	In vitro (NIH 3T3—mouse fibroblast cell line)	Enhanced biocompatibility	Increased fragility	[83]
Nanofibrous scaffold	Vitamin B12, PCL, gelatin (type A)	In vitro (L929—mouse fibroblast cell line), In vivo (rat model)	Enhanced wound closure rate and cell viability, increased epithelial thickness	Not provided	[74]
Hydrogel	Vitamin D3, alginate	In vitro (L929—mouse fibroblast cell line), In vivo (rat model)	Promoted cells proliferation, accelerated wound healing	Swelling percentage decreased with time	[84]
Hydrogel	Vitamin E, chitosan, alginate	In vitro (L929—mouse fibroblast cell line), In vivo (rat model)	Enhanced wound closure and re-epithelialization	Not provided	[80]
Gauzes/fibers	Vitamin E, <i>Lactobacillus plantarum</i> , Spanish Broom fibers, cotton	In vitro (BJ—normal human skin fibroblast cell line)	Enhanced antioxidant properties	Initial burst release of the vitamin E	[85]
Nanofibers mats	Vitamin E, silk fibroin, PVA, <i>Aloe vera</i>	In vitro (L929—mouse fibroblast cell line)	Enhanced cell-matrix interactions and cellular viability, antioxidant activity	Initial burst release of vitamin E	[87]
Nanofibers	Vitamin A and E, gelatin	In vitro (L929—mouse fibroblast cell line), In vivo (rat model)	Enhanced antibacterial activity (<i>E. coli</i> , <i>S. aureus</i>) and L929 fibroblast cells growth	Decreased fiber diameter	[86]

Among all the bioactive compounds that were presented in the work, vitamin-loaded dressings were characterized by the widest variety of improved properties and the lowest limitations. This indicates the possibility to significantly increase the biomedical potential of wound dressings by incorporation of vitamins into the structure of biomaterials during the production of wound care products.

4. Patented and Commercial Bioactive Dressings

Due to the high biomedical potential of some wound care products, more and more research units have decided to patent the method for wound dressing production. The European Patent Office holds thousands of patents covering wound dressings loaded with bioac-

tive agents. Our previous research resulted in two Polish patents (PL 236368, PL 236367) describing the production methods of foam-like and hydrogel-type curdlan/agarose dressing materials (Figure 4). Both types of developed wound dressings can be produced with the addition of bioactive compounds, such as vitamins, growth factors, antibiotics, or curcumin, which is reserved in the patent description. As a result of the incorporation of bioactive compounds, it is possible to obtain the preferred properties of the biomaterial and adapt it to a specific type of wound.



Figure 4. Foam-like agarose/curdlan dressing materials with different shapes and sizes produced according to Polish patent no. PL 236367.

Chinese patent, specification no. CN107475812A, describes the production method of a bioactive wound dressing based on chitosan and curcumin using electrostatic spinning. The described method allows users to obtain a porous structure of a biomaterial with antibacterial (*E. coli*) and anti-inflammatory properties. Moreover, due to the highly specific surface area of the biomaterial, it can be loaded with numerous drugs, acting as a drug delivery system. Another Chinese patent, specification no. CN110025817A, discloses a method for preparing a composite antibacterial fiber dressing containing essential oils. The obtained bioactive wound dressing is characterized by good permeability and antibacterial properties against *E. coli* and *S. aureus*. A Taiwan patent, specification no. TW201208717A, discloses a method for production of a bioactive wound dressing containing citrus extract. The method of wound dressing production with the citrus extract content is based on the wet spinning technique or soaking method. Conducted tests on chitosan biomaterial loaded with citrus extract showed enhanced cell proliferation and angiogenesis. Another Chinese patent, specification no. CN105963753A, describes the production method of an anti-bacterial film. The biomaterial described in the patent is a multicomponent dressing containing natural plant ingredients (marigold oil, tea polyphenols, red oak powder, and calendula oil) that contribute to its non-toxicity, good elasticity, and anti-infective properties.

The biomaterials presented within this article are the result of scientific activities and presently are not used in practice. However, there are many bioactive wound dressings currently available on the world market that are in wider usage as a medical wound care product. On the list of companies offering wound care materials, there are some that produce dressings enriched with a substance that accelerates the regeneration process. The German company Hartmann offers the HydroClean plus superabsorbent wound dressing, which is activated with Ringer's solution and contains polyhexanide (PHMB). Due to its composition, the dressing has antimicrobial properties, and thanks to the Ringer's fluid that is released into the wound bed, it stimulates the healing process [88]. The British company Advancis Medical offers an Algivon alginate dressing soaked in Manuka honey. Antibacterial properties are ensured by the glucose oxidase occurring in the honey. This enzyme enables the formation of hydrogen peroxide in the wound bed with an antiseptic effect and inhibits biofilm formation. In addition, biomaterial ensures the moist environment and accelerates the healing process. Algivon is dedicated to all types of wounds, especially for necrotic wounds [89]. A large group of commercial medical dressings contain silver particles, dedicated to combating a wide range of microorganisms in the wound bed. An example of commercial antimicrobial dressings containing silver particles is the

product of the Mölnlycke company, which offers Mepilex Border Ag foam dressing. This wound care silicone foam dressing contains activated carbon, silver sulphate, and a Safetac wound-contact layer. It is dedicated to moderately and highly exuding wounds, which include partial-thickness burns, surgical and traumatic wounds, pressure ulcers, or leg and foot ulcers [90]. Another dressing containing homogeneously distributed silver in its structure is called Biatain Ag. This foam-like wound care product provides a stable release of silver for up to 7 days upon contact with exudates. The conducted studies confirm its effectiveness in combating bacterial infections [91]. The Coloplast company also offers the highly absorbent Biatain[®] Alginate Ag dressing made of carboxymethyl cellulose, calcium alginate, and an ionic silver complex. Apart from antibacterial effect, this wound dressing also provides a hemostatic effect at the wound site [92]. Other silver-nanoparticle-based commercial dressings commonly used for the treatment of infected wounds include ACTICOAT[™], PolyMem WIC Silver[®], Suprasorb[®] A + Ag, and Atrauman[®] [92,93].

5. Conclusions

The presented review article focused on the recent findings regarding modifications of wound dressings that have contributed to the development of regenerative medicine. In this context, various production methods of dressing materials with improved pro-healing features were presented. The variety of already investigated bioactive compounds and applied production methods of wound dressings, which are described in the available literature, undoubtedly provide valuable scientific knowledge that can be potentially used to improve the biological properties of the existing wound dressings. Scientists around the world have modified dressing materials using various naturally derived compounds with antioxidant, anti-inflammatory, and anti-bacterial properties. The mentioned three features of the natural (often plant-derived) compounds are of high importance in the management of chronic non-healing wounds that are characterized by persistent infections, as well as excessive levels of ROS and proinflammatory cytokines. Another promising group of agents widely used for the modifications of wound dressings are vitamins, with a demonstrated positive impact on skin regeneration. Importantly, mentioned modifications of the biomaterials may not only improve the properties of the existing dressings, but also ensure the reclassification of the dressings from the ones dedicated for the treatment of acute wounds to chronic wounds. So far, scientists have proven that incorporation of bioactive molecules within the structure of the dressing material may significantly improve its biocompatibility and biological properties, ensuring a better healing process. Nevertheless, this kind of modification may negatively affect exudate absorption capacity and mechanical properties of the dressing. Therefore, there is still a necessity to continue research in order to overcome or minimize the appearance of side effects, such as mechanical property deterioration or cell proliferation reduction, associated with biomaterial modifications using bioactive agents. However, recent progress in the field of material sciences gives us hope for the development of a production method that would allow us to obtain bioactive-agent-loaded biomaterials without negative side effects. High hopes are associated with the electrospinning technique, enabling the production of advanced drug delivery systems with better predictability and control of the drug release compared to other techniques like physical/chemical adsorption or entrapment. Moreover, incorporation of bioactive agents within electrospun fibers carries lower risk of the mechanical properties worsening.

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