materials

MDPI

Review

Designing Composite Stimuli-Responsive Hydrogels for Wound Healing Applications: The State-of-the-Art and Recent Discoveries

Anna Michalicha [1], Anna Belcarz [1], Dimitrios A. Giannakoudakis [2], Magdalena Staniszewska [3] and Mariusz Barczak [4,*]

[1] Chair and Department of Biochemistry and Biotechnology, Medical University of Lublin, Chodzki 1, 20-093 Lublin, Poland
[2] Department of Chemistry, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece
[3] Institute of Health Sciences, Faculty of Medicine, The John Paul II Catholic University of Lublin, Konstantynów 1J, 20-708 Lublin, Poland
[4] Institute of Chemical Sciences, Faculty of Chemistry, Maria Curie-Sklodowska University, 20031 Lublin, Poland
* Correspondence: mariusz.barczak@mail.umcs.pl; Tel.: +48-81-537-79-92

Abstract: Effective wound treatment has become one of the most important challenges for healthcare as it continues to be one of the leading causes of death worldwide. Therefore, wound care technologies significantly evolved in order to provide a holistic approach based on various designs of functional wound dressings. Among them, hydrogels have been widely used for wound treatment due to their biocompatibility and similarity to the extracellular matrix. The hydrogel formula offers the control of an optimal wound moisture level due to its ability to absorb excess fluid from the wound or release moisture as needed. Additionally, hydrogels can be successfully integrated with a plethora of biologically active components (e.g., nanoparticles, pharmaceuticals, natural extracts, peptides), thus enhancing the performance of resulting composite hydrogels in wound healing applications. In this review, the-state-of-the-art discoveries related to stimuli-responsive hydrogel-based dressings have been summarized, taking into account their antimicrobial, anti-inflammatory, antioxidant, and hemostatic properties, as well as other effects (e.g., re-epithelialization, vascularization, and restoration of the tissue) resulting from their use.

Keywords: hydrogels; wound dressings; wound healing; controlled release; stimuli-responsive; drug delivery strategies

Citation: Michalicha, A.; Belcarz, A.; Giannakoudakis, D.A.; Staniszewska, M.; Barczak, M. Designing Composite Stimuli-Responsive Hydrogels for Wound Healing Applications: The State-of-the-Art and Recent Discoveries. *Materials* **2024**, *17*, 278. https://doi.org/10.3390/ma17020278

Academic Editor: Georgios Bokias

Received: 5 December 2023
Revised: 31 December 2023
Accepted: 2 January 2024
Published: 5 January 2024

1. Introduction

The major failure that medicine faces in terms of wound dressings is that despite their undeniable advances, they are still not as efficient as they are expected to be. Complications associated with the healing of wounds that are not cured with the currently used wound dressings still cause many global health risks as well as economic concerns. Wound-related complications affect over six million people annually in the United States, incurring a cost of USD 25 billion [1]. Chronic wounds are predominantly observed in the elderly, affecting approximately 3% of the U.S. population aged 65 and above. The aging demographic trend suggests that by 2060, over 77 million elderly individuals in the United States may deal with persistent open wounds. The advanced wound care market worldwide is expected to achieve a value of USD 18.7 billion by the year 2027, demonstrating a Compound Annual Growth Rate (CAGR) of 6.6% from 2020 to 2027 [2]. Global estimates indicate that approximately 463 million adults are currently living with diabetes, and this figure is anticipated to surge to USD 700 million by the year 2045 [2–4]. This is particularly relevant, as diabetes patients are at an increased risk of developing diabetes-related wounds. The global market for diabetic foot ulcers anticipates a favorable CAGR of 6.8% from 2019 to

2026, with a potential valuation of USD 11 billion by the end of 2026 [2]. Moreover, the global market for venous ulcers (VU) treatment is anticipated to reach USD 4.8 billion by 2026, with an annual growth rate of 6.4% from 2019 to 2026 [2,5]. Based on the data presented above, it is evident that there is an urgent need for the development of novel and effective wound dressing materials that meet the specific requirements in the treatment of different types of wounds.

Currently used commercial wound dressings show many limitations such as a lack of specific responsive properties to the changes in the environment. They are also usually applied in a one-for-all wounds manner [6]. Due to the high demand for effective wound care methods in the field of medicine, there is a growing pressure to create advanced materials tailored to accelerate the healing process in various clinical contexts [7,8]. Ideally, dressing materials are meant to protect the wound against external factors, support the epithelial renewal process, prevent bacterial infections and further damage of skin integrity, as well as to ensure adequate moisture of the wound environment [9]. Properties of available dressing materials, both the newest and the conventionally used ones, are limited by their rapid degradation, poor adhesion, inefficient exudate absorption, lack of therapeutic release properties, and inability to prevent protein adhesion to the wound dressing surface [10–12].

In the case of uncomplicated wounds, the healing process occurs in the form of a sequence of interrelated phases. These phases include hemostasis, inflammation, proliferation, and remodeling, often occurring concurrently and overlapping [13]. Depending on the consequences and pathogenesis, the wound can be qualified as acute or chronic. The primary distinction between them lies in the biochemical microenvironment and concentration of specific components within the wound site, which is schematically presented in Figure 1. Acute wounds result from trauma or surgical procedures and undergo a healing process over a specific period of time, usually within a few weeks [14,15]. They are often associated with common injuries such as cuts, lacerations, abrasions, burns, and surgical or accidental incisions [16,17]. Chronic wounds such as diabetic foot ulcers, venous leg ulcers, ischemic ulcers, pressure ulcers, and many more, are frequently associated with long-term health disorders. One of the most prevalent reasons for chronic wound occurrence is the improper treatment or infection of acute wounds [18,19]. The chronic wound healing process is delayed due to various factors. Those factors include aging, the stage of diabetic disease, medication compliance, associated peripheral neuropathy, immunocompromised status, as well as arterial and venous insufficiency [1]. In the case of chronic wounds, the inflammatory phase is prolonged [20,21]. Increased levels of inflammatory mediators can impair the functioning of growth factors and the extracellular matrix, both of which are crucial for the healing process [22,23]. They complicate the healing process and extend it up to three months. Additionally, chronic wounds often undergo bacterial infection, which can extend the inflammatory response [20,21]. It should also be noted that acute wounds, usually undergoing the above-mentioned healing stages within defined timeframes, can also be infected, which negatively affects the prognosis of their treatment [16,17].

The intact skin acts as a physical barrier, preventing bacteria and other pathogens from invading internal tissues. However, when the skin is cut, scraped, or otherwise damaged, it loses its protective integrity. The damage to the skin's protective barrier offers an opportunity for microbial invasion [24,25]. Wound infections, similar to the earlier mentioned inflammations, decrease the activity of growth factors. In addition, fibrin/fibrinogen is a target of bacterial proteins due to its role in defense against bacterial infection [20,21,26]. Bacterial infections not only have the potential to significantly slow down the wound healing process, but also pose a substantial risk of inflicting severe damage to tissues and cells. In extreme cases, they can even be life threatening.

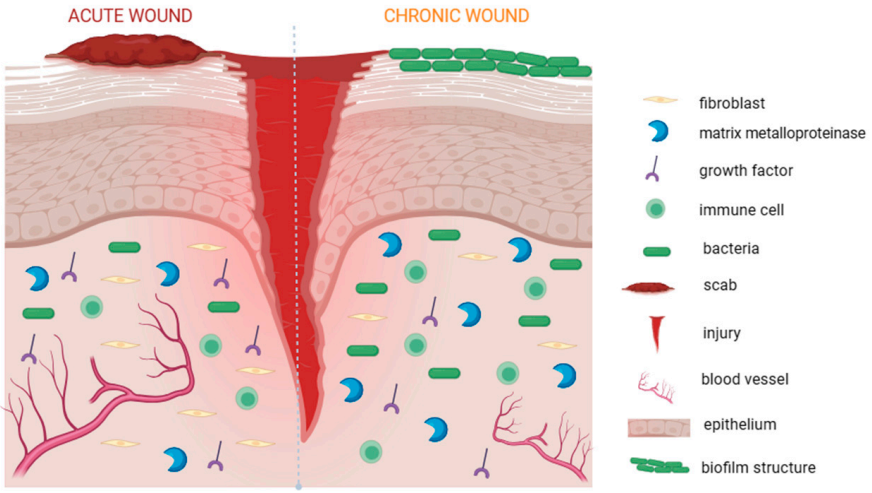

Figure 1. Differences between acute and chronic wounds, created with BioRender.com (accessed on 4 December 2023).

Interactions between the wound environment and bacteria include the contamination, colonization, local infection, and finally spreading of the infection and the emergence of a chronic wound condition [1]. As mentioned above, chronic wounds are frequently associated with bacterial infections, which can slow down the process of angiogenesis, due to the release of tissue-destroying (lytic) enzymes, exotoxins, and endotoxins; all of which potentially lead to the deterioration of wound healing [27,28]. Overall, bacterial infection can result in an imbalance of regulatory molecules that are crucial for the healing process, leading to impairment and a retention in tissue repair at one of the mentioned-before healing stages [29].

Historically, the primary approach to preventing and treating wound infections has involved the use of antibiotics. Conventional antibiotics (tetracyclines, aminoglycosides, quinolones, and cephalosporins) have traditionally been noted as successful in killing bacteria by disrupting their cell walls and interfering with essential processes such as protein and nucleic acid synthesis [30]. However, over the last few decades it has been shown that overuse or inappropriate utilization of these substances lead to consequences such as the emergence of multidrug-resistant strains with a propensity for bacterial biofilm formation [31,32]. The last is an important phenomenon because drugs usually cannot penetrate the bacterial biofilm structures [30]. Because of this, traditionally used pharmaceuticals and antibiotics have demonstrated reduced efficacy when compared to initial expectations [7,29,33]. Therefore, researchers and healthcare practitioners actively work on pioneering therapeutic strategies to prevent and manage infections in both acute and chronic wounds [1,2].

Numerous types of wound dressings have been developed to facilitate wound healing, including gauzes, transparent films, foam dressings, hydrogels, hydrocolloids, and hydroconductive dressings [34]. They are schematically presented in Figure 2. An ideal wound dressing should: (i) be characterized by a high biocompatibility and lack of toxicity, (ii) have adequate durability/mechanical properties, (iii) promote cell adhesion and differentiation, (iv) provide constant moisturization, (v) adhere well to the wound tissue but at the same time should be easy and painless to remove, (vi) ensure optimal gas exchange between the wound and the surroundings, and (vii) exhibit remarkable antimicrobial action [35].

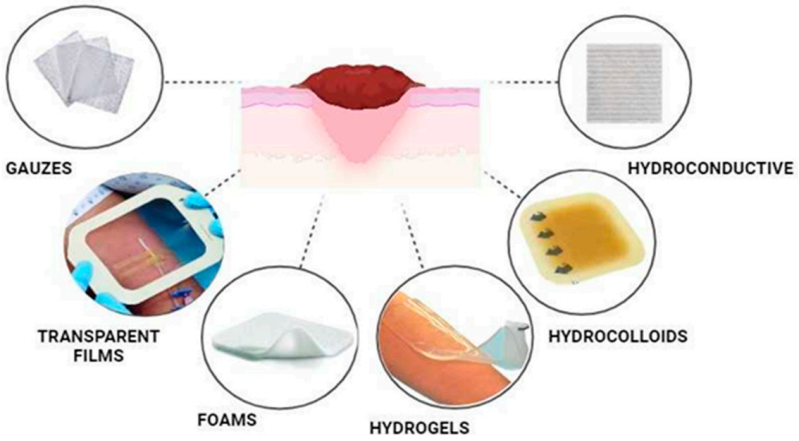

Figure 2. Types of wound dressings, created with BioRender.com (accessed on 4 December 2023).

Gauzes are the oldest and most economical, readily available, and highly absorbent traditional wound dressings. They can easily conform to the shape of the wound and they are widely used for dressing both infected and non-infected wounds with a significant amount of exudate. However, gauze dressings are not ideal for wounds, as upon removal, they may cause trauma, mechanical injury of the healing wound, and consequently, patient discomfort [34,36]. Transparent film dressings represent a refined progression from traditional gauzes, offering the capacity to maintain a moist wound environment, facilitate gas exchange, and protect against external bacterial contamination. Their easy adaptability and pain-free removal set them apart. Nonetheless, their lack of swelling capability makes them unsuitable for highly exudative or infected wounds, where the coexistence of exudate and infection can potentially exacerbate bacterial proliferation [34,36,37]. Foam dressings are recommended for managing wounds with high levels of exudate. This is associated with their outstanding ability to absorb substantial fluid volumes while providing thermal insulation and facilitating gas exchange. Due to its impressive absorbent capability, this type of dressing can be changed every seven days in non-infected wounds, while daily changes are recommended in the presence of infections [38,39]. Hydrocolloids are gel-forming systems made of an elastic matrix with hydrophilic polymers and they absorb fluids. They efficiently seal the wound bed without needing additional dressings. Hydrocolloids speed up healing by enhancing autolysis and debridement. However, they are not suitable for infected wounds due to their occlusive nature and can cause trauma during removal [34,36,40]. A hydroconductive dressing features a specific multilayer structure that allows for the absorption of wound exudate, removal of debris from the wound bed, and subsequent transport of these by-products into its core [34,36,41].

Among the wound dressings, hydrogels have emerged as the most promising candidates for wound dressings [42]. This is primarily due to their excellent hydrophilicity, biocompatibility, and three-dimensional porous structure that resembles the extracellular matrix (ECM) [43]. Compared to traditional dressings, hydrogels often exhibit better therapeutic effects on wounds that are prone to bacterial infections [44]. As a result, hydrogels have garnered significant attention among researchers for their tremendous promise in wound healing and formulation of wound dressings. This is related to a number of very desirable and often unique properties exhibited by hydrogel-based systems [45]. Firstly, the three-dimensional architecture of the hydrogel constructs favors the formation of an environment that fosters proper regeneration, acting as a framework for regeneration and healing processes. Additionally, their mechanical strength matches the native tissue to provide a highly bio-mimicked environment for better cell attachment, spreading, and proliferation. Moreover, the morphology of hydrogels mimics the morphology of the extracellular matrix and macromolecules, while hydrogel porosity provides effective cell infiltration and enhances transport of the various species needed for wound healing. It is also noteworthy that they are characterized by the capability for effective water retention

that provides a humid environment to display normal cell behavior (e.g., proliferation). Additionally, hydrogels can excessively absorb wound exudates, limiting the microbial growth near the wound. In this area stimuli-responsive composite hydrogels containing antibacterial agents attracted significant attention.

There is already a wide range of commercially available hydrogel-based dressings on the market, which are summarized in several papers [46–48]. However, there is still a lot of work and research going on to produce better and more effective hydrogel dressings (particularly stimuli-responsive hydrogels) and address the challenges associated with them, which are discussed in the next section.

2. Challenges Related to Hydrogel-Based Wound Dressings

Due to the combination of high water content, softness, flexibility, biocompatibility, and bioactivity, hydrogels have gained massive popularity in the wound dressings field. Their structure and properties make them dedicated formulations to overcome many complications related to the natural characteristics of chronic wounds [49]. These include the appearance of excessive exudates, massive bleeding, and persistent bacterial infections.

The hydrogel formulation, due to its high liquid absorption capacity, can usually absorb the excessive wound exudates. In the normal wound healing process, the exudate levels typically decrease over time. However, in the case of chronic wounds, such as various types of ulcers, exudate production is often excessive due to the ongoing inflammatory process [50,51]. Hydrogels' capacity to efficiently absorb exudate plays a vital role in managing chronic, bacterial infected wounds [52,53]. As a desired side effect, hydrated wound dressings help to control the temperature of the wound-affected area, accelerating the healing process [54–59].

Unregulated and massive bleeding resulting from trauma can give rise to a range of issues, including hypothermia, lowered blood pressure, susceptibility to bacterial infection, and even the onset of shock [60]. Hydrogels are a suitable platform for producing bleeding-controlling materials due to their exceptional liquid absorbing properties, which enable them to eliminate the excess of blood from the wound. Moreover, some hydrogels may be supplemented with substances promoting blood clot formation, including tannic acid [61–63], zeolite and kaolin [64–66], or polydopamine [67,68]. Such materials can actively and rapidly stop bleeding in wounds, promote clot formation, and minimize blood loss. This facilitates wound healing processes and reduces the risk of complications associated with uncontrolled bleeding [62,69–71].

Moreover, hydrogel wound dressings represent a promising platform for modifications using antimicrobials [68,72,73]. Antimicrobial-loaded hydrogels act as biological shields that hinder harmful elements such as bacteria from infiltrating the wound. They also show the ability to release therapeutic agents that aid the wound healing process in response to varying environmental conditions [45]. This is important in light of the information we provided in the previous chapter of this work.

Regardless of the factors resulting from the wounds themselves, hydrogels must also meet other conditions, such as good mechanical properties, which include both resistance to compression and resistance to stretching [74,75]. These properties allow the hydrogels to withstand heavy loads and strains during their application in critical places of the body, such as the joints or neck. First-generation hydrogels, when damaged (e.g., due mechanical compression), could easily lose their initial mechanical properties and their network structure could be affected, resulting in a reduction in their lifetime [76,77]. This appears because destroyed hydrogels cannot self-heal and reform the broken bonds. Self-healing hydrogels are a potential solution to this problem because they have a built-in ability to autonomously repair their original properties and structure in response to damage [78]. It should be always remembered that natural hydrogels are more susceptible to enzymatic degradation than their synthetic counterparts (e.g., polyethylene glycol, polyvinyl alcohol, poly(N-isopropyl acrylamide)), which exhibit slower degradation rates. Therefore, natural

hydrogels are usually coupled with various crosslinkers, bioactive compounds, antibiotics, or metal ions to achieve the enhanced performance [79].

The above-mentioned problems occurring during wound treatment (excessive exudates, blood flow, infections, the need for the dressing to adapt to the wound) can be solved by new generation hydrogels that react to stimuli occurring in the environment. Such hydrogels can respond to problems that arise during wound healing in response to internal (pH, wound temperature, the presence of free radicals) or external (near infrared (NIR)) stimuli [80,81]. This response may be the release of active factors (e.g., antibacterial substances), a change in absorption capacity or a change in structure, transparency, gel volume, mechanical characteristics, or surface properties [82,83]. Such incredibly versatile structures are referred to as "stimuli-responsive", "intelligent", or "smart" hydrogels [84,85]. This responsiveness allows for the controlled release of active substances, making them highly effective in wound management [33,86,87]. The development of such intelligent carriers that can adapt to internal conditions and prevent a bacterial infection is the big challenge in wound regenerative medicine. The advantages of stimuli-responsive hydrogels are graphically summarized in Figure 3.

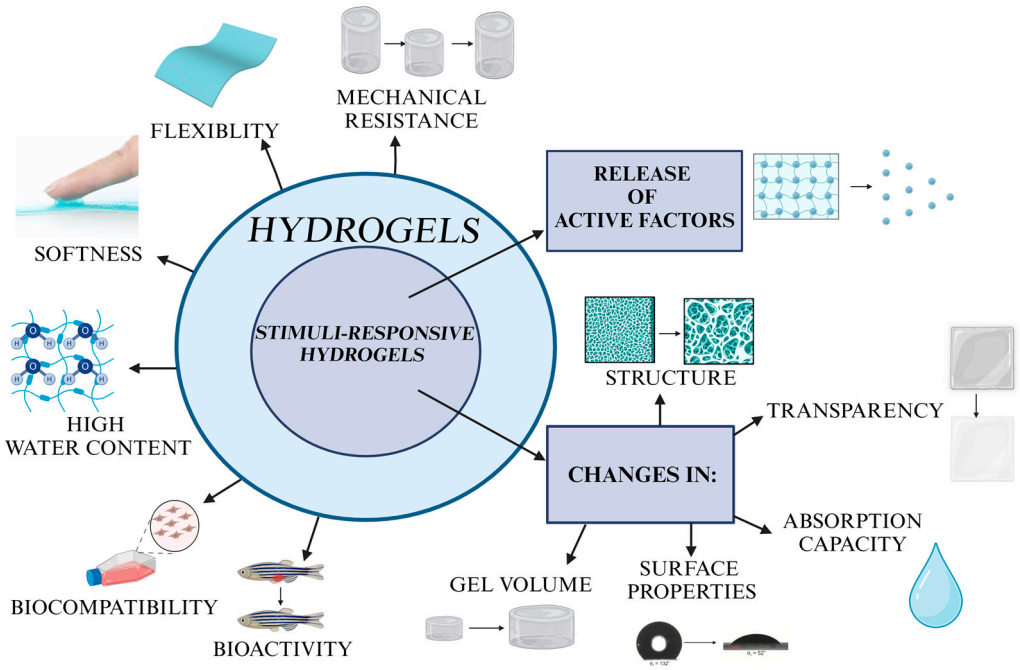

Figure 3. Advantages of stimuli-responsive hydrogels, created with BioRender.com (accessed on 4 December 2023).

When discussing materials responsive to stimuli, it is also worth mentioning shape memory polymers (SMPs). SMPs are a promising tool for designing new generation biomaterials for medical applications due to their unique capability of memorizing their initial shape and reverting to it from a deformed state when exposed to one or more suitable external stimuli, such as heat, light, pH, electricity, a magnetic field, and moisture [88]. In recent years, there has been a growing interest in these polymers in scientific research connected to biomedical applications [89–91]. For example, Panda et al. incorporated p-coumaric-acid-modified water-soluble chitosan (M-Cs) into the poly(vinyl alcohol) (PVA) polymer matrix. Compared to the PVA control variant, the addition of M-Cs resulted in improved water-induced shape memory behavior of the material, achieving a shape recovery ratio close to 100% [88].

3. Various Stimuli Triggering the Hydrogels' Response

Numerous stimuli-responsive hydrogels possess antibacterial, anti-inflammatory, or antioxidative properties [92,93]. Some even demonstrate dual properties, combining two of the abovementioned characteristics simultaneously [61,94–97], thus making them favorite candidates for the development of self-regulated drug delivery systems [98]. Currently, stimuli-responsive composite hydrogels containing antibacterial agents attracted the highest attention in scientific society and constitute a significant number of ongoing studies [99]. Therefore, in this review we focused on the stimuli-responsive hydrogels containing a wide range of antibacterial additives as an alternative to often unreliable antibiotics, in particular polyphenols, antibacterial polypeptides, and silver nanoparticles. Stimuli-responsive hydrogels can be categorized as [100]:

- non-contact stimuli-responsive hydrogels (e.g., light-responsive, thermo-responsive, magnetic/electric field-responsive),
- contact stimuli-responsive hydrogels (e.g., pH-responsive, ion-responsive, chemically/biochemically responsive),
- multistimuli-responsive hydrogels (susceptible to the simultaneous or sequential action of two or more stimuli).

Stimuli identified as the most promising and efficient for controlling behaviors of the resulting hydrogels are: pH, reactive oxygen species (ROS), temperature, and NIR, as schematically presented in Figure 4. This review focuses on these four types of stimuli as the most frequently used both in research and in medical translational studies. This, of course, does not limit the wide range of possibilities for using other types of stimuli, such as ionic strength for example, which can be precisely used not only to induce hydrogelation but also to modulate hydrogel properties (e.g., mechanical properties) and response (e.g., transport properties) [101–103].

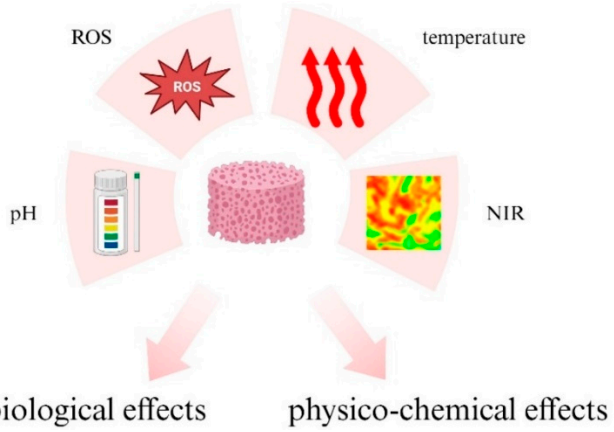

Figure 4. Various stimuli triggering the hydrogels' response, created with BioRender.com (accessed on 4 December 2023).

3.1. pH-Responsive Hydrogels

pH is a tightly regulated factor that plays a crucial role in maintaining the proper function of the skin and its levels vary across different skin layers, increasing from the surface to the deeper layers, therefore pH tends to fluctuate during differing stages of the wound healing process [104]. pH is as an indicator of the wound's condition, and changes in pH levels can be used to predict whether a wound is likely to heal or deteriorate [105]. The pH levels differ based on the condition of the skin: healthy skin typically maintains a slightly acidic pH (5–6), acute wounds exhibit a pH around 7.4, while chronic wounds tend to have a more alkaline pH, ranging from 7.3 to 10, partly due to the presence of proliferating bacterial colonies [106]. These pH fluctuations can impact bacterial infection as well as colonization, which are common characteristics of chronic wounds.

The appropriate regulation of wound pH during the different healing phases can accelerate wound healing. Restoration of the acidic environment in chronic wounds can reduce microbial colonization on the skin surface and enhance adipose tissue metabolism. However, the proliferation and migration of keratinocytes and fibroblasts favor a slightly more alkaline environment with a pH of around 8.3. For example, creating an acidic environment in the initial stages (hemostasis and inflammation) can inhibit bacterial infection and promote vascular regeneration, whereas the alkaline environment (observed during wound hyperplasia and remodeling) can enhance cell proliferation and skin remodeling [104]. Nevertheless, continuous wound pH regulation throughout all healing phases remains a challenging goal for scientists [107].

pH-responsive matrix degradation is one of methods designed for the control of drug release from hydrogels. The desired situation is, as bacteria multiply, this degradation is activated. During this phase, the strength of the hydrogel's three-dimensional structure diminishes, leading to the formation of larger internal pores that in consequence enables the release of the drug to inhibit the bacterial growth. Once the pH of the wound returns to its typical level, the above process stops [108].

This strategy was implemented by Bonetti et al. in the production of a methylcellulose-based hydrogel, which was crosslinked using ester bonds. Ester bonds are susceptible to hydrolysis in an alkaline environment, causing the hydrogel network to expand and facilitate drug release [15]. The change in swelling behavior can lead to the mentioned above shift in the pore size within the hydrogel structure used for pH-responsive drug delivery or signal transmission [109,110]. This method has also been reported in other studies related to pH-responsive hydrogel wound dressings. The pH-dependent alterations in hydrogel size predominantly concern the way these materials expand or contract [111,112].

To sum up, pH-responsive wound dressing hydrogels offer unique benefits in wound care due to their exceptional biochemical and mechanical characteristics [113]. They effectively assess the wound's condition by monitoring its pH, facilitate and accelerate the controlled wound healing, and lower the risk of infection. Such constructs have the capability to adjust their structure and active substances release in response to a pH stimulus [114,115].

3.2. ROS-Responsive Hydrogels

Reduction–oxidation (redox) potential is a biological parameter that can be influenced by various factors and may undergo alterations in certain states of disease, such as inflammation, cancer, or hypoxia [116]. ROSs are pivotal regulatory elements in the wound healing process, facilitating natural skin repair. They also play a significant role in oxidative bacterial elimination, thereby promoting angiogenesis and re-epithelialization at the wound site [117]. However, excessive ROS levels can lead to oxidative damage, hindering the proper healing process. It causes an inflammatory response that inhibits the functions of both endogenous stem cells and macrophages and also retards tissue regeneration [118,119]. As a consequence, the wound remains in the inflammatory phase for a long time. Therefore, the extended healing time does not allow for a smooth transition into the proliferation and remodeling phase [120]. Notably, hypoxia impedes the wound healing process by inhibition of fibroblast proliferation and collagen production. The overproduction and accumulation of ROSs in the wound environment is also the common reason for the emergence of bacterial infection or even a diabetic wound state. This is particularly evident in chronic wounds, where prolonged oxidative stress prevails. Clearly, the improvement in the healing process can be achieved by reducing the bacterial presence [20].

Hence, antioxidant hydrogels have the potential to reduce the excessive ROSs in wound sites by neutralizing free radicals, interrupting the free radical chain reactions, and alleviating dysfunction in the immune system [121]. Targeting oxidative stress in chronic wounds through the restoration of the redox equilibrium has demonstrated effectiveness in enhancing the proper wound repair [122]. The development of antioxidant hydrogels can be approached in two main ways: either by using hydrogels as carriers for ROS scavengers

or by creating hydrogels with inherent antioxidant properties, which can be achieved by using antioxidant macromolecules as hydrogel precursors. Considering this evidence, investigations into designing antioxidant wound dressing materials aimed to assess their impact on the healing process acceleration. This can be achieved by hydrogel loading with natural polyphenols such as tannins, gallic acid, and curcumin to capture and neutralize free radicals [22,46,123].

In the case of hydrogels responsive to ROSs within the wound environment, the current strategy applies either the introduction of an ROS-responsive block into the backbone of a hydrogel-forming polymer or the use of the polymers with ROS-responsive side chains [124]. An increase in ROS concentration in the surrounding environment leads to the hydrolysis or degradation of chemical bonds in the hydrogel with a hydrophobic-to-hydrophilic transition or polymer chain scission. This in turn leads to the controlled release of hydrogel-loaded drugs. As the level of ROSs varies depending on successive phases of the healing process [125], ROS-responsive hydrogels also release therapeutic substances in response to ROS fluctuations occurring during these phases [126]. Thus, this controlled release of therapeutic substances underlines their responsiveness to the dynamic environment of the wound.

Taking these facts into consideration, ROS-responsive biomaterials (RRBs) are gaining growing potential for mitigating oxidative stress in tissue microenvironments and serving as targeted carriers for drug release in response to physiological oxidative conditions in the wound environment. In particular, RRBs show a real potential in difficult wound management, including diabetic wound treatment, which is one of the greatest challenges of 21st century medicine.

3.3. Temperature-Responsive Hydrogels

Temperature plays a crucial role in wound healing as it affects the rates of enzyme responses, given their temperature-dependent nature. Additionally, temperature serves as a conventional indicator in the clinical assessment of chronic wounds, reflecting classic signs and symptoms [127]. The temperature could be a signal for specialized wound dressings to activate or respond in a particular way. Temperature-responsive hydrogels have significant potential in drug or cell delivery systems and injured tissue repair. They are commonly used in designing responsive systems due to their ease of control [128].

Hydrogels sensitive to temperature changes undergo the transition between a liquid and solid (adhesive) state, displaying enhanced flexibility for conforming to irregular wound surfaces [129]. Temperature-responsive hydrogels are usually formed using non-covalent interactions between the components, and their physical state depends on temperature. This phenomenon can trigger the sol–gel transition, enabling the gel to adapt perfectly to the wound site, in particular for injectable gel types. Incorporation of the drugs into the liquid-state hydrogel ensures their homogeneous dispersion. Meanwhile, the rapid gel formation (via the sol–gel transition, often occurring at a physiological temperature) prevents an initial drug burst release, providing the sustained delivery of active substances. Such materials can swell and shrink according to the environmental temperature [130], with related changes in volume due to the hydrophobic/hydrophilic functional groups present in the hydrogel structure [131,132]. This approach simplifies the use of hydrogels, making the therapeutic process straightforward and user-friendly [133,134].

Normal body temperature is approx. 37 °C. In relation to this fact, hydrogel wound dressings are often composed of thermal-sensitive materials with a critical solution temperature lower than body physiological temperature. So-called lower critical solution temperature (LCST) hydrogel can shrink when the temperature is above the LCST point. Hydrophobic moieties, such as propyl, ethyl, and methyl groups, are characteristic for temperature-responsive hydrogels. The polymers with LCST, which are currently used in biomedical applications, are as follows: polyethylene glycol (PEG) (106–115 °C), poly(propylene glycol) (PPG) (10–40 °C), poly(vinyl alcohol) (PVA) (125 °C), poly(N-isopropylacrylamide) (PNIPAAM) (32 °C), poly(methyl vinyl ether) (PMVE) (28–34 °C), poly(N-vinyl caprolac-

tam) (PNVCa) (30–50 °C), and Pluronic-F127 (PF-127) (26.5 °C) [135,136]. Chitosan (CH), chondroitin sulfate, hyaluronic acid (HA), alginate (Alg.), dextran, and cellulose belong to natural polymers that can be blended with thermosensitive hydrogel polymers. This opens the possibility for the development of innovative hydrogels with favorable characteristics suitable for tissue engineering applications [83,134,137].

Thermosensitive hydrogels with positive characteristics have the ability to increase their solubility above the upper critical solution temperature (UCST). Polymers exhibiting UCST behavior become less soluble at temperatures exceeding their critical point, leading to a sol–gel transition. In contrast, hydrogels with a lower critical solution temperature (LCST) contract and precipitate from the solution above their critical temperature. This phase transition is often reversible, allowing for controlled changes in the hydrogel state. Thermosensitive hydrogels with LCST behavior swell in response to a decrease in temperature [80,138].

3.4. NIR-Responsive Hydrogels

The near-infrared (NIR) light, falling within the wavelength range of 780–1700 nm, is considered a therapeutic window for light-activated delivery systems in vivo [139]. The distinctive feature of NIR light is its wide range of light wavelengths (780–1700 nm). This feature makes the NIR-responsive materials excellent candidates for use as therapeutic agents and biological tools in a variety of biomedical applications [140,141]. NIR's ability to penetrate tissues deeply with minimal phototoxicity and non-invasiveness is the big advantage in biomedicine [142–145].

Light-responsive materials, particularly those responding to NIR light, have emerged as a highly promising approach for managing bacterial infections during the wound healing process [146–149]. Scientists have shown the significant role of NIR stimulation in the development of wound dressing hydrogels with enhanced antibacterial properties [150–153]. The use of near infrared (NIR) in wound treatment offers benefits such as accelerating the healing process by stimulating collagen production [154], improving blood microcirculation, anti-inflammatory and bactericidal effects, and effectiveness in the treatment of chronic wounds [155].

Under NIR light the structure of materials changes as a result of chemical bonds breaking and changes in molecular structure, thus enabling the release of active substances. In order for a biomaterial to react to NIR by generating heat, it must contain factors responsive to NIR. Such materials containing NIR-responsive additives may lead to thermal decomposition of the hydrogels and, consequently, the release of active substances enclosed in their structure [148,156,157]. When the drug enclosed in a hydrogel structure is in the form of NIR-sensitive nanoparticles, heating the constructs may result in a faster controlled release. It is possible due to a change in the hydrogel structure, resulting in increased drug permeability. Such photothermal agents include gold nanoparticles [158], silver nanoparticles [159], or carbon nanomaterials [160], which can produce heat when exposed to NIR light, facilitating drug release [161].

It is worth mentioning that NIR stimulation can be used to obtain other effects besides targeted drug release. For example, it is also an amazing tool for the synthesis of self-removable wound dressings. For example, Zhao et al. [162] designed hydrogels consisting of catechol–Fe^{3+} coordination cross-linked poly(glycerol sebacate)-co-poly(ethylene glycol)-g-catechol and quadruple hydrogen bonding cross-linked ureido-pyrimidinone-modified gelatin. Upon exposure to near-infrared (NIR) light, the hydrogel exhibited photothermal effects. The rise in temperature caused the breakdown of hydrogen bonds, leading to the dissolution of the hydrogel and facilitating its easy removal from the skin wound.

3.5. Examples of Existing Stimuli-Responsive Hydrogels

Depending on the components used in their production process, the resulting constructs exhibit distinct characteristics and properties. Examples of various stimuli-responsive wound healing constructs were presented in Table 1 to highlight the huge diversity of such

technologies in wound treatment applications. The more systematic discussion is provided in Section 4.

Table 1. Examples of stimuli-responsive agents.

Composition	Stimuli Response Agent	Stimuli Mechanism	Material's Properties	Ref.
Dodecyl, chitosan, WS_2 nanosheet, ciprofloxacin	WS_2 nanosheets	WS_2 nanosheets generated heat upon exposure to near-infrared (NIR) light → triggering the release of the antibiotic at the wound site	Injectable, self-adapting, and rapidly molding hydrogels with good tissue adherence and antibacterial potential	[163]
AuNPs, Pluronic® F127, hydroxypropyl methylcellulose (HPMC)	Pluronic® F127	Stiff gel formation when temperature increased from 4 °C to 32–37 °C	Improved bioavailability, skin permeation, antibacterial and anti-inflammatory activity of the prepared AuNPs' thermoresponsive gels, burn wound treatment potential	[164]
Gelatin and chondroitin sulfate	Chondroitin sulfate	Tissue adherence at 37 °C, diminished at low temperatures (20 °C), enabling it to detach effortlessly from the tissue	Injectable self-healing bioadhesive, underwater adhesive properties, tissue adhesive and sealant for the closure of bleeding wounds	[165]
Catechol-modified quaternized chitosan, poly(d,l-lactide)-poly(ethylene glycol)-poly(d,lalactide) (PLEL)	PLEL	The temperature-dependent transition of PLEL solution from a reversible sol at 25 °C to a gel at 37 °C	Injectable, thermo-sensitive adhesive hydrogel with promoting wound healing ability, biocompatibility, and bioactivity through in vivo degradation, stimulated endothelial cell migration, and angiogenesis	[166]
Galactose-modified xyloglucan (MxG) and hydroxybutyl chitosan (HBC)	Galactose-modified xyloglucan	Gelation temperature and time can be modulated via adjusting the MxG/HBC ratio	The composite hydrogel could effectively prevent repeated adhesion after adhesiolysis, promote wound healing, and reduce scar formation	[167]
Pluronics, hyaluronic acid, corn silk extract, and nanosilver	Pluronics,	The viscoelastic parameters varied within the temperature range of 25 to 40 °C	Hydrogel with antibacterial activity toward Gram-positive and Gram-negative bacteria	[168]
Collagen (COL), guar gum (GG), poly(N-isopropylacrylamide) (PNIPAM), graphene oxide (GO)	PNIPAM and GO	Phase transition after human body temperature contact; thermosensitive, NIR responsive	Hydrogel with fast self-healing properties, super-ductile, injectable, remoldable, conductive, and skin wound-healing acceleration properties	[169]

4. Loading Stimuli-Responsive Hydrogels with Active Substances

Stimuli-responsive hydrogels can be classified not only based on the specific stimulus they respond to but also on the type of active substance they are loaded with. Both the hydrogel matrix and the loaded agent determine the final physiochemical and healing properties of the resulting biomaterial, which have been concisely summarized in Table 2. The dominant group of active substances in this type of hydrogel is compounds showing antibacterial activity, with particular emphasis on substances other than antibiotics. This trend is based on the search for alternatives to drugs that a significant number of bacterial strains have developed resistance to. Nowadays, polyphenols, antibacterial polypeptides, and silver nanoparticles are used most frequently for the preparation of stimuli-responsive hydrogels containing non-antibiotic substances. Below, the representatives of such hydrogels are described, taking into consideration various stimuli used for the liberation of their activity. At this point it is worth mentioning that instrumental techniques and modeling approaches employed to monitor stimuli-induced variations play an important role; the interested reader is therefore referred to a number of interesting publications in this field [100,170–172].

Table 2. Key characteristics of stimuli-responsive hydrogel matrices loaded with active substances.

Hydrogel-Modified Substance	Main Characteristics of Modified Matrices	Refs.
Polyphenols	mechanical strength, structural integrity, adhesion, high elasticity, self-healing properties, hemostatic properties, antibacterial properties, antioxidant properties, anti-inflammatory properties	[70,92,123,173–180]
Peptides, polypeptides, and proteins	Biocompatibility, regeneration processes, stimulation, antibacterial properties.	[181–186]
Silver nanoparticles	Antibacterial properties, anti-inflammatory properties, stability, durability.	[15,168,187–191]
Antibiotics	Antibacterial properties	[192–198]

4.1. Hydrogels Loaded with Polyphenols

Polyphenols are a diverse group of natural compounds that are widely distributed in plants, marine organisms, and various other sources. They have gained increasing attention in biomedical fields for their numerous potential health benefits, including their inherent biocompatibility, antioxidant and antibacterial activities [199]. Polyphenol compounds include functional groups such as catechol and pyrogallol, enabling them to engage with a multitude of molecules through the formation of diverse non-covalent interactions (e.g., hydrogen bonding, π–π interactions, cation–π interactions, etc.) as well as covalent interactions (e.g., Michael addition/Schiff-base reaction, polyphenol–metal coordination, etc.) [200,201]. It makes them great candidates for the synthesis and modification of hydrogels' biomaterials for medical purposes, including wound dressings (WDs).

The addition of polyphenols to polymers used for hydrogel WD synthesis allows for numerous interactions between these two compounds, leading to a tighter and more interconnected network. This contributes to improved mechanical strength and structural integrity of the matrix. Consequently, they often exhibit exceptional properties such as

adhesion, high elasticity, and self-healing, qualities that are highly desired in the design of "intelligent" hydrogels. These properties are particularly desired during the healing of wounds with continuous and persistent bleeding because they ensure excellent hemostatic performance even with deep wounds after adhering to the wound site [202,203]. Introducing polyphenols into the hydrogel structure enhances the overall performance of hydrogels.

Tannic acid (TA), belonging to the class of polyphenols, is one of the most widely recognized within this category. TA contains many hydroxyl groups showing the affinity for the formation of hydrogen bonds with proteins and other biomolecules. This property allowed for the use of TA for traditional medicine to treat a variety of maladies [204]. TA has been shown to reduce inflammation as an antioxidant and can induce apoptosis in several cancer types. TA has also displayed antiviral and antifungal activity. Moreover, taking into account the results of new preclinical and clinical studies and the growing resistance of bacteria to antibiotics, new intriguing perspectives emerge for this natural compound in relation to TA application as an antibacterial agent. In biomaterials research, as was already mentioned, TA can enhance the mechanical properties of natural and synthetic hydrogels and polymers due to its crosslinking property, imparting beneficial attributes to these materials [204,205].

Although other polyphenols, such as gallic acid and resveratrol have been employed in the production of stimuli-responsive hydrogel dressings, TA stands out as the most effective in this regard. The comparative analysis presented in Table 3 illustrates examples of hydrogels synthesized using various polyphenols; however, it is evident that TA is superior to others in terms of its suitability for the production of stimuli-responsive hydrogel dressings.

Table 3. Polyphenol-loaded stimuli-responsive wound dressing hydrogels.

Hydrogel Composition	Stimuli	Effects	Ref.
Gelatin (Gel), tannic acid (TA) Gel/TA	pH	pH-dependent release of TA.	[70]
Phenylboric acid-modified polyphosphazene (PPBA), tannic acid (TA), poly(vinyl alcohol) PPBA-TA-PVA	ROS	ROS-dependent release of TA (scavenging of 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals and OH radicals in vitro) ROS-responsive degradation.	[173]
Quaternized chitosan (QCS), tannic acid (TA) QCS/TA	ROS	Self-healing properties, free radical-scavenging activity due to TA presence.	[123]
Physical crosslinked quaternized chitosan (QCS), tannic acid (TA), ferric iron Fe(III) QCS/TA/Fe	NIR	Antibacterial activity induced by NIR-stimulated modified hydrogels.	[174]
Polydopamine (P), tannic acid (T), chitosan (C), poloxamer 407/188 (PP) PTCPP hydrogel	Temp. NIR	Sol–gel transition of liquid hydrogel formulation at around 30 °C, significant enhancement of hydrogel's antibacterial activity after NIR irradiation.	[175]
Poly(acrylamide) (PAM), naturally derived chitosan (CS), tannic acid/ferric ion chelates ($TA@Fe^{3+}$) $PAM/CS/TA@Fe^{3+}$	NIR	In vivo and in vitro antibacterial activity to prevent microbial infection after NIR stimulation.	[176]

Table 3. *Cont.*

Hydrogel Composition	Stimuli	Effects	Ref.
Hyaluronic acid (HA), poly(ether urethane), (D-DHP407), gallic acid (GA), HA/D-DHP407-GA	ROS Temp.	Reduction in intracellular ROS level due to ROS-induced GA release, sol–gel transition of liquid hydrogel precursor in response to temperature changes (37 °C).	[177]
Gallic-acid-functionalized hyaluronic acid (HAGA), hyaluronic acid methacrylate (HAMA) HAGA/HAMA hydrogel	pH Temp.	Swelling under acidic conditions and stability at neutral and basic pH. Self-healing ability at 37 °C and increased hydrogel-to-tissue adhesion due to gallic acid presence.	[178]
Resveratrol (RSV), polyethylene glycol (PEG)-cellulose nanofibrils (CNF) (RPC) Poly(vinyl alcohol) (PVA) RPC+PVA+BORAX→ RPC/PB hydrogel	pH	pH-dependent resveratrol release.	[92]
Hydroxypropyl chitin (HPCH), tannic acid (TA), ferric ion (Fe) HPCHC/TA/Fe	pH Temp.	pH-dependent TA release, temperature-dependent gelation.	[179]
polyvinyl alcohol (PVA), Bacterial cellulose (BC), graphene oxide (GO), curcumin, bacterial cellulose-functionalized-graphene oxide PVA/BC-*f*-GO Crosslinker: tetraethyl orthosilicate (TEOS)	pH	pH-dependent curcumin release.	[180]

The gelatin-TA (GelTA) hydrogel accelerates skin healing by releasing TA in a pH-dependent manner. This release is responsible for an antibacterial, antioxidant, hemostatic, and anti-inflammatory activity of the hydrogel. Moreover, the GelTA hydrogel significantly enhances extracellular matrix formation, wound closure, re-epithelialization, and collagen deposition in vivo by offering cell adhesion sites within the gelatin matrix [70]. Ni et al. synthesized TA-conjugated nanoparticle hydrogels (PPBA-TA-PVA) by mixing TA, phenylboric-acid-modified polyphosphazene (PPBA), and poly(vinyl alcohol) (PVA). PPBA–TA–PVA hydrogels were shown to be a promising platform for reducing inflammation and speeding up wound healing. They exhibited ROS-scavenging activity due to the ROS-responsive degradation depending on phenylboric acid presence. As a result of this degradation, the hydrogel released TA, which was responsible for the ROS-scavenging phenomenon. This led to shortening the healing time of diabetic wounds [173]. Pan et al. [123] synthesized injectable hydrogel with self-healing properties and antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* based on quaternized chitosan (QCS) and tannic acid. It also showed the ability to reduce free radicals. In vivo studies on diabetic rats have shown the suppression of inflammation and acceleration of collagen deposition in skin defects. The multifunctional QCS/TA/Fe hydrogel developed by Guo et al. [174] as a wound dressing for the closure and healing of wounds demonstrated antibacterial properties attributed to its responsiveness to NIR (temperature even increased by 60 °C). The photothermal effect was achieved through the presence of TA/Fe^{3+}, and it increased

with the increased Fe^{3+} content. In vivo study results indicated that this multifunctional hydrogel dressing effectively closed and healed wounds, eliminating *Staphylococcus aureus* infection, promoting angiogenesis, reducing the inflammation, and decreasing the secretion of various pro-inflammatory cytokines. Su et al. created a PTCPP hydrogel. Its liquid formula turned from sol to gel state at around 30 °C [175]. In vitro antibacterial results showed that the bactericidal rates of PTCPP against *Staphylococcus aureus* and *Escherichia coli* under NIR irradiation were 99.994% and 99.91%, respectively. In in vivo experiments, PTCPP adapted to the shape of the wound, showing good adhesion properties and promoting the healing of infected wounds. A simple one-pot synthesis procedure was utilized to prepare self-adhesive hydrogels composed of poly(acrylamide) (PAM), naturally derived chitosan (CS), and tannic acid/ferric ion chelates (TA@Fe^{3+}) [176]. The impressive near-infrared (NIR) photothermal conversion capabilities of TA@Fe^{3+} conferred the excellent antibacterial characteristics to the hydrogels, eliminating the necessity of antibiotics use. This has been confirmed through antibacterial experiments conducted both in laboratory settings (in vitro) and within living organisms (in vivo). Moreover, TA@Fe^{3+} exhibited favorable compatibility with fibroblasts cells, promoting cell attachment, proliferation, and the differentiation of the cells. This acceleration of these processes led to the faster closure of skin wounds and the maturation of tissues. A hydrogel was designed by Laurano et al. [177] that exhibited an ROS-stimulated release of gallic acid. In consequence, the reduction in ROS concentration mediated by gallic acid activity was observed. The hydrogel also had the ability to change consistency (from liquid to gel) in response to temperature changes (specifically to a temperature of 37 °C). Meanwhile, in response to lowering the temperature (up to 3 °C), the hydrogels turn back into a liquid state. A hydrogel composed of two components: gallic-acid-functionalized hyaluronic acid (HAGA) and hyaluronic acid methacrylate (HAMA) showed the ability to swell in an acidic environment while remaining stable in a neutral environment. Thus, the hydrogel exhibited pH-responsiveness [178]. This hydrogel also exhibited a response to the temperature. After 30 min of incubation at 37 degrees, the cut pieces of the hydrogel were able to rejoin. This indicates the self-healing ability of this hydrogel. Moreover, the presence of gallic acid increased the adhesiveness of the hydrogel to tissues, thus enhancing the probability of wound healing acceleration. Yang et al. synthesized a very complex hydrogel based on resveratrol, PEG, CNF (cellulose nanofibrils), and PVA, crosslinked by borax. The resulting hydrogel exhibited a 2.33 times greater release of the resveratrol under acidic pH conditions compared to a neutral pH [92]. Due to the presence of resveratrol, the hydrogel exhibited significant antibacterial and antioxidant properties with beneficial influence on the wound healing process. Ma et al. developed an HPCHC/TA/Fe smart hydrogel with dual stimuli responsiveness (pH and temperature) [179]. The presence of a TA addition in the hydrogel structure acted as a crosslinker to enhance the mechanical properties of the hydrogel and acted as an antibacterial agent. Such hydrogel exhibited a pH-dependent TA release process that was responsible for the antibacterial properties of hydrogel against *Escherichia coli* and *Staphylococcus aureus*. The HPCH/TA/Fe hydrogel precursor solution, prior to gelation at low temperatures, can be injected onto the wound site to fill irregular defects, rapidly forming a gel under physiological conditions. Additionally, in a mouse wound model, it demonstrated the remarkable ability to accelerate wound healing without scars. Increasing graphene oxide (GO) content in hydrogels designed by Alarjan et al. [180] slowed down biodegradation due to complex polymerization. However, it concurrently enhanced mechanical strength and hydrophilicity. The pH-sensitive swelling observed in buffer and non-buffer solutions indicates the hydrogels' suitability for controlled drug release. Thus, these hydrogels, with a higher GO content, can be employed for controlled curcumin release. Such constructs also possessed antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, and *Pseudomonas aeruginosa*.

4.2. Hydrogels Loaded with Peptides, Polypeptides, and Proteins

With more than one hundred products approved by the US Food and Drug Administration (and many more being actually developed), polypeptide/protein-based therapeutics have gained significant attention in all areas of medicine, including cancer therapies, inflammatory diseases, vaccines, and diagnostics. Polypeptides and proteins can provide highly specific and complex functions that are often unable to be provided by small synthetic compounds, including catalyzing desired biochemical reactions, participating in the formation of membrane receptors and channels, and transporting molecules providing intracellular and extracellular scaffolding support [206]. Therefore, polypeptides and proteins have always been widely studied as therapeutic agents for the treatment of various human diseases [207]. However, their physicochemical properties often render them difficult to be used as bare therapeutic agents [208]. Their incorporation in a three-dimensional hydrogel structure additionally provides a number of possibilities when it comes to therapeutic outcomes; examples of hydrogel systems loaded with polypeptides and proteins are summarized in Table 4.

Table 4. Polypeptides-loaded stimuli-responsive wound dressing hydrogels.

Hydrogel Composition	Stimuli	Effects	Ref.
PEG–PLGA–PEG triblock copolymer loaded with TGF-β1 polypeptide	Temp.	Temperature-initiatied re-epithelialization and collagen synthesis	[181]
N-carboxyethyl chitosan, hyaluronic acid–aldehyde, adipic acid dihydrazide, insulin	pH	pH-responsive insulin release	[182]
oxidized dextran, antimicrobial peptide DP7, ceftazidime	pH	pH-sensitive hydrogel erosion accelerating the release rate of the drugs	[183]
PEG-based Tβ4-loaded hydrogels	MMPs	Enzymatic activity-dependent release of Tβ4 mediated by tissue metalloproteinases	[184]
PEG–vinylsulfone-based Tβ4-loded hydrogels	MMPs	Enzymatic activity-dependent release of Tβ4 mediated by tissue metalloproteinases	[185]
Tβ4@TNT–PDA/PVHA	ROS	ROS-dependent Tβ4 release by borate bonding cleavage	[186]

Lee et al. synthesized a thermosensitive hydrogel made of a triblock copolymer, PEG–PLGA–PEG containing plasmid TGF-β1 (a protein known for its inhibitory action of autoimmune and chronic inflammatory diseases) and used the obtained material to accelerate diabetic wound healing [181]. The bare and TGF-β1-loaded hydrogels were administered to the wound and it was found that while bare hydrogel is slightly beneficial for re-epithealization at an early stage of healing (1–5 days), significantly accelerated re-epithelializaion is observed in the wound treated with a TGF-β1-loaded hydrogel. Moreover, the accelerated re-epithelialization was accompanied by increased cell proliferation, enhanced collagen synthesis, and more organized extracellular matrix deposition. A commercial wound dressing, Humatrix®, was also doped with TGF-β1 but the resulting formulation had little effect when compared with the obtained PEG–PLGA–PEG hydrogels, which shows the importance of the proper choice of the matrix.

Li et al. developed a self-healing hydrogel composed of N-carboxyethyl chitosan (N-chitosan) and adipic acid dihydrazide, which was crosslinked in situ by hyaluronic acid–aldehyde and loaded with insulin [182]. This construct exhibits pH-responsive long-term insulin release, offering an appealing mechanism to reduce glucose levels, making it particularly advantageous for diabetic skin wounds.

Temperature-sensitive and thermoreversible hydrogels based on a thermosensitive polymer, poly-(N-isopropylacrylamide) (PNIPAM), were obtained by a combination of a short peptide (I_3K) with PNIPAM [105]. An antibacterial peptide G(IIKK)$_3$I-NH$_2$ (a short cationic helical peptide with confirmed antimicrobial properties [209]) was encapsulated in the hydrogel matrix as a model drug. The fabricated composite hydrogel gave a sustained and controlled linear release of G(IIKK)$_3$I-NH$_2$ over time. Using the peptide nanofibrils as three-dimensional scaffolds, the obtained thermoresponsive hydrogels can mimic the extracellular matrix and could potentially be used for tissue engineering [210]. It should be mentioned that PNIMAM-based hydrogels enable faster drug release at an elevated temperature (e.g., during the inflammatory state of chronic wounds) and slower delivery at lower temperatures, which results from a low critical solution temperature, close to the body temperature [211]. This makes PNIMAM a very promising hydrogel matrix for use in the treatment of inflamed wounds [35].

Several short peptide-based wound healing systems have been reported in recent years [212]. For example, Wu et al. employed an antimicrobial peptide DP7 (a short twelve amino acid cationic peptide with broad-spectrum antibacterial activities [213]) to create a pH-sensitive hydrogel wound dressing, based on preoxidized dextran as the polymeric matrix [183]. The resulting hydrogel not only inhibited the growth of multidrug-resistant bacteria but it also did not cause an increase in bacterial resistance. To enhance its efficacy, the hydrogel was loaded with ceftazidime for synergistic antibacterial effects. The combined action of DP7, ceftazidime, and oxidized polysaccharides exhibited significant efficacy against a variety of multidrug-resistant *P. aeruginosa* strains. Remarkable wound healing was observed in the in vivo experiment, in both wild type C57 and diabetic mouse models [183], which is attributed to the hydrogel erosion accelerating the release rate of the drugs, which is schematically presented in Figure 5.

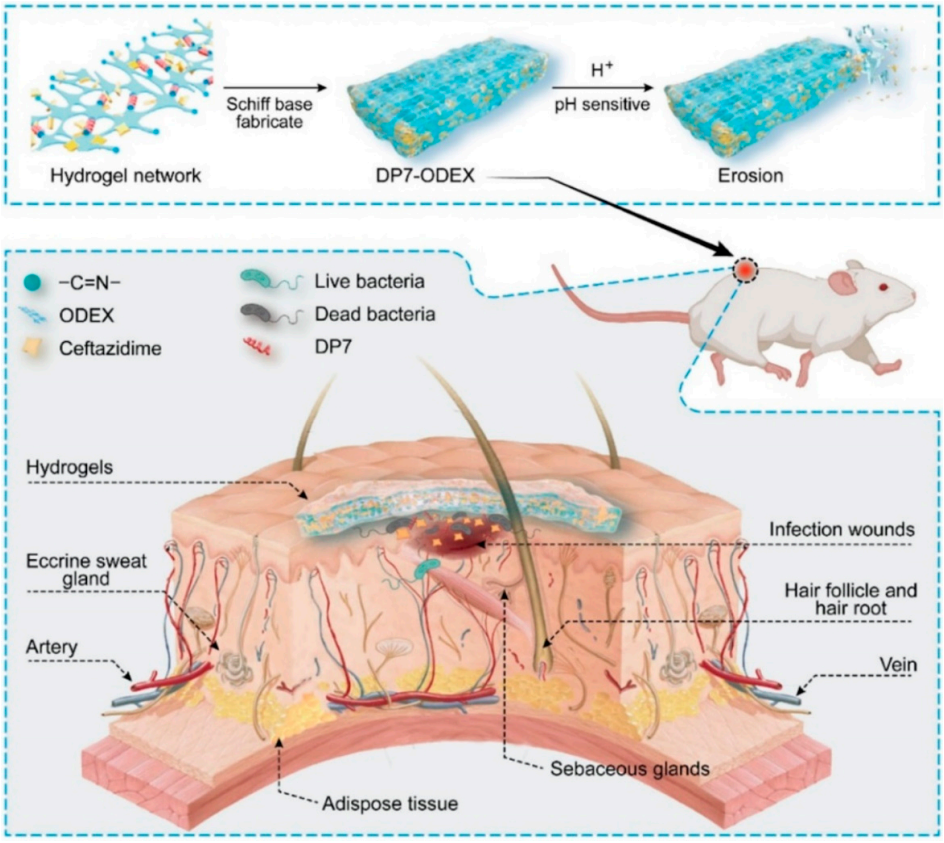

Figure 5. pH-sensitive dextran-based hydrogel erosion accelerating the release rate of the drugs: DP7 peptide and ceftazidime. Reprinted with permission from [183]. Copyright (2022) with permission from Elsevier. *Please note that the correct name is Adipose tissue, not Adispose tissue.*

Rezaei et al. synthesized thermo-responsive chitosan-based hydrogels loaded with various concentrations of piscidin-1 (a fish-derived 22-amino-acid cationic peptide with potent antimicrobial and antiendotoxin activities [214]) to fabricate an antibacterial wound dressing that is able to treat a resistant *Acinetobacter baumannii*. β-glycerolphosphate disodium salt pentahydrate was used to tune the gelation time of the resulting hydrogels. A total of 16 $\mu g \cdot mL^{-1}$ of piscidin-1 in the hydrogel was found to be the optimal concentration to provide effective antibacterial activity against resistant clinical isolates of *A. baumannii* and no signs of cytotoxicity for human cells were observed [215].

The above-discussed examples of the DP7 and piscidin-1 peptides show increasing interest in antimicrobial peptides (AMPs) as active ingredients of various hydrogel formulations. AMPs constitute an important part of the innate immune defense system in multicellular organisms and can act in two ways: (i) directly, i.e., kill microbial pathogens (most of AMPs), (ii) indirectly: modulate the host defense system [216,217].

Interesting example of Thymosin β4

One of the most prospectus polypeptides is thymosin β4 (Tβ4). Being the most abundant, it constitutes 70–80% of the β-thymosin polypeptides initially extracted and identified over four decades ago from the calf thymus. It was later shown to be expressed by multiple cells, including immune, brain, liver, testis, myocardium, and blood cells, except for erythrocytes [218]. This is a classical moonlight protein, showing different biological activities in eukaryotic cells, i.e., angiogenic, anti-inflammatory, and anti-microbial properties. Tβ4 upregulates vascular endothelial growth factor VEGF, promotes endothelial cell migration, tube formation, angiogenesis, and wound healing in vivo [219,220]. Via the downregulation of chemo- and cytokines, it can decrease inflammation [221,222], while in platelets it shows antimicrobial properties [223]. As Tβ4 is highly expressed in platelets and wound fluids, this explains its contribution to wound healing and tissue regeneration [224]. In preclinical models and in patients Tβ4 accelerated the rate of dermal healing when applied directly on the injured site or was given intraperitoneally [225]. When Tβ4 was injected intradermally on the second-degree burn wound site it promoted skin regeneration in mice [226], suggesting its potential therapeutic use in the treatment of severe burns. In addition, Tβ4, especially at the SDKP (serine–aspartate–lysine–proline) region, prevents or can reverse uncontrolled wound healing resulting in fibrosis/scarring via the inhibition of macrophage infiltration and secretion of fibrotic factors (TGF-b, IL-10, CTGF) [227].

Interestingly, in human clinical trials on patients with chronic cutaneous pressure ulcers and venous stasis ulcers accompanied with varicose veins and an open ulceration, the topical application of gel containing Tβ4 increased the rate of complete wound healing [225]. As it is a good candidate for future treatments, there are new developments toward new application modes of this factor to improve its effectiveness in wound healing. Transdermal administration of the encapsulated Tβ4 in the ethosomal gels can improve the percutaneous drug absorption and shorten wound recovery [228]. Future prospectives are also attracted to the possible application of Tβ4 in the regeneration of adult tissues such as the heart that was shown in mice where the peptide enhanced myocyte survival and improved cardiac function after coronary artery ligation [229]. For this application the new solutions were developed for Tβ4 delivery. The injectable collagen–chitosan-based hydrogels loaded with Tβ4 were shown to impact heart regeneration by the stimulation of angiogenesis and migration of epicardial heart cells [230]. The controlled delivery and release of Tβ4 into the infarct area was also achieved by the same type of hydrogels with a beneficial effect on the reduction in heart tissue loss and revascularization [231]. The hydrogel solution provides mechanical support to the host tissue, adapting to the geometry of the ventricular space, and offers a less invasive strategy compared to the scaffold patches or other solutions. A similar approach of the long-term Tβ4 delivery was presented with poly(ethylene glycol) (PEG)-based hydrogels [184] or another version [185]. The active factor is released by proteolytic activity tissue-present metalloproteinases (MMPs). This biomatrix provides a three-dimensional environment that is desired when considering the regeneration of vascular structures and networks.

4.3. Hydrogels Loaded with Silver Nanoparticles

Given the growing prevalence of multidrug resistant (MDR) bacteria, nanoparticles (NPs) with inherent antibacterial potential, such as silver (Ag) [232], copper (Cu) [233], gold (Au) [234], zinc oxide (ZnO) NPs [235], and more, have emerged as promising alternatives for bacterial infection treatment and preventing biofilm formation [236]. NPs possess distinct physicochemical, optical, and biological properties that are crucial in biomedical applications [33,34]. They also exhibit complex antimicrobial mechanisms, significantly reducing the likelihood of bacterial drug-resistance development. NPs can penetrate the bacterial cell walls, then positive charges of NPs are linked to negatively charged sectors at the surfaces of bacteria. As a result, hydrophobic interactions can lead to holes in bacteria surfaces. In addition, they adversely impact the proton efflux pumps and subsequently, with a modification of the pH range, destroy the membrane's surface charge [236].

Moreover, NPs with small sizes and large surface areas, including polymeric, liposomal, lipid-based, and inorganic NPs, have the capacity to transport and release therapeutic agents at wound sites. Furthermore, these NPs can be integrated into a variety of wound dressing systems to enhance the safety and effectiveness of infected wound treatment [237]. Consequently, the development of intelligent nanomaterial-based hydrogel carriers capable of responding in a controlled manner to the specific microenvironmental stimuli created by bacterial infections or external stimuli is an effective strategy for the design of wound dressings. These stimuli include an acidic pH, excess of ROSs, bacterial-secreted toxins and enzymes, light, heat, and magnetic fields. So far, these intelligent nanocarriers undergo extensive research and hold the potential for further integration into wound dressings to enhance the wound healing process [87,238].

Among the different metal NPs, silver nanoparticles (AgNPs) are widely employed as bactericidal agents in the treatment of burns and various types of ulcers to prevent bacterial infections [238–241]. This is due to their unique surface properties, characterized by a high ratio of surface atoms to inner surface atoms and elevated surface energy, along with their small size, resulting in a substantial specific surface area [242]. These features enable AgNPs to disrupt the membrane structure and hinder enzyme activity in bacteria. AgNPs adhere to the bacterial cell membrane, subsequently releasing silver ions or intact nanoparticles into the bacterial cells. Within these cells, they interact with phosphorus and sulfur groups present in proteins and DNA, effectively exerting their antibacterial effects [243]. AgNPs are used in wound healing due to their remarkable anti-inflammatory and antibacterial properties. When AgNPs come into contact with the wound site, they interact with bacterial cells, disrupting their cell membranes and interfering with their metabolic processes. This action helps prevent or reduce infections at the wound site, which is a crucial aspect of efficient wound healing. Moreover, AgNPs exhibit anti-inflammatory effects by reducing immune cell activation and the release of pro-inflammatory cytokines. They also modulate neutrophil activity, helping to control excessive inflammation and creating a more conducive environment for the wound healing process [244–246].

The utilization of natural substances obtained from plants and microorganisms for the biosynthesis of nanoparticles has gained significant interest, primarily driven by the growing need to develop environmentally sustainable and non-toxic approaches. This method, which relies on renewable materials and avoids the use of hazardous chemicals and environmentally unfriendly solvents, renders the nanoparticles more suitable for various biomedical applications. Table 5 presents the latest advancements in stimuli-responsive hydrogels for wound healing that are enriched with AgNPs.

Table 5. Silver nanoparticles (AgNPs)-loaded stimuli-responsive wound dressing hydrogels.

Hydrogel Composition	Stimuli	Effects	Ref.
Cassava starch modified by carboxymethylation (CMS), poly vinyl alcohol (PVA), CMS/PVA–H tannic acid (TA), Silver nanoparticles (AgNPs) H-AgNPs	NIR pH	NIR-stimulated antibacterial activity pH-responsive TA release	[187]
Methacrylic acid (mAA), acrylamide (AAm), N, N′-Methylenebisacrylamide (MBMa), poly(mAA-co-AAm) hydrogel Mercaptossucinic acid (MSA)-protected AgNPs (MSA–AgNPs) poly(mAA-co-AAm)–AgNPs	pH	pH-dependent AgNP release	[188]
N-isopropylacrylamide (Nipam)+acrylic acid (AAc)→ Pnipam AgNPs Pnipam–PAA–AgNPs	pH Temp.	pH-dependent AgNPs' release Controlled release and delivery of AgNPs	[189]
N-isopropylacrylamide (NIPAAm), acrylamide (AAm), Ag_2S quantum dots (Ag_2SQDs) modified by $mSiO_2$ mesoporous silica, (NP hydrogel), 3-(trimethoxylmethosilyl) propyl methacrylate (MPS), Ag_2S QDs/$mSiO_2$ NP–MPS	NIR	NIR laser-induced controlled release of silver ions (Ag+)	[190]
Pluronics F127 and F68, hyaluronic acid (HA), corn silk extract (CSE), AgNPs Pluronic/HA/CSE/Ag	Temp.	Temperature-dependent sol–gel transition	[168]
methylcellulose (MC), citric acid (CA), AgNPs MC/AgNPs nanocomposite hydrogels	Temp. pH	Temperature-induced changes in swelling rate and rheological properties pH-induced changes in swelling rate and rheological properties	[15]
Ag nanoparticles/phosphotungstic acid–polydopamine nano-flowers (AgNPs/POM–PDA), chitosan, gelatin, AgNPs/POM–PDA@ chitosan/gelatin	NIR	Ag^+ release under NIR light irradiation	[191]

Srikhao et al. reported CMS/PVA–H hydrogels based on the idea of AgNP incorporation into cassava starch modified by carboxymethylation (CMS), mixed with PVA and TA. NIR stimulation of the fabricated hydrogel resulted in the generation of elevated temperatures from 21.5 to 31.7 °C, demonstrating enhanced photothermal capabilities [187]. The addition of (TA-reduced) AgNPs to the hydrogel also allowed a pH-responsive release of TA as a therapeutic agent. The increased levels of loaded AgNPs enhanced the antibacterial and mechanical properties of hydrogel. The obtained nanocomposite hydrogel showed remarkable potential for future applications in wound dressings. Haidari et al. developed a facile synthetic procedure to polymerize methacrylic acid (mAA) in combination with acrylamide (AAm) crosslinked with N,N′-Methylenebisacrylamide (MBMa) to establish a

sensitive pH-responsive hydrogel delivery system for AgNPs [188]. The prepared hydrogel restricts the release of AgNPs at an acidic pH (pH = 4) but substantially amplifies it at an alkaline pH (pH = 7.4 and pH = 10). This facilitates a controlled AgNP release and exhibits strong antibacterial properties against both Gram-negative and Gram-positive bacteria, all while remaining non-toxic to mammalian cells. A dual-responsive hydrogel (pnipam–PAA–AgNPs) was prepared by the Haidari research group [189]. They achieved this by crosslinking N-isopropyl acrylamide with acrylic acid and incorporating ultrasmall AgNPs. This hydrogel operates by adapting to the physiological conditions of an infected wound, enabling the "on-demand" release of ultrasmall AgNPs based on the wound's pathological state. It contains a pH-responsive component that swells as the pH increases, promoting the gradual release of AgNPs. It responds to changes in both pH and temperature, by transitioning from a hydrophilic to a hydrophobic state at a temperature near 37 °C. In infected wounds, where the pH is higher, the release of Ag^+ ions is accelerated, effectively eliminating bacteria and supporting wound healing. Moreover, the Pnipam–PAA–AgNPs hydrogel maintains its ability to respond to body temperature regardless of the pH conditions in the wound environment. This is advantageous in the context of infection treatment and wound healing.

Du et al. [190] designed a composite Ag_2S quantum dot/mSiO_2NPs hydrogel (NP hydrogel) with an antibacterial ability. It was constructed by incorporating Ag_2S quantum dots (QDs) modified by mesoporous silica (mSiO_2) into the network structure of 3-(trimethoxylmethosilyl) propyl methacrylate based on free radical polymerization. The hydrogel demonstrated remarkable performance, with a photothermal conversion efficiency of 57.3% when exposed to 808 nm near-infrared (NIR) light. Moreover, the hydrogel released silver ions (Ag^+) in a controlled manner in response to NIR laser-induced volume changes, enhancing its antibacterial properties. It efficiently eliminated 99.7% of *Escherichia coli* and 99.8% of methicillin-resistant *Staphylococcus aureus* (MRSA) within just 4 min under NIR laser exposure. It was also responsive to photodynamic therapy (PDT), generating reactive oxygen species (ROS) upon NIR light exposure, further aiding bacterial eradication. Thermosensitive, injectable nanocomposite hydrogels (Pluronic/HA/CSE/Ag) containing AgNPs demonstrated good mechanical properties with a gelation temperature close to the body temperature, thus allowing for the easy possibility of an application. They exhibited antibacterial activity toward Gram-positive and Gram-negative bacterial strains and allowed for a facilitated accelerated wound closure and regeneration process [168].

Methylcellulose (MC) and AgNPs-loaded hydrogels were prepared and crosslinked with citric acid (CA) at three different crosslinking degrees: low (MC-L), medium (MC-M), and high (MC-H). Pristine hydrogel (MC) was used as a control. All hydrogel variants at 25 °C exhibited a rapid swelling behavior, reaching a high degree of swelling (SR = 4000–6000%). Subsequently, they dissolved within 72 h, irrespective of the pH. This suggests that at a temperature lower than the phase transition temperature (T_t), these hydrogels were in a liquid state and underwent rapid dissolution in the aqueous environment. Highly crosslinked hydrogels (MC-H) displayed remarkable pH-responsive characteristics, mainly due to selective hydrolysis in an alkaline environment. As an accompanying phenomenon, a significant release of AgNPs was detected (several times higher at pH 12 than at pH 4). Temperature also affected the properties of described hydrogels because they exhibited a significantly higher swelling ratio at lower temperatures (25 °C) than at higher ones (50 °C). MC-H hydrogels were identified as a promising approach for in-situ synthesis of AgNPs, followed by pH-triggered release. This platform seems to be the potential solution to effectively regulate pathogen growth in chronically infected wounds characterized by an alkaline pH environment [15].

A bactericidal nanocomposite was obtained using Ag nanoparticles/phosphotungstic acid–polydopamine nanoparticles (AgNPs/POM–PDA). The final multifunctional wound dressing was obtained by embedding the resulting nanocomposite into the chitosan–gelatin hydrogel [191]. Ag^+ release from the hydrogel took place under NIR light irradiation. That process was responsible for excellent synergistic anti-bacterial activity against Gram-

negative *Escherichia coli* and Gram-positive *Staphylococcus aureus*. The synergistic effect of the simultaneous presence of AgNPs/POM–PDA nanocomposites and CS/GE hydrogel in the final formula remarkably accelerated wound healing in vivo due to the excellent biocompatibility, hydroabsorptivity, and breathability of the hydrogel. The in vivo infectious wound healing test showed that the obtained multicomponent hydrogel-based scaffolds promoted wound healing by inhibiting wound infection and reducing the inflammatory response.

4.4. Hydrogels Loaded with Antibiotics and Drugs

Although stimuli-responsive systems can deliver drugs in a controlled manner, the antibiotic-based strategy proves inefficient in the long run, ultimately leading to undesirable effects. This includes increasing local drug concentration at infection sites, antibiotic accumulation in healthy host tissues, the risks of toxicity, and exposure of commensal microflora to sub-lethal antibiotic doses [236]. The biggest danger that systems based on antibiotics face is the risk of the potential development of antimicrobial resistance associated with prolonged exposure to these substances. Moreover, biofilm-forming bacteria are less prone to the action of the human immune system due to the formation of a mechanical barrier as well as antiphagocytic properties of the resulting biofilm, limiting penetration and further action of antimicrobial agents. Secondly, the biofilm environment enables bacterial communication and thus promotes phenotypic changes that are enhanced by the use of antibiotics [247,248]. Besides contributing to the development of resistance, the use of topical antibiotics may also trigger adverse effects, including delayed hypersensitivity reactions, superinfections, and contact dermatitis [249]. In Table 6, the examples of the drug-loaded stimuli-responsive hydrogel formulas are presented.

Zhao et al. created an ROS-scavenging hydrogel designed to eliminate high ROS levels in wound sites [192]. This PVA-based hydrogel was an ROS-responsive TPA linker. Such construct was loaded with mupirocin (MP) (antibiotic) and a tissue-regenerating growth factor (GM-CSF). It showed antibacterial activity and effectively lowered intracellular ROS levels. Additionally, it decreased the secretion of pro-inflammatory factors, controlled macrophage behavior, stimulated the formation of new blood vessels and collagen, and markedly enhanced wound healing capabilities. The study utilized a freeze–thaw method to develop a pH-responsive hydrogel named FTS-G@PC, which is composed of polyvinyl alcohol (PVA) and chitosan (CS), with gentamicin (GS) incorporated and crosslinked within. This hydrogel is exceptionally biocompatible due to its use of natural wood and the physical crosslinking achieved through repeated freezing and thawing. Additionally, gentamicin was released in a weakly acidic pH and enhanced antibacterial capabilities, reducing bacterial growth and increasing mortality rates, especially against *Staphylococcus aureus* and *Escherichia coli* [193]. The uniqueness of this hydrogel lies in its biocompatibility, owing to the use of natural wood and the physical crosslinking achieved through freeze–thaw cycles.

Rezaei et al. [194] proposed the pH-sensitive vancomycin-loaded silk fibroin–sodium alginate nanoparticles (SF–SANPs) embedded in a poly(N-isopropylacrylamide) (PNIPAM) hydrogel containing epidermal growth factor (EGF) for the treatment of chronic burn wound infections. Vancomycin exhibited a pH-dependent release behavior from the nanoparticles with a higher release rate in an alkaline pH compared to the neutral pH values. Hu et al. [195] proposed a dual-responsive hydrogel system (Hydrogel@AM&MIC and Hydrogel@NAP&MIC) by grafting phenylboronic acid to the side chain of the alginate polymer. By grafting phenylboronic acid onto the alginate polymer's side chain, a highly specific hydrogel responsive to a low pH and high ROS levels was obtained. The hydrogel was endowed with antibacterial and anti-inflammatory properties respectively via the effective assembly of amikacin (antibiotic) and naproxen (anti-inflammatory drug) preloaded into the micelles.

Table 6. Antibiotic- and drug-loaded stimuli-responsive wound dressing hydrogels.

Hydrogel Composition	Stimuli	Effects	Ref.
N^1-(4-boronobenzyl)-N^3-(4-boronophenyl)-N^1, N^1, N^3, N^3-tetramethylpropane-1, 3-diaminium (TPA), poly(vinyl alcohol) (PVA) TPA + PVA = Hydrogel mupirocin (MP), granulocyte-macrophage colony-stimulating factor (GM-CSF),	ROS	ROS-responsive degradation	[192]
Triplochitin scleroxylon wood (TS), gentamicin (G), polyvinyl alcohol (PVA), chitosan (CS), FTS-G@PC Flexible wood-based hydrogel	pH	pH-responsive gentamicin release	[193]
Poly(N-isopropylacrylamide) (PNIPAM), epidermal growth factor (EGF), silk fibroin–sodium alginate, nanoparticles (SF–SANPs), Vancomycin (VANCO) PNIPAM and EGF/SF–SANPs	pH	pH-responsive vancomycin release	[194]
Hyaluronic acid (HA), boronic acid (BA), HA + BA = hydrogel micelle-loaded amikacin (AM), micelle-loaded naproxen (NAP), Hydrogel@AM&MIC Hydrogel@NAP&MIC	pH ROS	pH-dependent amikacin release ROS-responsive naproxen release	[195]
Poloxamer 188, solution of poloxamer 407, gentamicin	Temp.	Sol–gel transition at around 37 °C	[196]
Vinyl carboxymethyl chitosan (CG), graphene (GM), N-isopropylacrylamide (NIPAM), ciprofloxacin hydrochloride, NIPAM–CG/GM	Temp.	Temperature-dependent drug release	[197]
Pluronic F127 (PF127), complex of zinc and metformin, (ZnMet); ZnMet-PF127	Temp.	Sol–gel transition at around 37 °C	[198]

Niyompanich et al. designed poloxamer hydrogels loaded with the gentamicin sulfate, which exhibited antibacterial properties against *Escherichia coli*, *Bacillus cereus*, *Staphylococcus aureus*, and MRSA [196]. Temperature-sensitive NIPAM–CG/GM hydrogels [197] showed strong mechanical properties and an excellent drug loading capacity. Its phase transition closely matches the human body temperature, facilitating efficient drug release. Additionally, the hydrogel effectively prevents microbial invasion in wounds and ensures a moist conducive environment for healing without harmful bacteria.

Sprayable ZnMet-PF127 developed by Liu et al. [198] was used to evenly cover the surface of an irregular skin defect. The application of ZnMet-PF127 promoted granulation tissue formation, collagen deposition, new vessel formation, and inhibited ROS accumulation and inflammation. It also showed antibacterial activity against *Staphylococcus aureus* or *Escherichia coli*.

5. Conclusions and Perspectives

This review presents and discusses the-state-of-the-art discoveries regarding stimuli-responsive hydrogels used in wound healing and skin tissue regeneration. Over the last

few years, a plethora of various additives (e.g., polyphenols, polypeptides, nanoparticles) have been investigated and promising results have been obtained, as discussed in this review. However, the use of new types of additives to support the wound healing process could lead to significant breakthroughs in this field; a very good example is thymosin β4 discussed in Section 4.2. Despite these significant achievements, there are still important issues that need to be addressed in the future.

Firstly, ensuring high biocompatibility and cytocompatibility not only of the hydrogel itself but also of its degradation products needs to be addressed. For this reason, the development of hydrogels based on natural hydrogelators such as hyaluronic acid, chitosan, gelatin, and collagen is often considered as a first choice.

Secondly, despite great progress being made in the targeted release of bioactive agents/drugs, this field requires further clarification to achieve effective therapies that could be translated to the clinic. Some of the challenges here are: (i) the proper dosage for optimal treatment, (ii) identification of the hydrogel matrix influence on the releasing drug side effects as well as on therapeutic outcomes, and (iii) the precise control over the drug release profile with the minimalization of the unwanted drug-leakage during transportation and avoidance of possible off-target.

Thirdly, new chemical and physical crosslinking approaches better mimicking in vivo dynamic behavior are needed to be developed to broaden hydrogels' applications; those approaches may include inter alia click chemistry or enzymatic reactions. The projected routes should also focus on the fabrication of pH-responsive hydrogels that are more effective at an alkaline pH, given that the chronic wound environment is alkaline, but most pH-responsive hydrogels currently appear more friendly to acidic environments.

In the future, stimuli-responsive hydrogel-based dressings may provide an excellent control over the wound healing processes, and if integrated with a miniaturized sensor system, they will enable the tailoring of therapeutic strategies. It is worth mentioning that smart hydrogels integrated with sensors are actually conceptualized to deliver real-time information about the wound healing process. Real-time monitoring of the wound healing process is of paramount importance as many related processes and parameters dynamically change, which makes it difficult to develop a dressing that could simultaneously meets the needs of the entire healing process.

Finally, integration with other functional ingredients (e.g., hemostatic, conductive, or adhesive materials) will certainly bring the potential clinical application much closer. This translational approach requires the concerted endeavors of researchers and clinicians in this booming field.

Author Contributions: Conceptualization, A.M. and M.B.; literature review and writing, A.M., A.B., M.S. and M.B.; writing—original draft preparation, A.M., A.B., D.A.G., M.S. and M.B.; editing, A.M. and M.B.; supervision, M.B.; visualization, A.M., D.A.G. and M.B.; funding acquisition, M.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Polish National Science Centre, grant number 2021/41/B/ST5/03490, titled *Hierarchically cross-linked hydrogels: theoretical and experimental design for biomedical applications*.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Ding, X.; Tang, Q.; Xu, Z.; Xu, Y.; Zhang, H.; Zheng, D.; Wang, S.; Tan, Q.; Maitz, J.; Maitz, P.K.; et al. Challenges and innovations in treating chronic and acute wound infections: From basic science to clinical practice. *Burn. Trauma* **2022**, *10*, tkac014. [CrossRef]
2. Sen, C.K. Human Wound and Its Burden: Updated 2020 Compendium of Estimates. *Adv. Wound Care* **2021**, *10*, 281–292. [CrossRef] [PubMed]
3. Lin, X.; Xu, Y.; Pan, X.; Xu, J.; Ding, Y.; Sun, X.; Song, X.; Ren, Y.; Shan, P.F. Global, regional, and national burden and trend of diabetes in 195 countries and territories: An analysis from 1990 to 2025. *Sci. Rep.* **2020**, *10*, 14790. [CrossRef]
4. Saeedi, P.; Petersohn, I.; Salpea, P.; Malanda, B.; Karuranga, S.; Unwin, N.; Colagiuri, S.; Guariguata, L.; Motala, A.A.; Ogurtsova, K.; et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res. Clin. Pract.* **2019**, *157*, 107843. [CrossRef] [PubMed]
5. Xie, T.; Ye, J.; Rerkasem, K.; Mani, R. The venous ulcer continues to be a clinical challenge: An update. *Burn. Trauma* **2018**, *6*, 18. [CrossRef]
6. Dong, R.; Guo, B. Smart wound dressings for wound healing. *Nano Today* **2021**, *41*, 101290. [CrossRef]
7. Gomez-Florit, M.; Pardo, A.; Domingues, R.M.A.; Graça, A.L.; Babo, P.S.; Reis, R.L.; Gomes, M.E. Natural-Based Hydrogels for Tissue Engineering Applications. *Molecules* **2020**, *25*, 5858. [CrossRef] [PubMed]
8. Francesko, A.; Petkova, P.; Tzanov, T. Hydrogel Dressings for Advanced Wound Management. *Curr. Med. Chem.* **2019**, *25*, 5782–5797. [CrossRef]
9. Zhang, A.; Liu, Y.; Qin, D.; Sun, M.; Wang, T.; Chen, X. Research status of self-healing hydrogel for wound management: A review. *Int. J. Biol. Macromol.* **2020**, *164*, 2108–2123. [CrossRef]
10. Rezvani Ghomi, E.; Khalili, S.; Nouri Khorasani, S.; Esmaeely Neisiany, R.; Ramakrishna, S. Wound dressings: Current advances and future directions. *J. Appl. Polym. Sci.* **2019**, *136*, 47738. [CrossRef]
11. Bal-Öztürk, A.; Özkahraman, B.; Özbaş, Z.; Yaşayan, G.; Tamahkar, E.; Alarçin, E. Advancements and future directions in the antibacterial wound dressings–A review. *J. Biomed. Mater. Res. Part B Appl. Biomater.* **2021**, *109*, 703–716. [CrossRef] [PubMed]
12. Sharda, D.; Attri, K.; Choudhury, D. Future research directions of antimicrobial wound dressings. In *Antimicrobial Dressings: The Wound Care Applications*; Springer: Berlin/Heidelberg, Germany, 2023; pp. 229–246, ISBN 9780323950749.
13. Lindley, L.E.; Stojadinovic, O.; Pastar, I.; Tomic-Canic, M. Biology and biomarkers for wound healing. *Plast. Reconstr. Surg.* **2016**, *138*, 18S–28S. [CrossRef] [PubMed]
14. Raziyeva, K.; Kim, Y.; Zharkinbekov, Z.; Kassymbek, K.; Jimi, S.; Saparov, A. Immunology of acute and chronic wound healing. *Biomolecules* **2021**, *11*, 700. [CrossRef] [PubMed]
15. Bonetti, L.; Fiorati, A.; D'agostino, A.; Pelacani, C.M.; Chiesa, R.; Farè, S.; De Nardo, L. Smart Methylcellulose Hydrogels for pH-Triggered Delivery of Silver Nanoparticles. *Gels* **2022**, *8*, 298. [CrossRef] [PubMed]
16. Yang, A.; Yassin, M.; Phan, T. Vibrio mimicus wound infection in a burn patient. *Radiol. Case Rep.* **2021**, *16*, 1348–1351. [CrossRef] [PubMed]
17. Fabian, T.C. Damage Control in Trauma: Laparotomy Wound Management Acute to Chronic. *Surg. Clin. N. Am.* **2007**, *87*, 73–93. [CrossRef] [PubMed]
18. Furtado, K.A.X.; Infante, P.; Sobral, A.; Gaspar, P.; Eliseu, G.; Lopes, M. Prevalence of acute and chronic wounds–with emphasis on pressure ulcers–in integrated continuing care units in Alentejo, Portugal. *Int. Wound J.* **2020**, *17*, 1002–1010. [CrossRef]
19. Boodhoo, K.; Vlok, M.; Tabb, D.L.; Myburgh, K.H.; van de Vyver, M. Dysregulated healing responses in diabetic wounds occur in the early stages postinjury. *J. Mol. Endocrinol.* **2021**, *66*, 141–155. [CrossRef]
20. Okur, M.E.; Karantas, I.D.; Şenyiğit, Z.; Üstündağ Okur, N.; Siafaka, P.I. Recent trends on wound management: New therapeutic choices based on polymeric carriers. *Asian J. Pharm. Sci.* **2020**, *15*, 661–684. [CrossRef]
21. Anderson, K.; Hamm, R.L. Factors that impair wound healing. *J. Am. Coll. Clin. Wound Spec.* **2012**, *4*, 84–91. [CrossRef]
22. Mo, F.; Zhang, M.; Duan, X.; Lin, C.; Sun, D.; You, T. Recent Advances in Nanozymes for Bacteria-Infected Wound Therapy. *Int. J. Nanomed.* **2022**, *17*, 5947–5990. [CrossRef]
23. Smith, F.; Sharp, A. Undertaking a person-centred assessment of patients with chronic wounds. *Nurs. Stand.* **2019**, *34*, 77–82. [CrossRef]
24. Han, G.; Ceilley, R. Chronic Wound Healing: A Review of Current Management and Treatments. *Adv. Ther.* **2017**, *34*, 599–610. [CrossRef] [PubMed]
25. Gushiken, L.F.S.; Beserra, F.P.; Bastos, J.K.; Jackson, C.J.; Pellizzon, C.H. Cutaneous wound healing: An update from physiopathology to current therapies. *Life* **2021**, *11*, 665. [CrossRef]
26. Kearney, K.J.; Ariëns, R.A.S.; MacRae, F.L. The Role of Fibrin(ogen) in Wound Healing and Infection Control. *Semin. Thromb. Hemost.* **2022**, *48*, 174–187. [CrossRef] [PubMed]
27. Dharmaraja, A.T. Role of Reactive Oxygen Species (ROS) in Therapeutics and Drug Resistance in Cancer and Bacteria. *J. Med. Chem.* **2017**, *60*, 3221–3240. [CrossRef] [PubMed]
28. Daeschlein, G. Antimicrobial and antiseptic strategies in wound management. *Int. Wound J.* **2013**, *10*, 9–14. [CrossRef] [PubMed]
29. Mallik, A.K.; Chisty, A.H.; Khan, M.N.; Kabir, S.F.; Shahruzzaman; Rahman, M.M. Antibacterial Surface Modification to Prevent Biofilm Formation on Polymeric Biomaterials. In *Nanoscale Engineering of Biomaterials: Properties and Applications*; Springer: Berlin/Heidelberg, Germany, 2022; pp. 425–455, ISBN 9789811636677.
30. Hutchings, M.; Truman, A.; Wilkinson, B. Antibiotics: Past, present and future. *Curr. Opin. Microbiol.* **2019**, *51*, 72–80. [CrossRef]

31. Han, D.; Li, Y.; Liu, X.; Li, B.; Han, Y.; Zheng, Y.; Yeung, K.W.K.; Li, C.; Cui, Z.; Liang, Y.; et al. Rapid bacteria trapping and killing of metal-organic frameworks strengthened photo-responsive hydrogel for rapid tissue repair of bacterial infected wounds. *Chem. Eng. J.* **2020**, *396*, 125194. [CrossRef]
32. Chen, Y.; Wu, W.; Xu, Z.; Jiang, C.; Han, S.; Ruan, J.; Wang, Y. Photothermal-assisted antibacterial application of graphene oxide-Ag nanocomposites against clinically isolated multi-drug resistant *Escherichia coli*. *R. Soc. Open Sci.* **2020**, *7*, 192019. [CrossRef]
33. Liang, Y.; Liang, Y.; Zhang, H.; Guo, B. Antibacterial biomaterials for skin wound dressing. *Asian J. Pharm. Sci.* **2022**, *17*, 353–384. [CrossRef] [PubMed]
34. Laurano, R.; Boffito, M.; Ciardelli, G.; Chiono, V. Wound dressing products: A translational investigation from the bench to the market. *Eng. Regen.* **2022**, *3*, 182–200. [CrossRef]
35. Serpico, L.; Dello Iacono, S.; Cammarano, A.; De Stefano, L. Recent Advances in Stimuli-Responsive Hydrogel-Based Wound Dressing. *Gels* **2023**, *9*, 451. [CrossRef] [PubMed]
36. Sood, A.; Granick, M.S.; Tomaselli, N.L. Wound Dressings and Comparative Effectiveness Data. *Adv. Wound Care* **2014**, *3*, 511–529. [CrossRef] [PubMed]
37. Wei, S.; You, Y.; Ma, Y.; Huang, W.; Liang, X.; Zhang, A.; Lin, Y. Bi-layer supramolecular polydimethylsiloxane elastomer film: Synthesis, characterization, and application in wound dressing on normal and diabetic rat. *React. Funct. Polym.* **2019**, *141*, 21–32. [CrossRef]
38. Gwak, H.C.; Han, S.H.; Lee, J.; Park, S.; Sung, K.S.; Kim, H.J.; Chun, D.; Lee, K.; Ahn, J.H.; Kwak, K.; et al. Efficacy of a povidone-iodine foam dressing (Betafoam) on diabetic foot ulcer. *Int. Wound J.* **2020**, *17*, 91–99. [CrossRef] [PubMed]
39. Andersen, K.E.; Franken, C.P.M.; Gad, P.; Larsen, A.M.; Larsen, J.R.; van Neer, P.A.F.; Vuerstaek, J.; Wuite, J.; Neumann, H.A.M. A randomized, controlled study to compare the effectiveness of two foam dressings in the management of lower leg ulcers. *Ostomy Wound Manag.* **2002**, *48*, 34–41.
40. Pele, K.G.; Amaveda, H.; Mora, M.; Marcuello, C.; Lostao, A.; Alamán-Díez, P.; Pérez-Huertas, S.; Ángeles Pérez, M.; García-Aznar, J.M.; García-Gareta, E. Hydrocolloids of Egg White and Gelatin as a Platform for Hydrogel-Based Tissue Engineering. *Gels* **2023**, *9*, 505. [CrossRef]
41. Truhan-Ortiz, R.; Moffatt, L.T.; Robson, M.C.; Jordan, M.H.; Shupp, J.W. In vivo and in vitro evaluation of the properties of Drawtex®Levafiber™ wound dressing in an infected burn wound model. *Wound Repair Regen.* **2012**, *20*, A42.
42. Shen, Z.; Zhang, C.; Wang, T.; Xu, J. Advances in Functional Hydrogel Wound Dressings: A Review. *Polymers* **2023**, *15*, 2000. [CrossRef]
43. Xu, Q.; Torres, J.E.; Hakim, M.; Babiak, P.M.; Pal, P.; Battistoni, C.M.; Nguyen, M.; Panitch, A.; Solorio, L.; Liu, J.C. Collagen- and hyaluronic acid-based hydrogels and their biomedical applications. *Mater. Sci. Eng. R Rep.* **2021**, *146*, 100641. [CrossRef] [PubMed]
44. Shi, X.; Chen, Z.; He, Y.; Lu, Q.; Chen, R.; Zhao, C.; Dong, D.; Sun, Y.; He, H. Dual light-responsive cellulose nanofibril-based in situ hydrogel for drug-resistant bacteria infected wound healing. *Carbohydr. Polym.* **2022**, *297*, 120042. [CrossRef] [PubMed]
45. Norahan, M.H.; Pedroza-González, S.C.; Sánchez-Salazar, M.G.; Álvarez, M.M.; Trujillo de Santiago, G. *Structural and Biological Engineering of 3D Hydrogels for Wound Healing*; Elsevier: Amsterdam, The Netherlands, 2023; Volume 24, pp. 197–235.
46. Huang, C.; Dong, L.; Zhao, B.; Lu, Y.; Huang, S.; Yuan, Z.; Luo, G.; Xu, Y.; Qian, W. Anti-inflammatory hydrogel dressings and skin wound healing. *Clin. Transl. Med.* **2022**, *12*, e1094. [CrossRef] [PubMed]
47. Caló, E.; Khutoryanskiy, V.V. Biomedical applications of hydrogels: A review of patents and commercial products. *Eur. Polym. J.* **2015**, *65*, 252–267. [CrossRef]
48. Aswathy, S.H.; Narendrakumar, U.; Manjubala, I. Commercial hydrogels for biomedical applications. *Heliyon* **2020**, *6*, e03719. [CrossRef]
49. Zeng, Z.; Zhu, M.; Chen, L.; Zhang, Y.; Lu, T.; Deng, Y.; Ma, W.; Xu, J.; Huang, C.; Xiong, R. Design the molecule structures to achieve functional advantages of hydrogel wound dressings: Advances and strategies. *Compos. Part B Eng.* **2022**, *247*, 110313. [CrossRef]
50. Sathyaraj, W.V.; Prabakaran, L.; Bhoopathy, J.; Dharmalingam, S.; Karthikeyan, R.; Atchudan, R. Therapeutic Efficacy of Polymeric Biomaterials in Treating Diabetic Wounds—An Upcoming Wound Healing Technology. *Polymers* **2023**, *15*, 1205. [CrossRef]
51. Li, T.; Sun, M.; Wu, S. State-of-the-Art Review of Electrospun Gelatin-Based Nanofiber Dressings for Wound Healing Applications. *Nanomaterials* **2022**, *12*, 784. [CrossRef]
52. Huang, Y.; Bai, L.; Yang, Y.; Yin, Z.; Guo, B. Biodegradable gelatin/silver nanoparticle composite cryogel with excellent antibacterial and antibiofilm activity and hemostasis for Pseudomonas aeruginosa-infected burn wound healing. *J. Colloid Interface Sci.* **2022**, *608*, 2278–2289. [CrossRef]
53. Ahmad, N.; Ahmad, M.M.; Alruwaili, N.K.; Alrowaili, Z.A.; Alomar, F.A.; Akhtar, S.; Alsaidan, O.A.; Alhakamy, N.A.; Zafar, A.; Elmowafy, M.; et al. Antibiotic-loaded psyllium husk hemicellulose and gelatin-based polymeric films for wound dressing application. *Pharmaceutics* **2021**, *13*, 236. [CrossRef]
54. Li, Z.; Huang, J.; Jiang, Y.; Liu, Y.; Qu, G.; Chen, K.; Zhao, Y.; Wang, P.; Wu, X.; Ren, J. Novel Temperature-Sensitive Hydrogel Promotes Wound Healing Through YAP and MEK-Mediated Mechanosensitivity. *Adv. Healthc. Mater.* **2022**, *11*, e2201878. [CrossRef]

55. Alven, S.; Peter, S.; Aderibigbe, B.A. Polymer-Based Hydrogels Enriched with Essential Oils: A Promising Approach for the Treatment of Infected Wounds. *Polymers* **2022**, *14*, 3772. [CrossRef]
56. Koehler, J.; Brandl, F.P.; Goepferich, A.M. Hydrogel wound dressings for bioactive treatment of acute and chronic wounds. *Eur. Polym. J.* **2018**, *100*, 1–11. [CrossRef]
57. Kamoun, E.A.; Kenawy, E.R.S.; Chen, X. A review on polymeric hydrogel membranes for wound dressing applications: PVA-based hydrogel dressings. *J. Adv. Res.* **2017**, *8*, 217–233. [CrossRef] [PubMed]
58. Liu, Y.; Song, S.; Liu, S.; Zhu, X.; Wang, P. Application of Nanomaterial in Hydrogels Related to Wound Healing. *J. Nanomater.* **2022**, *2022*, 4656037. [CrossRef]
59. Wang, S.; Wang, Z.; Xu, C.; Cui, L.; Meng, G.; Yang, S.; Wu, J.; Liu, Z.; Guo, X. PEG-α-CD/AM/liposome @amoxicillin double network hydrogel wound dressing—Multiple barriers for long-term drug release. *J. Biomater. Appl.* **2021**, *35*, 1085–1095. [CrossRef] [PubMed]
60. Fan, P.; Zeng, Y.; Zaldivar-Silva, D.; Agüero, L.; Wang, S. Chitosan-Based Hemostatic Hydrogels: The Concept, Mechanism, Application, and Prospects. *Molecules* **2023**, *28*, 1473. [CrossRef]
61. Guo, S.; Ren, Y.; Chang, R.; He, Y.; Zhang, D.; Guan, F.; Yao, M. Injectable Self-Healing Adhesive Chitosan Hydrogel with Antioxidative, Antibacterial, and Hemostatic Activities for Rapid Hemostasis and Skin Wound Healing. *ACS Appl. Mater. Interfaces* **2022**, *14*, 34455–34469. [CrossRef]
62. Wu, C.; Zhou, Z.; You, X.; Guo, Y.; Chen, P.; Li, H.; Tong, X. Tannic acid-loaded hydrogel coating endues polypropylene mesh with hemostatic and anti-inflammatory capacity for facilitating pelvic floor repair. *Regen. Biomater.* **2022**, *9*, rbac074. [CrossRef]
63. Zhou, Z.; Xiao, J.; Guan, S.; Geng, Z.; Zhao, R.; Gao, B. A hydrogen-bonded antibacterial curdlan-tannic acid hydrogel with an antioxidant and hemostatic function for wound healing. *Carbohydr. Polym.* **2022**, *285*, 119235. [CrossRef]
64. Sun, X.; Tang, Z.; Pan, M.; Wang, Z.; Yang, H.; Liu, H. Chitosan/kaolin composite porous microspheres with high hemostatic efficacy. *Carbohydr. Polym.* **2017**, *177*, 135–143. [CrossRef] [PubMed]
65. Laurenti, J.B.; Zazeri, G.; Povinelli, A.P.R.; de Godoy, M.F.; Braile, D.M.; da Rocha, T.R.F.; D'Amico, É.A.; Nery, J.G. Enhanced pro-coagulant hemostatic agents based on nanometric zeolites. *Microporous Mesoporous Mater.* **2017**, *239*, 263–271. [CrossRef]
66. Liang, Y.; Xu, C.; Li, G.; Liu, T.; Liang, J.F.; Wang, X. Graphene-kaolin composite sponge for rapid and riskless hemostasis. *Colloids Surf. B Biointerfaces* **2018**, *169*, 168–175. [CrossRef] [PubMed]
67. Liu, C.; Yao, W.; Tian, M.; Wei, J.; Song, Q.; Qiao, W. Mussel-inspired degradable antibacterial polydopamine/silica nanoparticle for rapid hemostasis. *Biomaterials* **2018**, *179*, 83–95. [CrossRef] [PubMed]
68. Michalicha, A.; Roguska, A.; Przekora, A.; Budzyńska, B.; Belcarz, A. Poly(levodopa)-modified β-glucan as a candidate for wound dressings. *Carbohydr. Polym.* **2021**, *272*, 118485. [CrossRef]
69. Cheng, C.; Peng, X.; Xi, L.; Wan, C.; Shi, S.; Wang, Y.; Yu, X. An agar-polyvinyl alcohol hydrogel loaded with tannic acid with efficient hemostatic and antibacterial capacity for wound dressing. *Food Funct.* **2022**, *13*, 9622–9634. [CrossRef] [PubMed]
70. Ahmadian, Z.; Correia, A.; Hasany, M.; Figueiredo, P.; Dobakhti, F.; Eskandari, M.R.; Hosseini, S.H.; Abiri, R.; Khorshid, S.; Hirvonen, J.; et al. A Hydrogen-Bonded Extracellular Matrix-Mimicking Bactericidal Hydrogel with Radical Scavenging and Hemostatic Function for pH-Responsive Wound Healing Acceleration. *Adv. Healthc. Mater.* **2021**, *10*, 2001122. [CrossRef] [PubMed]
71. Zhang, X.; Ma, Z.; Ke, Y.; Xia, Y.; Xu, X.; Liu, J.; Gong, Y.; Shi, Q.; Yin, J. An injectable serotonin-chondroitin sulfate hydrogel for bio-inspired hemostatic adhesives with high wound healing capability. *Mater. Adv.* **2021**, *2*, 5150–5159. [CrossRef]
72. Michalicha, A.; Pałka, K.; Roguska, A.; Pisarek, M.; Belcarz, A. Polydopamine-coated curdlan hydrogel as a potential carrier of free amino group-containing molecules. *Carbohydr. Polym.* **2021**, *256*, 117524. [CrossRef]
73. He, R.; Zhou, D.; Xiao, L.; Li, Y. Chlorella vulgaris Extract-Decorated Gold Nanoparticle Hybridized Antimicrobial Hydrogel as a Potential Dressing. *Gels* **2023**, *9*, 11. [CrossRef]
74. Wu, Y.; Li, X.; Wang, Y.; Shi, Y.; Wang, F.; Lin, G. Research progress on mechanical properties and wear resistance of cartilage repair hydrogel. *Mater. Des.* **2022**, *216*, 110575. [CrossRef]
75. Alven, S.; Aderibigbe, B.A. Fabrication of hybrid nanofibers from biopolymers and poly (Vinyl alcohol)/poly (ε-caprolactone) for wound dressing applications. *Polymers* **2021**, *13*, 2104. [CrossRef] [PubMed]
76. Wang, Z.; An, G.; Zhu, Y.; Liu, X.; Chen, Y.; Wu, H.; Wang, Y.; Shi, X.; Mao, C. 3D-printable self-healing and mechanically reinforced hydrogels with host-guest non-covalent interactions integrated into covalently linked networks. *Mater. Horiz.* **2019**, *6*, 733–742. [CrossRef] [PubMed]
77. Wei, Z.; Yang, J.H.; Zhou, J.; Xu, F.; Zrínyi, M.; Dussault, P.H.; Osada, Y.; Chen, Y.M. Self-healing gels based on constitutional dynamic chemistry and their potential applications. *Chem. Soc. Rev.* **2014**, *43*, 8114–8131. [CrossRef] [PubMed]
78. Karvinen, J.; Kellomäki, M. Characterization of self-healing hydrogels for biomedical applications. *Eur. Polym. J.* **2022**, *181*, 111641. [CrossRef]
79. Nasra, S.; Patel, M.; Shukla, H.; Bhatt, M.; Kumar, A. Functional hydrogel-based wound dressings: A review on biocompatibility and therapeutic efficacy. *Life Sci.* **2023**, *334*, 122232. [CrossRef]
80. Zhang, S.; Ge, G.; Qin, Y.; Li, W.; Dong, J.; Mei, J.; Ma, R.; Zhang, X.; Bai, J.; Zhu, C.; et al. Recent advances in responsive hydrogels for diabetic wound healing. *Mater. Today Bio* **2023**, *18*, 100508. [CrossRef] [PubMed]
81. Rasool, A.; Ata, S.; Islam, A. Stimuli responsive biopolymer (chitosan) based blend hydrogels for wound healing application. *Carbohydr. Polym.* **2019**, *203*, 423–429. [CrossRef]

82. Deng, Z.; Yu, R.; Guo, B. Stimuli-responsive conductive hydrogels: Design, properties, and applications. *Mater. Chem. Front.* **2021**, *5*, 2092–2123. [CrossRef]
83. Koetting, M.C.; Peters, J.T.; Steichen, S.D.; Peppas, N.A. Stimulus-responsive hydrogels: Theory, modern advances, and applications. *Mater. Sci. Eng. R Rep.* **2015**, *93*, 1–49. [CrossRef]
84. Sikdar, P.; Uddin, M.M.; Dip, T.M.; Islam, S.; Hoque, M.S.; Dhar, A.K.; Wu, S. Recent advances in the synthesis of smart hydrogels. *Mater. Adv.* **2021**, *2*, 4532–4573. [CrossRef]
85. Mantha, S.; Pillai, S.; Khayambashi, P.; Upadhyay, A.; Zhang, Y.; Tao, O.; Pham, H.M.; Tran, S.D. Smart Hydrogels in Tissue Engineering and Regenerative Medicine. *Materials* **2019**, *12*, 3323. [CrossRef] [PubMed]
86. Yang, X.; Zhang, C.; Deng, D.; Gu, Y.; Wang, H.; Zhong, Q. Multiple Stimuli-Responsive MXene-Based Hydrogel as Intelligent Drug Delivery Carriers for Deep Chronic Wound Healing. *Small* **2022**, *18*, 2104368. [CrossRef] [PubMed]
87. Pang, Q.; Jiang, Z.; Wu, K.; Hou, R.; Zhu, Y. Nanomaterials-Based Wound Dressing for Advanced Management of Infected Wound. *Antibiotics* **2023**, *12*, 351. [CrossRef]
88. Panda, P.K.; Yang, J.M.; Chang, Y.H. Water-induced shape memory behavior of poly (vinyl alcohol) and p-coumaric acid-modified water-soluble chitosan blended membrane. *Carbohydr. Polym.* **2021**, *257*, 117633. [CrossRef]
89. Cui, Y.; Tan, M.; Zhu, A.; Guo, M. Mechanically strong and stretchable PEG-based supramolecular hydrogel with water-responsive shape-memory property. *J. Mater. Chem. B* **2014**, *2*, 2978–2982. [CrossRef]
90. Gu, L.; Jiang, Y.; Hu, J. Bioinspired poly(vinyl alcohol)-silk hybrids: Two-way water-sensitive shape-memory materials. *Mater. Today Commun.* **2018**, *17*, 419–426. [CrossRef]
91. Panda, P.K.; Dash, P.; Biswal, A.K.; Chang, Y.H.; Misra, P.K.; Yang, J.M. Synthesis and Characterization of Modified Poly(vinyl alcohol) Membrane and Study of Its Enhanced Water-Induced Shape-Memory Behavior. *J. Polym. Environ.* **2022**, *30*, 3409–3419. [CrossRef]
92. Yang, G.; Zhang, Z.; Liu, K.; Ji, X.; Fatehi, P.; Chen, J. A cellulose nanofibril-reinforced hydrogel with robust mechanical, self-healing, pH-responsive and antibacterial characteristics for wound dressing applications. *J. Nanobiotechnol.* **2022**, *20*, 312. [CrossRef]
93. Xu, Z.; Liu, G.; Li, Q.; Wu, J. A novel hydrogel with glucose-responsive hyperglycemia regulation and antioxidant activity for enhanced diabetic wound repair. *Nano Res.* **2022**, *15*, 5305–5315. [CrossRef]
94. Zhou, X.; Zhou, Q.; Chen, Q.; Ma, Y.; Wang, Z.; Luo, L.; Ding, Q.; Li, H.; Tang, S. Carboxymethyl Chitosan/Tannic Acid Hydrogel with Antibacterial, Hemostasis, and Antioxidant Properties Promoting Skin Wound Repair. *ACS Biomater. Sci. Eng.* **2023**, *9*, 437–448. [CrossRef]
95. Ninan, N.; Forget, A.; Shastri, V.P.; Voelcker, N.H.; Blencowe, A. Antibacterial and Anti-Inflammatory pH-Responsive Tannic Acid-Carboxylated Agarose Composite Hydrogels for Wound Healing. *ACS Appl. Mater. Interfaces* **2016**, *8*, 28511–28521. [CrossRef] [PubMed]
96. Sahiner, N.; Sagbas, S.; Sahiner, M.; Silan, C.; Aktas, N.; Turk, M. Biocompatible and biodegradable poly(Tannic Acid) hydrogel with antimicrobial and antioxidant properties. *Int. J. Biol. Macromol.* **2016**, *82*, 150–159. [CrossRef] [PubMed]
97. Vivero-Lopez, M.; Muras, A.; Silva, D.; Serro, A.P.; Otero, A.; Concheiro, A.; Alvarez-Lorenzo, C. Resveratrol-loaded hydrogel contact lenses with antioxidant and antibiofilm performance. *Pharmaceutics* **2021**, *13*, 532. [CrossRef] [PubMed]
98. Gaharwar, A.K.; Peppas, N.A.; Khademhosseini, A. Nanocomposite hydrogels for biomedical applications. *Biotechnol. Bioeng.* **2014**, *111*, 441–453. [CrossRef] [PubMed]
99. Liu, J.; Qu, S.; Suo, Z.; Yang, W. Functional hydrogel coatings. *Natl. Sci. Rev.* **2021**, *8*, 2021. [CrossRef] [PubMed]
100. Li, Z.; Zhou, Y.; Li, T.; Zhang, J.; Tian, H. Stimuli-responsive hydrogels: Fabrication and biomedical applications. *View* **2022**, *3*, 20200112. [CrossRef]
101. Vigata, M.; Meinert, C.; Bock, N.; Dargaville, B.L.; Hutmacher, D.W. Deciphering the molecular mechanism of water interaction with gelatin methacryloyl hydrogels: Role of ionic strength, ph, drug loading and hydrogel network characteristics. *Biomedicines* **2021**, *9*, 574. [CrossRef]
102. Andrade, F.; Roca-Melendres, M.M.; Durán-Lara, E.F.; Rafael, D.; Schwartz, S. Stimuli-Responsive Hydrogels for Cancer Treatment: The Role of pH, Light, Ionic Strength and Magnetic Field. *Cancers* **2021**, *13*, 1164. [CrossRef]
103. Feng, Y.; Taraban, M.; Yu, Y.B. The effect of ionic strength on the mechanical, structural and transport properties of peptide hydrogels. *Soft Matter* **2012**, *8*, 11723–11731. [CrossRef]
104. Cui, T.; Yu, J.; Wang, C.F.; Chen, S.; Li, Q.; Guo, K.; Qing, R.; Wang, G.; Ren, J. Micro-Gel Ensembles for Accelerated Healing of Chronic Wound via pH Regulation. *Adv. Sci.* **2022**, *9*, 2201254. [CrossRef] [PubMed]
105. Schneider, L.A.; Korber, A.; Grabbe, S.; Dissemond, J. Influence of pH on wound-healing: A new perspective for wound-therapy? *Arch. Dermatol. Res.* **2007**, *298*, 413–420. [CrossRef]
106. Jiang, H.; Ochoa, M.; Waimin, J.F.; Rahimi, R.; Ziaie, B. A pH-regulated drug delivery dermal patch for targeting infected regions in chronic wounds. *Lab Chip* **2019**, *19*, 2265–2274. [CrossRef] [PubMed]
107. Villanueva, M.E.; Cuestas, M.L.; Pérez, C.J.; Campo Dall′ Orto, V.; Copello, G.J. Smart release of antimicrobial ZnO nanoplates from a pH-responsive keratin hydrogel. *J. Colloid Interface Sci.* **2019**, *536*, 372–380. [CrossRef] [PubMed]
108. Han, Z.; Yuan, M.; Liu, L.; Zhang, K.; Zhao, B.; He, B.; Liang, Y.; Li, F. pH-Responsive wound dressings: Advances and prospects. *Nanoscale Horiz.* **2023**, *8*, 422–440. [CrossRef] [PubMed]

109. Khan, M.U.A.; Iqbal, I.; Ansari, M.N.M.; Razak, S.I.A.; Raza, M.A.; Sajjad, A.; Jabeen, F.; Mohamad, M.R.; Jusoh, N. Development of antibacterial, degradable and ph-responsive chitosan/guar gum/polyvinyl alcohol blended hydrogels for wound dressing. *Molecules* **2021**, *26*, 5937. [CrossRef]
110. Ghobashy, M.M.; Elbarbary, A.M.; Hegazy, D.E.; Maziad, N.A. Radiation synthesis of pH-sensitive 2-(dimethylamino)ethyl methacrylate/ polyethylene oxide/ZnS nanocomposite hydrogel membrane for wound dressing application. *J. Drug Deliv. Sci. Technol.* **2022**, *73*, 103399. [CrossRef]
111. Fan, X.; Yang, L.; Wang, T.; Sun, T.; Lu, S. pH-responsive cellulose-based dual drug-loaded hydrogel for wound dressing. *Eur. Polym. J.* **2019**, *121*, 109290. [CrossRef]
112. Qu, J.; Zhao, X.; Liang, Y.; Zhang, T.; Ma, P.X.; Guo, B. Antibacterial adhesive injectable hydrogels with rapid self-healing, extensibility and compressibility as wound dressing for joints skin wound healing. *Biomaterials* **2018**, *183*, 185–199. [CrossRef]
113. Shao, W.; Liu, H.; Wu, J.; Wang, S.; Liu, X.; Huang, M.; Xu, P. Preparation, antibacterial activity and pH-responsive release behavior of silver sulfadiazine loaded bacterial cellulose for wound dressing applications. *J. Taiwan Inst. Chem. Eng.* **2016**, *63*, 404–410. [CrossRef]
114. Qureshi, M.A.; Khatoon, F. In Vitro Study of Temperature and pH-Responsive Gentamycin Sulphate-Loaded Chitosan-Based Hydrogel Films for Wound Dressing Applications. *Polym.-Plast. Technol. Eng.* **2015**, *54*, 573–580. [CrossRef]
115. Ding, C.; Tian, M.; Feng, R.; Dang, Y.; Zhang, M. Novel Self-Healing Hydrogel with Injectable, pH-Responsive, Strain-Sensitive, Promoting Wound-Healing, and Hemostatic Properties Based on Collagen and Chitosan. *ACS Biomater. Sci. Eng.* **2020**, *6*, 3855–3867. [CrossRef]
116. Morey, M.; Pandit, A. Responsive triggering systems for delivery in chronic wound healing. *Adv. Drug Deliv. Rev.* **2018**, *129*, 169–193. [CrossRef] [PubMed]
117. Augustine, R.; Dominic, E.A.; Reju, I.; Kaimal, B.; Kalarikkal, N.; Thomas, S. Investigation of angiogenesis and its mechanism using zinc oxide nanoparticle-loaded electrospun tissue engineering scaffolds. *RSC Adv.* **2014**, *4*, 51528–51536. [CrossRef]
118. Hu, J.; Liu, Z.; Yu, Q.; Ma, T. Preparation of reactive oxygen species-responsive antibacterial hydrogels for efficient anti-infection therapy. *Mater. Lett.* **2020**, *263*, 127254. [CrossRef]
119. Liu, S.; Li, X.; Han, L. Recent developments in stimuli-responsive hydrogels for biomedical applications. *Biosurf. Biotribol.* **2022**, *8*, 290–306. [CrossRef]
120. Dunnill, C.; Patton, T.; Brennan, J.; Barrett, J.; Dryden, M.; Cooke, J.; Leaper, D.; Georgopoulos, N.T. Reactive oxygen species (ROS) and wound healing: The functional role of ROS and emerging ROS-modulating technologies for augmentation of the healing process. *Int. Wound J.* **2017**, *14*, 89–96. [CrossRef] [PubMed]
121. Thirupathi, A.; Gu, Y.; Pinho, R.A. Exercise cuts both ways with ROS in remodifying innate and adaptive responses: Rewiring the redox mechanism of the immune system during exercise. *Antioxidants* **2021**, *10*, 1846. [CrossRef]
122. Ma, N.; Li, Y.; Xu, H.; Wang, Z.; Zhang, X. Dual redox responsive assemblies formed from diselenide block copolymers. *J. Am. Chem. Soc.* **2010**, *132*, 442–443. [CrossRef]
123. Pan, W.; Qi, X.; Xiang, Y.; You, S.; Cai, E.; Gao, T.; Tong, X.; Hu, R.; Shen, J.; Deng, H. Facile formation of injectable quaternized chitosan/tannic acid hydrogels with antibacterial and ROS scavenging capabilities for diabetic wound healing. *Int. J. Biol. Macromol.* **2022**, *195*, 190–197. [CrossRef]
124. Ye, H.; Zhou, Y.; Liu, X.; Chen, Y.; Duan, S.; Zhu, R.; Liu, Y.; Yin, L. Recent Advances on Reactive Oxygen Species-Responsive Delivery and Diagnosis System. *Biomacromolecules* **2019**, *20*, 2441–2463. [CrossRef]
125. Khorsandi, K.; Hosseinzadeh, R.; Esfahani, H.S.; Zandsalimi, K.; Shahidi, F.K.; Abrahamse, H. Accelerating skin regeneration and wound healing by controlled ROS from photodynamic treatment. *Inflamm. Regen.* **2022**, *42*, 40. [CrossRef] [PubMed]
126. Alves, P.M.; Barrias, C.C.; Gomes, P.; Martins, M.C.L. Smart biomaterial-based systems for intrinsic stimuli-responsive chronic wound management. *Mater. Today Chem.* **2021**, *22*, 100623. [CrossRef]
127. Fierheller, M.; Sibbald, R.G. A clinical investigation into the relationship between increased periwound skin temperature and local wound infection in patients with chronic leg ulcers. *Adv. Skin Wound Care* **2010**, *23*, 369–379. [CrossRef] [PubMed]
128. Said, S.S.; Campbell, S.; Hoare, T. Externally Addressable Smart Drug Delivery Vehicles: Current Technologies and Future Directions. *Chem. Mater.* **2019**, *31*, 4971–4989. [CrossRef]
129. Chen, Y.; Wang, X.; Tao, S.; Wang, Q.; Ma, P.Q.; Li, Z.B.; Wu, Y.L.; Li, D.W. Research advances in smart responsive-hydrogel dressings with potential clinical diabetic wound healing properties. *Mil. Med. Res.* **2023**, *10*, 37. [CrossRef] [PubMed]
130. Ullah, F.; Othman, M.B.H.; Javed, F.; Ahmad, Z.; Akil, H.M. Classification, processing and application of hydrogels: A review. *Mater. Sci. Eng. C* **2015**, *57*, 414–433. [CrossRef] [PubMed]
131. Huang, C.L.; Huang, H.Y.; Lu, Y.C.; Cheng, C.J.; Lee, T.M. Development of a flexible film made of polyvinyl alcohol with chitosan based thermosensitive hydrogel. *J. Dent. Sci.* **2023**, *18*, 822–832. [CrossRef]
132. Lin, X.; Guan, X.; Wu, Y.; Zhuang, S.; Wu, Y.; Du, L.; Zhao, J.; Rong, J.; Zhao, J.; Tu, M. An alginate/poly(N-isopropylacrylamide)-based composite hydrogel dressing with stepwise delivery of drug and growth factor for wound repair. *Mater. Sci. Eng. C* **2020**, *115*, 111123. [CrossRef]
133. Chatterjee, S.; Hui, P.C.L.; Kan, C. Thermoresponsive hydrogels and their biomedical applications: Special insight into their applications in textile based transdermal therapy. *Polymers* **2018**, *10*, 480. [CrossRef]
134. Klouda, L. Thermoresponsive hydrogels in biomedical applications A seven-year update. *Eur. J. Pharm. Biopharm.* **2015**, *97*, 338–349. [CrossRef] [PubMed]

135. Juang, R.S.; Wang, K.S.; Cheng, Y.W.; Wu, W.E.; Lin, Y.H.; Jeng, R.J.; Huang, L.Y.; Yang, M.C.; Liu, S.H.; Liu, T.Y. Intelligent and thermo-responsive Au-pluronic®F127 nanocapsules for Raman-enhancing detection of biomolecules. *Spectrochim. Acta Part A Mol. Biomol. Spectrosc.* **2022**, *279*, 121475. [CrossRef] [PubMed]
136. Zhang, K.; Xue, K.; Loh, X.J. Thermo-responsive hydrogels: From recent progress to biomedical applications. *Gels* **2021**, *7*, 77. [CrossRef] [PubMed]
137. Qureshi, D.; Nayak, S.K.; Maji, S.; Anis, A.; Kim, D.; Pal, K. Environment sensitive hydrogels for drug delivery applications. *Eur. Polym. J.* **2019**, *120*, 109220. [CrossRef]
138. Ward, M.A.; Georgiou, T.K. Thermoresponsive polymers for biomedical applications. *Polymers* **2011**, *3*, 1215. [CrossRef]
139. Tang, Y.; Wang, G. NIR light-responsive nanocarriers for controlled release. *J. Photochem. Photobiol. C Photochem. Rev.* **2021**, *47*, 100420. [CrossRef]
140. Psarrou, M.; Mitraki, A.; Vamvakaki, M.; Kokotidou, C. Stimuli-Responsive Polysaccharide Hydrogels and Their Composites for Wound Healing Applications. *Polymers* **2023**, *15*, 986. [CrossRef]
141. Liu, X.; Wu, Y.; Lin, Q.; Cheng, J.; Lin, F.; Tang, L.; Huang, B.; Lu, B. Polydopamine-coated cellulose nanocrystal as functional filler to fabricate nanocomposite hydrogel with controllable performance in response to near-infrared light. *Cellulose* **2021**, *28*, 2255–2271. [CrossRef]
142. Eells, J.T.; Gopalakrishnan, S.; Valter, K. Near-infrared photobiomodulation in retinal injury and disease. *Adv. Exp. Med. Biol.* **2016**, *854*, 437–441.
143. Qiu, H.; Tan, M.; Ohulchanskyy, T.Y.; Lovell, J.F.; Chen, G. Recent progress in upconversion photodynamic therapy. *Nanomaterials* **2018**, *8*, 344. [CrossRef]
144. Wu, S.; Butt, H.J. Near-Infrared-Sensitive Materials Based on Upconverting Nanoparticles. *Adv. Mater.* **2016**, *28*, 1208–1226. [CrossRef] [PubMed]
145. Yu, Z.; Sun, J.; Deng, H.; Kan, H.; Xu, C.; Dong, K. Skin-permissible NIR-actuated hyperthermia using a photothermally responsive hydrogel membrane for the effective treatment of antibiotic-resistant bacterial infection. *Biomater. Sci.* **2022**, *10*, 960–969. [CrossRef]
146. Han, Q.; Lau, J.W.; Do, T.C.; Zhang, Z.; Xing, B. Near-Infrared Light Brightens Bacterial Disinfection: Recent Progress and Perspectives. *ACS Appl. Bio Mater.* **2021**, *4*, 3937–3961. [CrossRef] [PubMed]
147. Xie, G.; Du, S.; Huang, Q.; Mo, M.; Gao, Y.; Li, M.; Tao, J.; Zhang, L.; Zhu, J. Photonic Hydrogels for Synergistic Visual Bacterial Detection and On-Site Photothermal Disinfection. *ACS Appl. Mater. Interfaces* **2022**, *14*, 5856–5866. [CrossRef] [PubMed]
148. Liu, C.; Wang, Z.; Wei, X.; Chen, B.; Luo, Y. 3D printed hydrogel/PCL core/shell fiber scaffolds with NIR-triggered drug release for cancer therapy and wound healing. *Acta Biomater.* **2021**, *131*, 314–325. [CrossRef] [PubMed]
149. Wang, W.; Sheng, H.; Cao, D.; Zhang, F.; Zhang, W.; Yan, F.; Ding, D.; Cheng, N. S-nitrosoglutathione functionalized polydopamine nanoparticles incorporated into chitosan/gelatin hydrogel films with NIR-controlled photothermal/NO-releasing therapy for enhanced wound healing. *Int. J. Biol. Macromol.* **2022**, *200*, 77–86. [CrossRef]
150. Feng, L.; Chen, Q.; Cheng, H.; Yu, Q.; Zhao, W.; Zhao, C. Dually-Thermoresponsive Hydrogel with Shape Adaptability and Synergetic Bacterial Elimination in the Full Course of Wound Healing. *Adv. Healthc. Mater.* **2022**, *11*, e2201049. [CrossRef]
151. Yang, M.; Qiu, S.; Coy, E.; Li, S.; Załęski, K.; Zhang, Y.; Pan, H.; Wang, G. NIR-Responsive TiO_2 Biometasurfaces: Toward In Situ Photodynamic Antibacterial Therapy for Biomedical Implants. *Adv. Mater.* **2022**, *34*, 2106314. [CrossRef]
152. Lima-Sousa, R.; de Melo-Diogo, D.; Alves, C.G.; Cabral, C.S.D.; Miguel, S.P.; Mendonça, A.G.; Correia, I.J. Injectable in situ forming thermo-responsive graphene based hydrogels for cancer chemo-photothermal therapy and NIR light-enhanced antibacterial applications. *Mater. Sci. Eng. C* **2020**, *117*, 111294. [CrossRef]
153. Ma, T.; Zhai, X.; Jin, M.; Huang, Y.; Zhang, M.; Pan, H.; Zhao, X.; Du, Y. Multifunctional wound dressing for highly efficient treatment of chronic diabetic wounds. *View* **2022**, *3*, 20220045. [CrossRef]
154. Koyuncu, A.; Koç, S.; Akdere, Ö.E.; Çakmak, A.S.; Gümüşderelioğlu, M. Investigation of the synergistic effect of platelet-rich plasma and polychromatic light on human dermal fibroblasts seeded chitosan/gelatin scaffolds for wound healing. *J. Photochem. Photobiol. B Biol.* **2022**, *232*, 112476. [CrossRef] [PubMed]
155. Zhou, L.; Zhou, L.; Wei, C.; Guo, R. A bioactive dextran-based hydrogel promote the healing of infected wounds via antibacterial and immunomodulatory. *Carbohydr. Polym.* **2022**, *291*, 119558. [CrossRef] [PubMed]
156. Ye, J.J.; Li, L.F.; Hao, R.N.; Gong, M.; Wang, T.; Song, J.; Meng, Q.H.; Zhao, N.N.; Xu, F.J.; Lvov, Y.; et al. Phase-change composite filled natural nanotubes in hydrogel promote wound healing under photothermally triggered drug release. *Bioact. Mater.* **2023**, *21*, 284–298. [CrossRef] [PubMed]
157. Niu, C.; Liu, X.; Wang, Y.; Li, X.; Shi, J. Photothermal-modulated drug release from a composite hydrogel based on silk fibroin and sodium alginate. *Eur. Polym. J.* **2021**, *146*, 110267. [CrossRef]
158. Moorcroft, S.C.T.; Roach, L.; Jayne, D.G.; Ong, Z.Y.; Ong, Z.Y.; Evans, S.D. Nanoparticle-Loaded Hydrogel for the Light-Activated Release and Photothermal Enhancement of Antimicrobial Peptides. *ACS Appl. Mater. Interfaces* **2020**, *12*, 24544–24554. [CrossRef] [PubMed]
159. Liu, Y.; Li, F.; Guo, Z.; Xiao, Y.; Zhang, Y.; Sun, X.; Zhe, T.; Cao, Y.; Wang, L.; Lu, Q.; et al. Silver nanoparticle-embedded hydrogel as a photothermal platform for combating bacterial infections. *Chem. Eng. J.* **2020**, *382*, 122990. [CrossRef]

160. Huang, S.; Liu, H.; Liao, K.; Hu, Q.; Guo, R.; Deng, K. Functionalized GO Nanovehicles with Nitric Oxide Release and Photothermal Activity-Based Hydrogels for Bacteria-Infected Wound Healing. *ACS Appl. Mater. Interfaces* **2020**, *12*, 28952–28964. [CrossRef] [PubMed]
161. Dong, Y.; Li, S.; Li, X.; Wang, X. Smart MXene/agarose hydrogel with photothermal property for controlled drug release. *Int. J. Biol. Macromol.* **2021**, *190*, 693–699. [CrossRef]
162. Zhao, X.; Liang, Y.; Huang, Y.; He, J.; Han, Y.; Guo, B. Physical Double-Network Hydrogel Adhesives with Rapid Shape Adaptability, Fast Self-Healing, Antioxidant and NIR/pH Stimulus-Responsiveness for Multidrug-Resistant Bacterial Infection and Removable Wound Dressing. *Adv. Funct. Mater.* **2020**, *30*, 1910748. [CrossRef]
163. Yang, N.; Zhu, M.; Xu, G.; Liu, N.; Yu, C. A near-infrared light-responsive multifunctional nanocomposite hydrogel for efficient and synergistic antibacterial wound therapy and healing promotion. *J. Mater. Chem. B* **2020**, *8*, 3908–3917. [CrossRef]
164. Arafa, M.G.; El-Kased, R.F.; Elmazar, M.M. Thermoresponsive gels containing gold nanoparticles as smart antibacterial and wound healing agents. *Sci. Rep.* **2018**, *8*, 13674. [CrossRef] [PubMed]
165. Zhou, L.; Dai, C.; Fan, L.; Jiang, Y.; Liu, C.; Zhou, Z.; Guan, P.; Tian, Y.; Xing, J.; Li, X.; et al. Injectable Self-Healing Natural Biopolymer-Based Hydrogel Adhesive with Thermoresponsive Reversible Adhesion for Minimally Invasive Surgery. *Adv. Funct. Mater.* **2021**, *31*, 2007457. [CrossRef]
166. Zheng, Z.; Bian, S.; Li, Z.; Zhang, Z.; Liu, Y.; Zhai, X.; Pan, H.; Zhao, X. Catechol modified quaternized chitosan enhanced wet adhesive and antibacterial properties of injectable thermo-sensitive hydrogel for wound healing. *Carbohydr. Polym.* **2020**, *249*, 116826. [CrossRef] [PubMed]
167. Zhang, E.; Guo, Q.; Ji, F.; Tian, X.; Cui, J.; Song, Y.; Sun, H.; Li, J.; Yao, F. Thermoresponsive polysaccharide-based composite hydrogel with antibacterial and healing-promoting activities for preventing recurrent adhesion after adhesiolysis. *Acta Biomater.* **2018**, *74*, 439–453. [CrossRef]
168. Makvandi, P.; Ali, G.W.; Della Sala, F.; Abdel-Fattah, W.I.; Borzacchiello, A. Biosynthesis and characterization of antibacterial thermosensitive hydrogels based on corn silk extract, hyaluronic acid and nanosilver for potential wound healing. *Carbohydr. Polym.* **2019**, *223*, 115023. [CrossRef]
169. Zhang, M.; Deng, F.; Tang, L.; Wu, H.; Ni, Y.; Chen, L.; Huang, L.; Hu, X.; Lin, S.; Ding, C. Super-ductile, injectable, fast self-healing collagen-based hydrogels with multi-responsive and accelerated wound-repair properties. *Chem. Eng. J.* **2021**, *405*, 126756. [CrossRef]
170. Magazzù, A.; Marcuello, C. Investigation of Soft Matter Nanomechanics by Atomic Force Microscopy and Optical Tweezers: A Comprehensive Review. *Nanomaterials* **2023**, *13*, 963. [CrossRef] [PubMed]
171. Pepelyshev, A.; Borodich, F.M.; Galanov, B.A.; Gorb, E.V.; Gorb, S.N. Adhesion of Soft Materials to Rough Surfaces: Experimental Studies, Statistical Analysis and Modelling. *Coatings* **2018**, *8*, 350. [CrossRef]
172. Azeera, M.; Vaidevi, S.; Ruckmani, K. Characterization Techniques of Hydrogel and Its Applications. *Polym. Polym. Compos. A Ref. Ser.* **2019**, 737–761. [CrossRef]
173. Ni, Z.; Yu, H.; Wang, L.; Huang, Y.; Lu, H.; Zhou, H.; Liu, Q. Multistage ROS-Responsive and Natural Polyphenol-Driven Prodrug Hydrogels for Diabetic Wound Healing. *ACS Appl. Mater. Interfaces* **2022**, *14*, 52643–52658. [CrossRef]
174. Guo, S.; Yao, M.; Zhang, D.; He, Y.; Chang, R.; Ren, Y.; Guan, F. One-Step Synthesis of Multifunctional Chitosan Hydrogel for Full-Thickness Wound Closure and Healing. *Adv. Healthc. Mater.* **2022**, *11*, 2101808. [CrossRef] [PubMed]
175. Su, R.; Li, P.; Zhang, Y.; Lv, Y.; Wen, F.; Su, W. Polydopamine/tannic acid/chitosan/poloxamer 407/188 thermosensitive hydrogel for antibacterial and wound healing. *Carbohydr. Polym.* **2023**, *302*, 120349. [CrossRef] [PubMed]
176. Li, P.; She, W.; Luo, Y.; He, D.; Chen, J.; Ning, N.; Yu, Y.; De Beer, S.; Zhang, S. One-pot, self-catalyzed synthesis of self-adherent hydrogels for photo-thermal, antimicrobial wound treatment. *J. Mater. Chem. B* **2021**, *9*, 159–169. [CrossRef] [PubMed]
177. Laurano, R.; Torchio, A.; Ciardelli, G.; Boffito, M. In Situ Forming Bioartificial Hydrogels with ROS Scavenging Capability Induced by Gallic Acid Release with Potential in Chronic Skin Wound Treatment. *Gels* **2023**, *9*, 731. [CrossRef] [PubMed]
178. Jongprasitkul, H.; Parihar, V.S.; Turunen, S.; Kellomäki, M. pH-Responsive Gallol-Functionalized Hyaluronic Acid-Based Tissue Adhesive Hydrogels for Injection and Three-Dimensional Bioprinting. *ACS Appl. Mater. Interfaces* **2023**, *15*, 33972–33984. [CrossRef] [PubMed]
179. Ma, M.; Zhong, Y.; Jiang, X. Thermosensitive and pH-responsive tannin-containing hydroxypropyl chitin hydrogel with long-lasting antibacterial activity for wound healing. *Carbohydr. Polym.* **2020**, *236*, 116096. [CrossRef]
180. Al-Arjan, W.S.; Khan, M.U.A.; Almutairi, H.H.; Alharbi, S.M.; Razak, S.I.A. pH-Responsive PVA/BC-f-GO Dressing Materials for Burn and Chronic Wound Healing with Curcumin Release Kinetics. *Polymers* **2022**, *14*, 1949. [CrossRef]
181. Lee, P.Y.; Li, Z.; Huang, L. Thermosensitive Hydrogel as a Tgf-β1 Gene Delivery Vehicle Enhances Diabetic Wound Healing. *Pharm. Res.* **2003**, *20*, 1995–2000. [CrossRef]
182. Li, Z.; Zhao, Y.; Liu, H.; Ren, M.; Wang, Z.; Wang, X.; Liu, H.; Feng, Y.; Lin, Q.; Wang, C.; et al. pH-responsive hydrogel loaded with insulin as a bioactive dressing for enhancing diabetic wound healing. *Mater. Des.* **2021**, *210*, 110104. [CrossRef]
183. Wu, S.; Yang, Y.; Wang, S.; Dong, C.; Zhang, X.; Zhang, R.; Yang, L. Dextran and peptide-based pH-sensitive hydrogel boosts healing process in multidrug-resistant bacteria-infected wounds. *Carbohydr. Polym.* **2022**, *278*, 118994. [CrossRef]
184. Kraehenbuehl, T.P.; Ferreira, L.S.; Zammaretti, P.; Hubbell, J.A.; Langer, R. Cell-responsive hydrogel for encapsulation of vascular cells. *Biomaterials* **2009**, *30*, 4318–4324. [CrossRef] [PubMed]

185. Kraehenbuehl, T.P.; Ferreira, L.S.; Hayward, A.M.; Nahrendorf, M.; van der Vlies, A.J.; Vasile, E.; Weissleder, R.; Langer, R.; Hubbell, J.A. Human embryonic stem cell-derived microvascular grafts for cardiac tissue preservation after myocardial infarction. *Biomaterials* **2011**, *32*, 1102–1109. [CrossRef] [PubMed]
186. Li, X.; Xu, K.; He, Y.; Tao, B.; Li, K.; Lin, C.; Hu, J.; Wu, J.; Wu, Y.; Liu, S.; et al. ROS-responsive hydrogel coating modified titanium promotes vascularization and osteointegration of bone defects by orchestrating immunomodulation. *Biomaterials* **2022**, *287*, 121683. [CrossRef] [PubMed]
187. Srikhao, N.; Theerakulpisut, S.; Chindaprasirt, P.; Okhawilai, M.; Narain, R.; Kasemsiri, P. Green synthesis of nano silver-embedded carboxymethyl starch waste/poly vinyl alcohol hydrogel with photothermal sterilization and pH-responsive behavior. *Int. J. Biol. Macromol.* **2023**, *242*, 125118. [CrossRef] [PubMed]
188. Haidari, H.; Kopecki, Z.; Sutton, A.T.; Garg, S.; Cowin, A.J.; Vasilev, K. pH-Responsive "Smart" Hydrogel for Controlled Delivery of Silver Nanoparticles to Infected Wounds. *Antibiotics* **2021**, *10*, 49. [CrossRef] [PubMed]
189. Haidari, H.; Vasilev, K.; Cowin, A.J.; Kopecki, Z. Bacteria-Activated Dual pH- and Temperature-Responsive Hydrogel for Targeted Elimination of Infection and Improved Wound Healing. *ACS Appl. Mater. Interfaces* **2022**, *14*, 51744–51762. [CrossRef] [PubMed]
190. Du, T.; Xiao, Z.; Cao, J.; Wei, L.; Li, C.; Jiao, J.; Song, Z.; Liu, J.; Du, X.; Wang, S. NIR-activated multi-hit therapeutic Ag_2S quantum dot-based hydrogel for healing of bacteria-infected wounds. *Acta Biomater.* **2022**, *145*, 88–105. [CrossRef] [PubMed]
191. Zhou, K.; Zhang, Z.; Xue, J.; Shang, J.; Ding, D.; Zhang, W.; Liu, Z.; Yan, F.; Cheng, N. Hybrid Ag nanoparticles/polyoxometalate-polydopamine nano-flowers loaded chitosan/gelatin hydrogel scaffolds with synergistic photothermal/chemodynamic/Ag+ anti-bacterial action for accelerated wound healing. *Int. J. Biol. Macromol.* **2022**, *221*, 135–148. [CrossRef]
192. Zhao, H.; Huang, J.; Li, Y.; Lv, X.; Zhou, H.; Wang, H.; Xu, Y.; Wang, C.; Wang, J.; Liu, Z. ROS-scavenging hydrogel to promote healing of bacteria infected diabetic wounds. *Biomaterials* **2020**, *258*, 120286. [CrossRef]
193. He, L.; Liu, Y.; Chen, F.; Shi, J.; Song, P.; Feng, F.; Cui, J.; Zhang, J.; Ma, X.; Shen, J. Flexible wood-based pH-responsive hydrogel excipient for rapid recovery of infected wounds. *React. Funct. Polym.* **2023**, *192*, 105707. [CrossRef]
194. Rezaei, F.; Damoogh, S.; Reis, R.L.; Kundu, S.C.; Mottaghitalab, F.; Farokhi, M. Dual drug delivery system based on pH-sensitive silk fibroin/alginate nanoparticles entrapped in PNIPAM hydrogel for treating severe infected burn wound. *Biofabrication* **2020**, *13*, 015005. [CrossRef] [PubMed]
195. Hu, C.; Zhang, F.; Long, L.; Kong, Q.; Luo, R.; Wang, Y. Dual-responsive injectable hydrogels encapsulating drug-loaded micelles for on-demand antimicrobial activity and accelerated wound healing. *J. Control. Release* **2020**, *324*, 204–217. [CrossRef]
196. Niyompanich, J.; Chuysinuan, P.; Pavasant, P.; Supaphol, P. Development of thermoresponsive poloxamer in situ gel loaded with gentamicin sulfate for cavity wounds. *J. Polym. Res.* **2021**, *28*, 128. [CrossRef]
197. Kang, W.; Liang, J.; Liu, T.; Long, H.; Huang, L.; Shi, Q.; Zhang, J.; Deng, S.; Tan, S. Preparation of silane-dispersed graphene crosslinked vinyl carboxymethyl chitosan temperature-responsive hydrogel with antibacterial properties. *Int. J. Biol. Macromol.* **2022**, *200*, 99–109. [CrossRef] [PubMed]
198. Liu, Z.; Tang, W.; Liu, J.; Han, Y.; Yan, Q.; Dong, Y.; Liu, X.; Yang, D.; Ma, G.; Cao, H. A novel sprayable thermosensitive hydrogel coupled with zinc modified metformin promotes the healing of skin wound. *Bioact. Mater.* **2023**, *20*, 610–626. [CrossRef] [PubMed]
199. Lin, X.; Zhang, H.; Li, S.; Huang, L.; Zhang, R.; Zhang, L.; Yu, A.; Duan, B. Polyphenol-driving assembly for constructing chitin-polyphenol-metal hydrogel as wound dressing. *Carbohydr. Polym.* **2022**, *290*, 119444. [CrossRef]
200. Patil, N.; Jérôme, C.; Detrembleur, C. Recent advances in the synthesis of catechol-derived (bio)polymers for applications in energy storage and environment. *Prog. Polym. Sci.* **2018**, *82*, 34–91. [CrossRef]
201. Faure, E.; Falentin-Daudré, C.; Jérôme, C.; Lyskawa, J.; Fournier, D.; Woisel, P.; Detrembleur, C. Catechols as versatile platforms in polymer chemistry. *Prog. Polym. Sci.* **2013**, *38*, 236–270. [CrossRef]
202. Qiao, Z.; Lv, X.; He, S.; Bai, S.; Liu, X.; Hou, L.; He, J.; Tong, D.; Ruan, R.; Zhang, J.; et al. A mussel-inspired supramolecular hydrogel with robust tissue anchor for rapid hemostasis of arterial and visceral bleedings. *Bioact. Mater.* **2021**, *6*, 2829–2840. [CrossRef]
203. Liang, Y.; Zhao, X.; Hu, T.; Chen, B.; Yin, Z.; Ma, P.X.; Guo, B. Adhesive Hemostatic Conducting Injectable Composite Hydrogels with Sustained Drug Release and Photothermal Antibacterial Activity to Promote Full-Thickness Skin Regeneration During Wound Healing. *Small* **2019**, *15*, 1900046. [CrossRef]
204. Baldwin, A.; Booth, B.W. Biomedical applications of tannic acid. *J. Biomater. Appl.* **2022**, *36*, 1503–1523. [CrossRef] [PubMed]
205. Kaczmarek, B. Tannic acid with antiviral and antibacterial activity as a promising component of biomaterials-A minireview. *Materials* **2020**, *13*, 3224. [CrossRef] [PubMed]
206. Vermonden, T.; Censi, R.; Hennink, W.E. Hydrogels for protein delivery. *Chem. Rev.* **2012**, *112*, 2853–2888. [CrossRef] [PubMed]
207. Abune, L.; Wang, Y. Affinity Hydrogels for Protein Delivery. *Trends Pharmacol. Sci.* **2021**, *42*, 300. [CrossRef] [PubMed]
208. Malta, R.; Marques, A.C.; da Costa, P.C.; Amaral, M.H. Stimuli-Responsive Hydrogels for Protein Delivery. *Gels* **2023**, *9*, 802. [CrossRef] [PubMed]
209. Chen, C.; Hu, J.; Zeng, P.; Chen, Y.; Xu, H.; Lu, J.R. High cell selectivity and low-level antibacterial resistance of designed amphiphilic peptide G(IIKK)3I-NH2. *ACS Appl. Mater. Interfaces* **2014**, *6*, 16529–16536. [CrossRef] [PubMed]
210. Cao, M.; Wang, Y.; Hu, X.; Gong, H.; Li, R.; Cox, H.; Zhang, J.; Waigh, T.A.; Xu, H.; Lu, J.R. Reversible Thermoresponsive Peptide-PNIPAM Hydrogels for Controlled Drug Delivery. *Biomacromolecules* **2019**, *20*, 3601–3610. [CrossRef]
211. Haq, M.A.; Su, Y.; Wang, D. Mechanical properties of PNIPAM based hydrogels: A review. *Mater. Sci. Eng. C* **2017**, *70*, 842–855. [CrossRef]

212. Das, S.; Das, D. Rational Design of Peptide-based Smart Hydrogels for Therapeutic Applications. *Front. Chem.* **2021**, *9*, 770102. [CrossRef]
213. Zhang, R.; Wang, Z.; Tian, Y.; Yin, Q.; Cheng, X.; Lian, M.; Zhou, B.; Zhang, X.; Yang, L. Efficacy of antimicrobial peptide DP7, designed by machine-learning method, against methicillin-resistant staphylococcus aureus. *Front. Microbiol.* **2019**, *10*, 452678. [CrossRef]
214. Kumar, A.; Mahajan, M.; Awasthi, B.; Tandon, A.; Harioudh, M.K.; Shree, S.; Singh, P.; Shukla, P.K.; Ramachandran, R.; Mitra, K.; et al. Piscidin-1-analogs with double L- and D-lysine residues exhibited different conformations in lipopolysaccharide but comparable anti-endotoxin activities. *Sci. Rep.* **2017**, *7*, 39925. [CrossRef] [PubMed]
215. Rezaei, N.; Hamidabadi, H.G.; Khosravimelal, S.; Zahiri, M.; Ahovan, Z.A.; Bojnordi, M.N.; Eftekhari, B.S.; Hashemi, A.; Ganji, F.; Darabi, S.; et al. Antimicrobial peptides-loaded smart chitosan hydrogel: Release behavior and antibacterial potential against antibiotic resistant clinical isolates. *Int. J. Biol. Macromol.* **2020**, *164*, 855–862. [CrossRef] [PubMed]
216. Lazzaro, B.P.; Zasloff, M.; Rolff, J. Antimicrobial peptides: Application informed by evolution. *Science* **2020**, *368*, eaau5480. [CrossRef] [PubMed]
217. Mahlapuu, M.; Håkansson, J.; Ringstad, L.; Björn, C. Antimicrobial peptides: An emerging category of therapeutic agents. *Front. Cell. Infect. Microbiol.* **2016**, *6*, 235805. [CrossRef] [PubMed]
218. Huff, T.; Müller, C.S.G.; Otto, A.M.; Netzker, R.; Hannappel, E. β-Thymosins, small acidic peptides with multiple functions. *Int. J. Biochem. Cell Biol.* **2001**, *33*, 205–220. [CrossRef] [PubMed]
219. Malinda, K.M.; Goldstein, A.L.; Kueinman, H.K. Thymosin β4 stimulates directional migration of human umbilical vein endothelial cells. *FASEB J.* **1997**, *11*, 474–481. [CrossRef]
220. Malinda, K.M.; Sidhu, G.S.; Mani, H.; Banaudha, K.; Maheshwari, R.K.; Goldstein, A.L.; Kleinman, H.K. Thymosin β4 Accelerates Wound Healing. *J. Investig. Dermatol.* **1999**, *113*, 364–368. [CrossRef] [PubMed]
221. Shah, R.; Reyes-Ordillo, K.; Cheng, Y.; Varatharajalu, R.; Ibrahim, J.; Lakshman, M.R. Thymosin β 4 prevents oxidative stress, inflammation, and fibrosis in ethanol- and lps-induced liver injury in mice. *Oxid. Med. Cell. Longev.* **2018**, *2018*, 9630175. [CrossRef]
222. Sosne, G.; Szliter, E.A.; Barrett, R.; Kernacki, K.A.; Kleinman, H.; Hazlett, L.D. Thymosin Beta 4 Promotes Corneal Wound Healing and Decreases Inflammation in Vivo Following Alkali Injury. *Exp. Eye Res.* **2002**, *74*, 293–299. [CrossRef]
223. Tang, Y.Q.; Yeaman, M.R.; Selsted, M.E. Antimicrobial Peptides from Human Platelets. *Infect. Immun.* **2002**, *70*, 6524. [CrossRef]
224. Xing, Y.; Ye, Y.; Zuo, H.; Li, Y. Progress on the Function and Application of Thymosin β4. *Front. Endocrinol.* **2021**, *12*, 767785. [CrossRef] [PubMed]
225. Treadwell, T.; Kleinman, H.K.; Crockford, D.; Hardy, M.A.; Guarnera, G.T.; Goldstein, A.L. The regenerative peptide thymosin β4 accelerates the rate of dermal healing in preclinical animal models and in patients. *Ann. N. Y. Acad. Sci.* **2012**, *1270*, 37–44. [CrossRef] [PubMed]
226. Kim, S.; Kwon, J. Thymosin β4 has a major role in dermal burn wound healing that involves actin cytoskeletal remodelling via heat-shock protein 70. *J. Tissue Eng. Regen. Med.* **2017**, *11*, 1262–1273. [CrossRef] [PubMed]
227. Kleinman, H.K.; Kulik, V.; Goldstein, A.L. Thymosin β4 and the anti-fibrotic switch. *Int. Immunopharmacol.* **2023**, *115*, 109628. [CrossRef] [PubMed]
228. Fu, X.; Shi, Y.; Wang, H.; Zhao, X.; Sun, Q.; Huang, Y.; Qi, T.; Lin, G. Ethosomal Gel for Improving Transdermal Delivery of Thymosin β-4. *Int. J. Nanomed.* **2019**, *14*, 9275. [CrossRef] [PubMed]
229. Bock-Marquette, I.; Maar, K.; Maar, S.; Lippai, B.; Faskerti, G.; Gallyas, F.; Olson, E.N.; Srivastava, D. Thymosin beta-4 denotes new directions towards developing prosperous anti-aging regenerative therapies. *Int. Immunopharmacol.* **2023**, *116*, 109741. [CrossRef] [PubMed]
230. Shaghiera, A.D.; Widiyanti, P.; Yusuf, H. Synthesis and Characterization of Injectable Hydrogels with Varying Collagen–Chitosan–Thymosin β4 Composition for Myocardial Infarction Therapy. *J. Funct. Biomater.* **2018**, *9*, 33. [CrossRef] [PubMed]
231. Chiu, L.L.Y.; Reis, L.A.; Momen, A.; Radisic, M. Controlled release of thymosin β4 from injected collagen-chitosan hydrogels promotes angiogenesis and prevents tissue loss after myocardial infarction. *Regen. Med.* **2012**, *7*, 523–533. [CrossRef]
232. Chen, T.; Yang, Y.; Peng, H.; Whittaker, A.K.; Li, Y.; Zhao, Q.; Wang, Y.; Zhu, S.; Wang, Z. Cellulose nanocrystals reinforced highly stretchable thermal-sensitive hydrogel with ultra-high drug loading. *Carbohydr. Polym.* **2021**, *266*, 118122. [CrossRef]
233. Peng, Y.; He, D.; Ge, X.; Lu, Y.; Chai, Y.; Zhang, Y.; Mao, Z.; Luo, G.; Deng, J.; Zhang, Y. Construction of heparin-based hydrogel incorporated with Cu5.4O ultrasmall nanozymes for wound healing and inflammation inhibition. *Bioact. Mater.* **2021**, *6*, 3109–3124. [CrossRef]
234. Chitra, G.; Franklin, D.S.; Sudarsan, S.; Sakthivel, M.; Guhanathan, S. Noncytotoxic silver and gold nanocomposite hydrogels with enhanced antibacterial and wound healing applications. *Polym. Eng. Sci.* **2018**, *58*, 2133–2142. [CrossRef]
235. Janpetch, N.; Saito, N.; Rujiravanit, R. Fabrication of bacterial cellulose-ZnO composite via solution plasma process for antibacterial applications. *Carbohydr. Polym.* **2016**, *148*, 335–344. [CrossRef] [PubMed]
236. Kaiser, P.; Wächter, J.; Windbergs, M. Therapy of infected wounds: Overcoming clinical challenges by advanced drug delivery systems. *Drug Deliv. Transl. Res.* **2021**, *11*, 1545–1567. [CrossRef] [PubMed]
237. Nethi, S.K.; Das, S.; Patra, C.R.; Mukherjee, S. Recent advances in inorganic nanomaterials for wound-healing applications. *Biomater. Sci.* **2019**, *7*, 2652–2674. [CrossRef] [PubMed]

238. Makabenta, J.M.V.; Nabawy, A.; Li, C.H.; Schmidt-Malan, S.; Patel, R.; Rotello, V.M. Nanomaterial-based therapeutics for antibiotic-resistant bacterial infections. *Nat. Rev. Microbiol.* **2021**, *19*, 23–36. [CrossRef] [PubMed]
239. Mendes, C.; Thirupathi, A.; Corrêa, M.E.A.B.; Gu, Y.; Silveira, P.C.L. The Use of Metallic Nanoparticles in Wound Healing: New Perspectives. *Int. J. Mol. Sci.* **2022**, *23*, 15376. [CrossRef] [PubMed]
240. Naderi, N.; Karponis, D.; Mosahebi, A.; Seifalian, A.M. Nanoparticles in wound healing; from hope to promise, from promise to routine. *Front. Biosci.-Landmark* **2018**, *23*, 1038–1059. [CrossRef]
241. Burdușel, A.C.; Gherasim, O.; Grumezescu, A.M.; Mogoantă, L.; Ficai, A.; Andronescu, E. Biomedical applications of silver nanoparticles: An up-to-date overview. *Nanomaterials* **2018**, *8*, 681. [CrossRef]
242. Wu, Y.; Yang, Y.; Zhang, Z.; Wang, Z.; Zhao, Y.; Sun, L. A facile method to prepare size-tunable silver nanoparticles and its antibacterial mechanism. *Adv. Powder Technol.* **2018**, *29*, 407–415. [CrossRef]
243. Rajendran, N.K.; Kumar, S.S.D.; Houreld, N.N.; Abrahamse, H. A review on nanoparticle based treatment for wound healing. *J. Drug Deliv. Sci. Technol.* **2018**, *44*, 421–430. [CrossRef]
244. Paladini, F.; Pollini, M. Antimicrobial silver nanoparticles for wound healing application: Progress and future trends. *Materials* **2019**, *12*, 2540. [CrossRef] [PubMed]
245. Chakrabarti, S.; Chattopadhyay, P.; Islam, J.; Ray, S.; Raju, P.S.; Mazumder, B. Aspects of Nanomaterials in Wound Healing. *Curr. Drug Deliv.* **2018**, *16*, 26–41. [CrossRef] [PubMed]
246. Zhang, X.F.; Liu, Z.G.; Shen, W.; Gurunathan, S. Silver nanoparticles: Synthesis, characterization, properties, applications, and therapeutic approaches. *Int. J. Mol. Sci.* **2016**, *17*, 1534. [CrossRef] [PubMed]
247. Hoffman, S.B. Mechanisms of Antibiotic Resistance. *Compend. Contin. Educ. Pract. Vet.* **2001**, *23*, 464–472. [CrossRef]
248. Salisbury, A.M.; Woo, K.; Sarkar, S.; Schultz, G.; Malone, M.; Mayer, D.O.; Percival, S.L. Tolerance of Biofilms to Antimicrobials and Significance to Antibiotic Resistance in Wounds. *Surg. Technol. Int.* **2018**, *33*, 59–66.
249. Gjødsbøl, K.; Christensen, J.J.; Karlsmark, T.; Jørgensen, B.; Klein, B.M.; Krogfelt, K.A. Multiple bacterial species reside in chronic wounds: A longitudinal study. *Int. Wound J.* **2006**, *3*, 225–231. [CrossRef]