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Mini Review

Leveraging the Advancements in Functional Biomaterials and Scaffold Fabrication Technologies for Chronic Wound Healing Applications

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Abstract

Exploring new avenues for clinical management of chronic wounds holds the key to eliminate socioeconomic burdens and health-related concerns associated with this silent killer. Engineered biomaterials offer great promise to repair and regenerate chronic wounds because of their ability to deliver therapeutics, protect the wound environment, and support the skin matrices to facilitate tissue growth. This mini review presents recent advances in biomaterial functionalities for enhancing wound healing and demonstrates a move from sub-optimal methods to multi-functionalized treatment approaches. In this context, we discuss the recently reported biomaterial characteristics such as bioadhesiveness, antimicrobial properties, proangiogenic attributes, and anti-inflammatory properties that promote chronic wound healing. In addition, we highlight the necessary mechanical and mass transport properties of such biomaterials. Then, we discuss the characteristic properties of various biomaterial templates, including hydrogels, cryogels, nanomaterials, and biomolecule-functionalized materials. These biomaterials can be microfabricated into various structures, including smart patches, microneedles, electrospun scaffolds, and 3D-bioprinted structures to advance the field of biomaterial scaffolds for effective wound healing. Finally, we provide an outlook for the future while emphasizing the need for their detailed functional behaviour and inflammatory response studies under complex *in vivo* environment for superior clinical outcomes and reduced regulatory hurdles.

1. Introduction

Materials science has seen a drastic shift in paradigm recently, where the introduction of functional biomaterials have substantially enhanced its applicability in the field of biomedicine [1]. The previously sub-optimal designs have transitioned into biologically active materials capable of providing cues to the host cells and manipulating the cellular microenvironment in unprecedented ways. Further, various clinical challenges are present with the drug incorporated dressings, skin substitutes, topical administration of insulin, antioxidants, skin glues, hyperbaric oxygen, and electrical stimulation therapy to effectively heal chronic wounds. These dressings mainly cause infections, produce scar contraction and pigmentations, and pose a substantial financial burden to the patient's pocket [2]–[4]. With all these clinical challenges, one solution is to use functionalized biomaterials. These bioactive biomaterials could have inherent antimicrobial, bioadhesive, anti-inflammatory and proangiogenic properties, which help in producing promising results with minor complications in the healing efficacy of chronic wounds. Also, these biologically active materials have tunable mechanical properties, such as viscoelasticity, and stiffness, among others, that can decide the fate of the cellular phenotypes [5]. Such mechanically relevant materials have also seen upgrades in the form of contact-free remote exploitation, where external energy sources, such as light, sound, and magnetic and electric fields, are frequently being employed to enhance the therapeutic effect of the platform [6]. In the present context, we define functional biomaterials as biologically active substances that can (a) host living cells, (b) carry therapeutically active components, and (c) can be upgraded to highly programmable, remotely triggered, "smart" materials for drug delivery and tissue engineering-based applications. The need for such biomaterials has become prominent in cases of chronic wound healing where underlying causes, such as diabetes, alter the healthy physiological processes involved with wound healing [7]. In chronic ulcer-based applications, where the wound fails to heal because of various limitations including severe inflammation and lack of angiogenesis, wound dressings derived from functional biomaterials provide superior therapeutic effects in contrast to their previously sub-optimal counterpart [8], [9]. This is because such scaffolds have low moisture retention capacities and can absorb limited amounts of the wound exudates, thereby increasing the chances of developing infection at the wound bed [9]. Such scaffolds primarily include skin substitutes in the form of autografts, allografts, and xenografts, which exhibit intense immune rejection [10], [11]. These substitutes promote negligible cell-to-cell interactions and display weak adherence to cells and biomolecules. Hence, they cannot effectively mimic the biological microenvironment and functionalities of a healthy tissue site [12], [13]. Instead, this causes hindrance to the natural wound healing process at the injured tissue region. Incorporating growth factors to these scaffolds have shown early promising results [14]. However, unprotected growth factors undergo rapid enzymatic degradation when delivered *in vivo* to the wounded site, where protease enzymes are abundantly present [15]. Some of these growth factors also have a very short half-life that limits their potential [16]. Due to all these limitations, such skin graft-based therapies, even when supplemented with growth factors, have turned into a less desirable treatment for chronic wound healing [9].

Alternatively, tissue-engineered functional biomaterials provide a suitable protective environment to the growth factors for their improved efficacy [17]. Furthermore, such functional biomaterials containing active ions or therapeutic molecules help to accelerate the healing efficacy of the chronic wound with negligible side effects. The primary role of such biomaterials in the treatment of non-healing wounds is to augment the healing process by interacting with cells and supporting the wound

microenvironment [10]. These patches provide a platform for the controlled delivery of various wound repair therapeutics, support matrices for cellular growth, and establish a barrier against infections. Dressings developed from protein and sugar-based biopolymers have shown significant improvement in the closure of chronic wounds. One such biocompatible and biodegradable polymeric material, chitosan, derived from chitin, is a polysaccharide that possesses inherent antimicrobial properties [18]. However, protein-based polymers, such as collagen, hyaluronic acid, and gelatin, provide a favourable platform to interact with cells and present biomolecule binding structures [19]–[23]. Furthermore, their structural features offer excellent properties for loading wound healing drugs and therapeutic nanomaterials. However, functional biomaterials derived purely from natural sources show weak mechanical properties. This has led to the era of next generation designs that incorporate various organic and inorganic nanomaterials within the polymeric matrices. This incorporation functionalizes the natural dressings by improving their mechanical properties and promoting wound healing by enhancing angiogenesis, accelerating reepithelization, and supporting the remodelling of tissues [24]–[26]. Several parameters, including the size and shape of nanomaterials play a critical role in determining their biological efficiency [27]. For instance, size and shape of nanomaterials influence active substance delivery, determines the penetrability of the nanomaterials through the cell membranes, and control cellular responses [27]. The nanomaterials can also provide biomaterials with contact-free external stimuli-based responsiveness [28]. These smart dressings may also be loaded with active biomolecules, such as DNA, cytokines, hormones, angiogenic factors, anti-inflammatory drugs, genes, mRNA, and microRNA to supplement the bioactivity of the dressings [16], [29]–[31]. Such composite materials provide better cell adhesion, proliferation, and migration properties to enhance the repairing process of chronic wounds.

Designing appropriate fabrication strategies to apply these functional biomaterials effectively at the wound site is equally important for successful biomedical applications. Hydrogelation is one such strategy where biomaterial-based polymers can be crosslinked to prepare biocompatible, water-swellable, native tissue-mimicking three-dimensional (3D) constructs [32]. Hydrogelation can be personalized by 3D bioprinting-based fabrication strategies, where the developed tissue constructs can conform to the shapes of individual wounds [33]. However, the network structures formulated by hydrogelation results in small pores, which are inefficient in transporting macromolecular solutes to the core of the designed construct. Cryogelation is an alternative strategy where interconnected macropores are generated, increasing nutrient transport and providing larger space for cell seeding and migration [34]. Another fabrication strategy for applying biomaterials comes in the form of microneedles [35]. Microneedles are applied frequently in immunobiological applications, drug delivery, disease detection, and so on. Microneedles have also found use in chronic wound healing systems where they help in retaining drug at constantly exuding wound beds [36]. **Figure 1** displays various fabrication strategies along with the potential functionalities introduced by their biologically derived constituents. Such novel systems hold tremendous potential in effectively treating chronic wounds.

This mini review aims to report the latest technological advancement of functional biomaterials and their fabrication strategies intended for healing chronic wounds. We explore the biomaterials functionalities such as bioadhesiveness, antimicrobial characteristics, proangiogenic nature, and anti-inflammatory properties to leverage the treatment and management of numerous complexities of the chronic wound. Further, the importance of mechanical properties and mass transport properties of these advanced biomaterials is highlighted here. Lastly, we discuss the modern trends in fabrication

strategies for applying new engineered, functional biomaterials, and highlight the potential concerns that need to be addressed to improve their chances for translational success.

2. Functional biomaterials with unique biological and mechanical properties

Biomaterials play a vast role in providing a biologically active platform to the chronic wound environment and facilitate the wound healing process by interacting with cells, extracellular matrices (ECM), and multiple growth factors. Biomaterials can be derived and developed from natural or synthetic polymers, ceramics, metals, or the combination of all [9], [37]. Specific considerations should be taken to explore biomaterials based on the success of *in vivo* biocompatibility, biodegradation, and stability assays. Advanced biomaterials bring in some unique functionalities such as bioadhesive, antimicrobial, proangiogenic, and anti-inflammatory properties. These functionalities are important for designing advanced chronic wound healing therapeutics.

a. Bioadhesiveness. Bioadhesive properties of biomaterials are an important consideration in providing a robust wound healing environment because wounds often secrete mucus through mucous membranes that are wet and slippery, limiting the ability of the dressing to adhere with the wound. Various bioadhesive bandages have been developed to improve drug delivery to the wound site [38], [39]. Chitosan and poly(acrylic acid) are among them and possess extensive mucoadhesive properties [40], [41]. Adhesion to skin occurs when hydrogen bonds from poly(acrylic acid) react with the mucosa, while negatively charged surfaces and cells interact electrostatically with positively charged chitosan molecules [40], [41]. These mucoadhesive polymers have shown prolonged and sustained drug delivery to the wound site [40], [41]. A gallic acid-modified chitosan-based wound dressing was developed by *Sun et al.* for providing bioadhesiveness to the impaired wound [38]. The presence of catechol groups and additional hydroxyl groups makes gallic acid a promising material for tissue adhesive properties [38]. Interestingly Yuk et al. developed a double-sided tissue adhesive tape provided with the biologically inspired dry crosslinking mechanism that can be used as a potential tissue adhesive [42]. The tape was combined with gelatin, or chitosan attached with the crosslinked chain of N-hydrosuccinimide ester grafted on polyacrylic acid. The designed tape can remove the interfacial fluid from the surface and leads to temporary crosslinking with the tissue for enhancing the adhesion ability and strength of the tape.

Our recently published work developed polydopamine-coated gelatin–alginate hydrogel as a binding platform for bioactive molecules used for various tissue engineering applications [43]. Polydopamine is extensively investigated as an adhesive material due to numerous catecholic amino acids in its structure that binds them to various surfaces in both wet and saline conditions [43]–[45]. Further, Mooney and his team developed bioinspired active adhesive dressings, shown in **Figure 2A**, illustrating the firm adhesion of the hydrogel to the injured skin that was triggered by the changes of the skin temperature, resulting in successful wound contraction [46]. Taken together, the bioadhesivity of biomaterials provides suitable attachment to the skin and enhances the recovery of the affected wound.

b. Antimicrobial properties. The nature of the diabetic wound environment promotes high chances of wound infections because of high blood glucose levels. High levels of glucose reduce the proper function of immune cells. The condition often leads to multiple pathogenic bacteria colonizing the ECM and forming a complex biofilm [10]. 60-90% of diabetic wounds develop biofilms resulting in chronic inflammation and delayed healing [47]. Various biomaterial-based antimicrobial wound

dressings have been developed to reduce the chances of getting an infection. Recently, Ding et al. developed a polyurethane-based foam functionalized with different cationic groups (poly(ethylenimine), poly(L-lysine), and chitosan to present the antimicrobial potential [48]. The designed platform showed good antimicrobial properties when tested against both gram-positive and gram-negative bacteria [48]. Moreover, silver nanoparticles (AgNPs) have widely been used as an antimicrobial agent for the treatment of chronic wounds [49]. They work by deactivating pathogenic microorganisms by breaking disulfide bonds, which changes the tertiary structure of the proteins [50]. To summarize, multiple biomaterial-based fabrication techniques and therapeutics have been developed to prevent chronic wounds from getting an infection or developing biofilms, thereby increasing the chance of rapid healing of chronic wounds.

c. Proangiogenic properties. The lack of blood supply orchestrates poor vascularization in chronic wounds resulting in reduced angiogenesis and becoming the leading cause for delayed healing of chronic wounds. [51]. Growth factors have been commonly used as therapeutics to induce angiogenesis in chronic wounds. One of the main limitations associated with growth factors is their instability and cost [15], [16]. Alternatively, biomaterials show a more promising approach by releasing ions or molecules that may enhance angiogenesis in the complex and poorly healing chronic wound environment [52], [53]. Silica-based nanocomposite hydrogels have recently shown highly angiogenic and antimicrobial properties that are promising for chronic wound healing [54]. Further, europium oxide nanorods were reinforced in a nanocomposite hydrogel for skin regeneration [52]. At low concentrations, these nanorods enhance the activity of reactive oxygen species both *in vitro* and *in vivo,* leading to providing the pro-angiogenic potential to the material [55]. Also, such nanomaterials show anti-inflammatory responses, accelerating wound healing in a mouse skin defect model [52]. In addition, nitric oxide (NO) has been used as a potent mediator encapsulated into composite biomaterials to leverage its angiogenic potential to enhance chronic wound healing [53], [56]. The endothelial nitric oxide synthase or eNOS pathway stimulates the proliferation and migration of endothelial cells needed for the angiogenic process, which is essential for the healing and regeneration of impaired wounds [53], [56]. Such advanced approaches exhibit tremendous potential for high angiogenesis, thereby providing superior healing efficacy for chronic wounds.

d. Anti-inflammatory properties. Anti-inflammatory cues to the wound have been researched via various strategies, including but not limited to the delivery of anti-inflammatory drugs, endogenous/exogenous production of NO synthase, promotion of antioxidant activity, and activating immune regulation. The inflammation in chronic wounds results in intense pain to the patient, causing severe complications to wound healing. Biomaterial-derived anti-inflammatory therapeutics have attracted much attention to improving the recovery of chronic wounds. For instance, biomaterial-based therapy may achieve controlled and responsive release of various inflammatory inhibition drugs [57]. Interestingly, sericin has demonstrated excellent anti-inflammatory properties that have been recently used in a composite hydrogel for developing an effective wound dressing [58]. Sericin reduces inflammatory cell levels, which promotes anti-inflammatory efficacy, thereby accelerating the wound healing process [59]. Most biomaterials possess more than one bio-functionality. For example, in **Figure 2B**, polydopamine-modified graphene oxide (GDFE) hybrid hydrogels were fabricated to show proangiogenic, anti-inflammatory, and antimicrobial properties [60]. The developed GDFE composite hydrogels reduced inflammation and stimulated M2 polarization of macrophages in diabetic wounds [60]. Therefore, various biomaterial platforms based on anti-inflammatory responses have been

researched to provide a practical approach for inflammatory wounds to promote healing in chronic models.

Briefly, **Table 1** shows the functionalities of various biomaterials. All such beneficial biological functionalities must be paired with the appropriate mechanical cues to form next generation chronic wound healing platforms, discussed in the following section.

e. Mechanical properties. The selection of mechanically robust biomaterial characteristics, including excellent stretchability, toughness, and high fatigue resistance for developing wound patches may hold significant importance in the healing potential of chronic wounds. In the case of healthy skin, the characteristic range of Young's modulus is between 56.8 to 141 MPa [61]. In addition, the stretchability of human skin is between 20% to 180% [61]. Numerous biomaterial-derived dressings have shown superior stretchability and toughness that can hold the possibility to mimic the native healthy skin environment and repair chronic wounds. The mechanical properties of such biomaterials are enhanced mainly by combining two or three materials such as polymers, ceramics, and metals. For example, chitosan hydrogels were enforced with silver nanoparticles to gain extensive mechanical properties and support wound structure [62]. Here, chitosan served as a chelating agent to interact with silver ions through a coordination complex to gain ultra-high mechanical strength [62].

It has been demonstrated that the stretchability and toughness of healthy skin depend on age and anatomical location [63]. Primarily the skin is composed of collagen and elastin, among other components [63]. So, in the case of chronic wounds, the distribution and ratio among these components become distorted. The structure appears tough but is more susceptible to damage. During this stage, biomaterials may help regenerate the skin by mimicking the parameters and behaviour of native skin. Moreover, the stiffness of the biomaterial is an important parameter because it is stress/strain dependent. If the pressure on the hydrogel becomes too high, it causes mechanical failure and ultimately breaks the hydrogel [64]. The stiffness of hydrogels should be equal to or higher than the forces within the biological system to accelerate the wound healing mechanism. Thus, these mechanical properties of biomaterials are highly desirable in designing a dressing for promoting chronic wounds.

The mass transport properties of biomaterials are also significant, specifically for diabetic wound healing. During the angiogenesis phase, the distribution of cell nutrients and oxygen is vitally dependent on the biomaterial diffusion kinetics. The diffusion of these essential components depends on the porosity and permeability of the biomaterials. However, when enough oxygen and nutrients cannot reach the deep structure of biomaterials, the cells undergo necrosis and programmed cell death [65]. In a recently published report, the authors use an advanced numerical processing software, COMSOL Multiphysics, to determine a porous biomaterial's mass transport characteristics [66]. Primarily the governing equation of Navier-Stokes is implemented in developing a computation fluid dynamics (CFD) model for determining the mass transport characteristics of the biomaterials [66].

$$\rho \frac{\partial \upsilon}{\partial t} - (\upsilon \times \nabla)\upsilon + \frac{1}{\rho}\nabla P - \mu \nabla^2 - F = 0$$

$$\upsilon \times \nabla = 0 \qquad (1)$$

Where ρ is the density of the background fluid, υ fluid velocity, μ dynamic viscosity coefficient, P stands for pressure while ∇ is the del operator and F represents force. Other than mass transport, the

biomaterials' rheological characteristics, especially for hydrogels, are widely studied to determine the viscosity, storage, loss, and compression modulus. For example, understanding shear-rheology helps in designing injectable biomaterials. Therefore, information on both mass transport phenomena and rheological properties are critical for preparing biomaterials for diabetic wound healing.

For decades, the conventional method for tuning the mechanical, mass transport and rheological properties have been implemented by trial and error in the lab. However, this is both laborious and expensive. The advancement of COMSOL-like processing tools and artificial intelligence (AI) technology through deep machine learning has opened a new way to predict and learn biomaterial behaviour in advance. The technology has already shown promising results in bioinformatics and biomedicine [67]. Further, AI has been used in combination with *in vitro* and *in vivo* data along with clinical trial results to predict the pharmacokinetics and pharmacodynamics of the drugs in the designed model, mainly in the case of drug discovery [68]. Although the field is still in its infancy, Han and co-workers have used the Fuzzy neural network-based deep machine learning program to predict and develop high-strength titanium and aluminium alloys [69]. Such AI-based predictions of physicochemical properties will pave the path to novel physiologically relevant biomaterials.

3. Various scaffold fabrication strategies: implications in wound healing

Non-healing chronic wounds place a significant burden on healthcare systems as well as individual patients. These wounds, especially diabetic wounds, will ultimately lead to compromised mobility, amputation, and sometimes death. The main problem with sub-optimal traditional dressings is that the patient suffers from severe pain when removing the bandages from the wounds, which worsens the wound health and increases inflammation to the site, hampering the healing process [70]. **Figure 3** has been developed to provide a comprehensive view of the material constituents, various therapeutics, and the functional properties for wound healing scaffolds.

Over time, a wide variety of wound dressings have been developed with the potential to detect the wound healing percentage in a real-time manner that helps to apply the suitable treatment efficiently. These versatile, intelligent wearable dressings may contain numerous optical components that enable fluorescence, colorimetry, and electrical impedance. These mechanisms are mounted onto the conventional wound bandage substrates to form smart wound dressings to sense and transfer the data from biomarkers at the wound site to generate electrical signals for applying suitable actions [9]. These dressings are smart enough to identify bacterial films because of the presence of bacterial infection markers dependent on pH, temperature, toxins, and secreted enzymes. Further, it can release impregnated particles or molecules to the wound bed in a controlled fashion [9]. For example, Ochoa et al. designed a low-cost paper-based innovative, flexible real-time continuous oxygen-generating and sensing patch for a wound bed to enhance wound healing. The designed platform detected oxygen in a range of 5-26 ppm leading to a promising technique for developing smart diabetic wound patches [71].

To incorporate such innovative properties, a new class of advanced wound dressings must be developed to monitor the healing process and reduce the current limitations associated with healing, simultaneously. Natural and synthetic polymers or their composites have been used in different techniques, including membranes, foams, hydrogels, cryogels, nanofibers, nanomaterials, microneedles, and 3D bioprinting as wound healing scaffolds or dressings. The key to selecting the above techniques depends on the type, depth, extent of damage to the wound, and prevention of

wound exudates and infections to the wound site. The idea is to mitigate the limitations related to the traditional dressings and provide a better moist environment to the wound and enhance the healing process.

a. Membranes. Membranes or films are also used as a wound dressing. They are usually composed of thin and transparent adhesive sheets of one or different combinations of biopolymers. Membranes provide suitable permeability for gas and water vapours, however being impermeable to fluid and bacteria. This mechanism helps in protecting the wound against water loss and invasion of microorganisms. Membranes serve as a good wound dressing material, but they do not possess enough swelling properties. As a result, it develops excess exudate to the wound site and may cause a reason for infection [72]. However, it can be encapsulated with anti-infection therapeutics and drugs to alleviate the limitations. Further, the fabrication technique is cost-effective and produces a large yield of membranes in a short time. Also, membranes can be easily used to achieve the desired bioadhesive properties by selecting appropriate functionalized biomaterial. Therefore, membranes are being considered as a potential technique for developing effective wound healing scaffolds.

b. Hydrogels and Cryogels. In this context, hydrogels and cryogels have become one of the most attractive and promising wound dressings because of their considerable moisture retention, biocompatibility, biodegradability, and therapeutic properties [53], [73], [74]. They are of great interest in wound healing applications and are composed of the 3D macromolecular structure of crosslinked polymer network. Hydrogels are highly hydrophilic and can retain a large amount of aqueous medium while keeping their form intact. It keeps the wound surface moist and acts as a carrier for cells and therapeutics. The physical characteristics of hydrogels provide continuous and flexible nano/micro-structures, good swelling capabilities, and are easy to mould into different shapes [73], [75]. Several investigators have proposed various strategies and formulations for making hydrogels based on the type of biomaterials [53], [73]. However, a few limitations need to be overcome before upscaling the use of hydrogels, including the costly and lengthy synthesis of the gels and the potential involvement of hazardous crosslinking materials. Lastly, the scaffolding technique of hydrogel can be leveraged to gain good bioadhesive, antimicrobial, proangiogenic and anti-inflammatory properties when the adequate functional biomaterial is selected. Overall, hydrogels have emerged as a promising scaffold method for chronic wound applications.

c. Nanofibers. Nanofibers are another highly attractive group of scaffolds implemented in chronic wound healing. Their nanostructure resembles the extracellular matrix (ECM) and thus helps cells grow and mimic the native tissue environment [16]. However, the preparation strategies must ensure the complete and safe removal of the inorganic solvents that are used for synthesizing the scaffolds. Any remaining traces of the solvents in the porous structure of the scaffold may adversely affect the cells and tissues. Overcoming the challenges, studies have been reported that highlight the potential of nanofiber dressings for drug loading and controlled release [16], [19], as well as protein and genetic material delivery [76], [77]. In addition, the nanofiber's mesh sizes and pore diameter can be easily tuned to attain the desired drug delivery rate to the wound [16]. Hence, the characteristic properties of nanofibers hold an excellent potential to be used as a wound healing scaffold.

d. Nanomaterials and nanoparticles. Nanomaterials have several properties that offer unique advantages for chronic wound healing applications. Their small size, large surface to volume ratio,

biocompatibility, and ability to encapsulate a variety of molecules make them excellent drug delivery vehicles for the delivery of therapeutics for chronic wound healing [78]. In addition, many of these nanomaterials are stable, biodegradable, tuneable, and versatile [79]. Some examples of such nanomaterial drug delivery vehicles that have been studied and used for the controlled release of drugs are polymeric nanoparticles, liposomes, and micelles. While these materials are used to encapsulate and deliver the bioactive agent and are typically incorporated in a scaffold, several other nanomaterials themselves have properties that play a direct role in wound healing. A number of inorganic nanoparticles have shown antibacterial activity, an important factor for chronic wound healing. Silver nanoparticles are the most prominent antibacterial nanoparticles; however, gold, titanium dioxide, and terbium oxide nanoparticles have also been used [78], [80], [81]. Copper nanoparticles, in addition to having antimicrobial properties, are also bioactive and have been shown to regulate the biological processes of wound healing in favour of improved treatment [82]. However, one limitation of inorganic nanoparticles is their potential to cause an immunogenic response. To overcome it, another class of nanomaterials being explored are derived from natural sources. An example is exosomes. Exosomes are nanosized vesicles secreted by cells. Exosomes from stem cells have been successfully used to promote favourable would healing processes such as angiogenesis, collagen synthesis, and recruitment of several factors [83], [84]. The results from several *in vitro* and *in vivo* studies have shown that nanomaterials can successfully be used to treat chronic wounds [80], [82]–[84].

e. Microneedles Array. The other promising approach is through microneedle technology which pierces the outermost layer of the skin, the stratum corneum. The stratum corneum constitutes an impenetrable barrier to hydrophilic or high molecular weight drugs. These drugs or molecules can only be delivered into or through the skin if any of the few available methods disrupt the barrier function of the stratum corneum. The microneedle arrays have emerged as a promising minimally invasive method that can bypass the skin's stratum corneum and allow for the sustained delivery of wound healing drugs at a predetermined distance within the skin [85]. They are composed of a network of microneedles fabricated from silicon, metal, or polymeric material. For example, in **Figure 4A**, shark tooth inspired microneedles were developed by integrating with an intelligent wound management system. The *in vivo* results on diabetic mouse models present the completely healed wound area among other groups [85]. Given this example, microneedles can painlessly puncture the epidermis, thereby making microscopic pores through which wound healing drugs can quickly diffuse through to reach the tissue microenvironment and facilitate the wound healing process. However, a limitation of microneedles that needs to be considered for therapeutics and bioactive molecules delivery for wound healing is that the thickness of the skin layer varies from patient to patient. Therefore, the penetration depth of the microneedles could widely vary, leading to broad anomalies in delivering therapeutics and drugs.

f. 3D bioprinting. 3D bioprinting is among the latest techniques that combines living cells, growth factors, biomolecules and biomaterials in a controlled manner to print complex 3D constructs [86]. Bioprinting in recent years has advanced the development in healthcare areas such as personalized prosthetics, implants, and tissue regeneration [86]–[88]. 3D bioprinted hydrogels show low mechanical strength and, therefore, would require frequent dressing changes resulting in the potential to lower patient compliance. However, in contrast to other dressing fabrication techniques, bioprinting is (i) more precise, (ii) provides incredible flexibility in the manufacturing process, and (iii)

delivers a much faster and reproducible construction of the desired scaffold to the affected wound. For example, collagen has been used frequently as a bioink to develop wound healing scaffolds [89]. As shown in **Figure 4B**, Xiaoxue et al. designed a 3D printed bionic hydrogel fabricated using carboxymethyl cellulose/ε-polylysine (CP) cured via UV irradiation [90]. The wound healing effect of the developed hydrogel dressing was examined on the full thickness infected rat skin defect model. The chosen printing technique of hydrogel with the respective biomaterial shows significant wound closure compared to the commercial dressing (Tegaderm™ film). Hence, 3D bioprinting techniques have exhibited a promising approach for wound management and can be further leveraged to enhance the wound healing process in chronic patients.

4. Conclusions and Outlook

Biomaterials have progressed rapidly in regenerative therapy and have become an integral part of chronic wound healing. However, despite the promising advancement in the field, several challenges are yet to be overcome. Although derived from natural sources containing biological cues for favourable cellular interaction, many natural biocompatible materials hold weak mechanical properties and are prone to rapid degradation. Novel mechanical reinforcement strategies, such as the addition of nanomaterials or the formation of interpenetrating polymeric networks, are being developed to address these limitations. Another challenge lies in the heterogeneity in patients, leading to variability in therapeutic outcomes. More patient-specific approaches must be undertaken to overcome this problem and improve the clinical relevance of the designed scaffolds. 3D bioprinting is an excellent tool for such personalization, where patient-specific stem cells can be used to print bandages catering to the needs of the wound [91]. Along with addressing these issues, a new wave of composite biomaterials is being designed, which brings in unique functionalities including antimicrobial and anti-inflammatory properties, among others, to this therapeutic platform. As a result, such a quickly expanding area of research needs critical analysis and insightful commentary to improve the translational potential of the fabricated biomaterials. This demand in literature has led us to write this mini review, where we have provided the readers with state-of-the-art strategies that are being implemented to fabricate multifunctional bioactive biomaterials for chronic wound repair. Here, we also predict the diverse biomaterials that have immense potential to excel in the upcoming decade.

External stimuli-responsive biomaterials are such new-age candidates in wound healing applications. Stimuli-responsive biomaterials may promote the wound healing mechanism in a variety of ways. Biomaterials with external stimuli cues such as photo and electrical stimulation, ultrasound, and magnetic field triggers can transduce an external energy source into a signal for cells in the physiological environment. They can be controlled temporally and spatially, which in turn enables precise control over the cellular response. For example, piezoelectric polymers can be potential biomaterials that respond to generate an electrical charge by applying mechanical stress. This electrical charge helps to promote fibroblast and keratinocyte proliferation and migration and expedites collagen deposition, angiogenesis, and re-epithelialization [92]. In addition, photothermal cues from biomaterials have also gained substantial attention in antimicrobial applications due to deep tissue penetration, remote triggering, and non-invasiveness [93]. These photothermal biomaterials may be composed of metallic and non-metallic nanomaterials, carbon-based nanomaterials, or organic dye, among others [94], [95]. Recently Yunlong et al. developed a stimuli-responsive photothermal cryogels for wound healing [93]. In another work, Ninan et al., developed composite hydrogel loaded tannic acid/ferric ion works as a photothermal agent stimulated via near-

infrared radiation to kill the bacteria in the microenvironment [96]. Overall, external stimuli-responsive biomaterials hold significant importance in terms of the healing of a chronic wound.

Another interesting approach is designing an inflammatory-responsive scaffold. It is well known that untreated or prolonged inflammatory reactions can be a reason for the delayed healing of chronic wounds. In normal conditions, these inflammatory responses deliver cytokines that alter the phenotype of macrophages from pro-inflammatory to anti-inflammatory polarization [97]. Nitin and his team developed a flare-responsive hydrogel for the treatment of inflammatory arthritis. They used a triglycerol monostearate (TG-18) hydrogel, which can disintegrate in response to enzymatic activity in inflammatory milieus [98]. In addition, corticosteroid triamcinolone acetonide (TA) was used as a model drug that was encapsulated within the TG-18 hydrogel. This drug-loaded hydrogel activates in response to arthritis-related enzyme activity [98]. Their results showed that the flare responsive hydrogel was disassembled successfully in a mouse model and emerged as a next-generation drug delivery platform for treating inflammation. This idea can be used to treat prolonged inflammation of chronic wounds that may efficiently circumvent the issues related to inflammation. Lastly, the alteration of cytokines through inflammatory responsive biomaterials may help recover the healing in chronic wound models.

Aside from altering and leveraging biomaterials functionalities and other bioactive compounds for wound healing, another promising approach is to use gene-editing technology via clustered regularly interspaced short palindromic repeat (CRISPR)-associated protein (Cas9) technology for the treatment of chronic wounds at genetic levels. The technology has already shown proof of concept over developing nuclease-responsive hydrogels that can be engineered to deliver bioactive molecules, nanomaterials, and cells [99], [100]. For example, English et al. developed a stimuli-responsive DNA hydrogel based on CRISPR technology that responds to associated programmable nucleases. The designed biomaterial attained rapid and sensitive cues to Cas enzymes and enhanced the modularity of DNA hydrogels [99]. Overall, the technology provides untapped opportunities in the field of tissue engineering and regenerative medicine.

Although material engineers have been able to successfully increase the functionality and complexity of various biomaterials for diverse biomedical applications, we would like to emphasize here that close attention should be given to properly understand the immunological response, mass transport and biodegradation properties of such new biomaterials to maximize their translatability into the clinic and avoid regulatory and economic hurdles. One of the significant issues for the clinical translation of biomaterials is the foreign body response. It is a slow onset process, and the test of new devices or technologies for longer trials remains a significant challenge. Consequently, avoiding the process and implantation of a device without promising results may turn the body to severe fibrotic responses [101]. One solution is to play around with the surface properties of biomaterials that can be tuned with the patient's DNA, protein, or cells in modulating and eliminating the foreign body cues. The target is to generate non-cytotoxic materials that evoke a minimal immune response. Another concern for biomaterial translation into the clinic is scaffold vascularization. For example, a prefabricated biomimetic vascular scaffold may provide the angiogenic molecules and can promote angiogenesis at the site. However, they may exhibit limited abilities of conjunction with the host vascular network [102]. The adhesion of ligands and advanced therapeutics to the scaffold with spatial control of biophysical and biochemical responses may help to circumvent this gap. Also, the pharmacokinetics and pharmacodynamics of the biomaterial need to be explicitly addressed for small molecules to

ensure adequate bioactivity and timely excretion. On the other hand, the evolving technology of omics and machine learning may help decrease the challenge associated with the safe design of the material and conduct various risk assessments before its implementation [103]. Additionally, with the ongoing development of biomaterials properties, AI-based technology may be used to envisage further and predict the promising potential of biomaterials.

In conclusion, our mini-review discusses the latest multi-functional, stimuli-responsive, bioactive materials and their fabrication technologies for chronic wound healing applications. A thorough understanding of the underlying mechanisms by which these biomaterials improve the healing process will enhance their translational potential.

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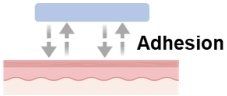
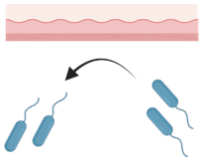
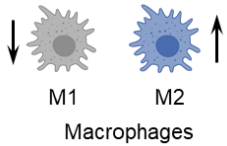
Table 1: Examples of biomaterials developed as therapeutics for diabetic wound healing applications.

Functionalities	Biomaterials	Nanoparticles/Therapeutics	Biomaterial-therapeutic and/or Biomaterial-nanoparticle Interaction	Types of scaffolds	Testing Model	References
Bio adhesive properties 	Poly (acrylic acid)	Salicylamide	N/A	Hydrogel	Intestinal Pig (Yorkshire) mucosa	[41]
	Gelatin-Alginate	Dexamethasone	$\pi - \pi$ interaction	Hydrogel	Sprague-Dawley (female) rats	[43]
	Polydopamine	Hemoglobin Nanoparticle	Covalent & Non-covalent interactions	Polydopamine coated hemoglobin nanoparticles	N/A	[44]
Antimicrobial 	Polyurethane	imidazolium	Ionic	Foam	BALB/c (male) mice	[48]
Proangiogenic	Hyaluronic Acid-alendronate	Europium Oxide Nanorods	Coordination Interactions	Hydrogel	Female mice	[52]

	Polyethylene glycol diacrylate (PEGDA)	Bioactive Glass Nanoparticles containing copper and sodium alginate	Photocrosslinking	Hydrogel	Male ICR mice	[54]
	Chitosan-poly(vinyl alcohol)	S-nitroso-N-acetyl-DL-penicillamine (SNAP)	Physical encapsulation	Hydrogel	Fertilized Chicken Egg *(Gallus domesticus)*	[53]
Anti-inflammatory 	Diphenylalanine–dilysine (FFKK-OH)	Steroidal and non-steroidal anti-inflammatory drugs (NSAIDs)	Hydrogen Bonding	Hydrogel	N/A	[57]
	Tannic Acid-Carboxylated agarose	Tannic Acid	Ionic Interactions	Hydrogel	N/A	[96]
	Poly(vinyl alcohol)/Chitosan/Silk sericin	Tetracycline	Physical encapsulation	Nanofibers	BALB/c (Male) mice	[58]
	Silk sericin	N/A	N/A	Hydrogel	Db/db mice	[59]

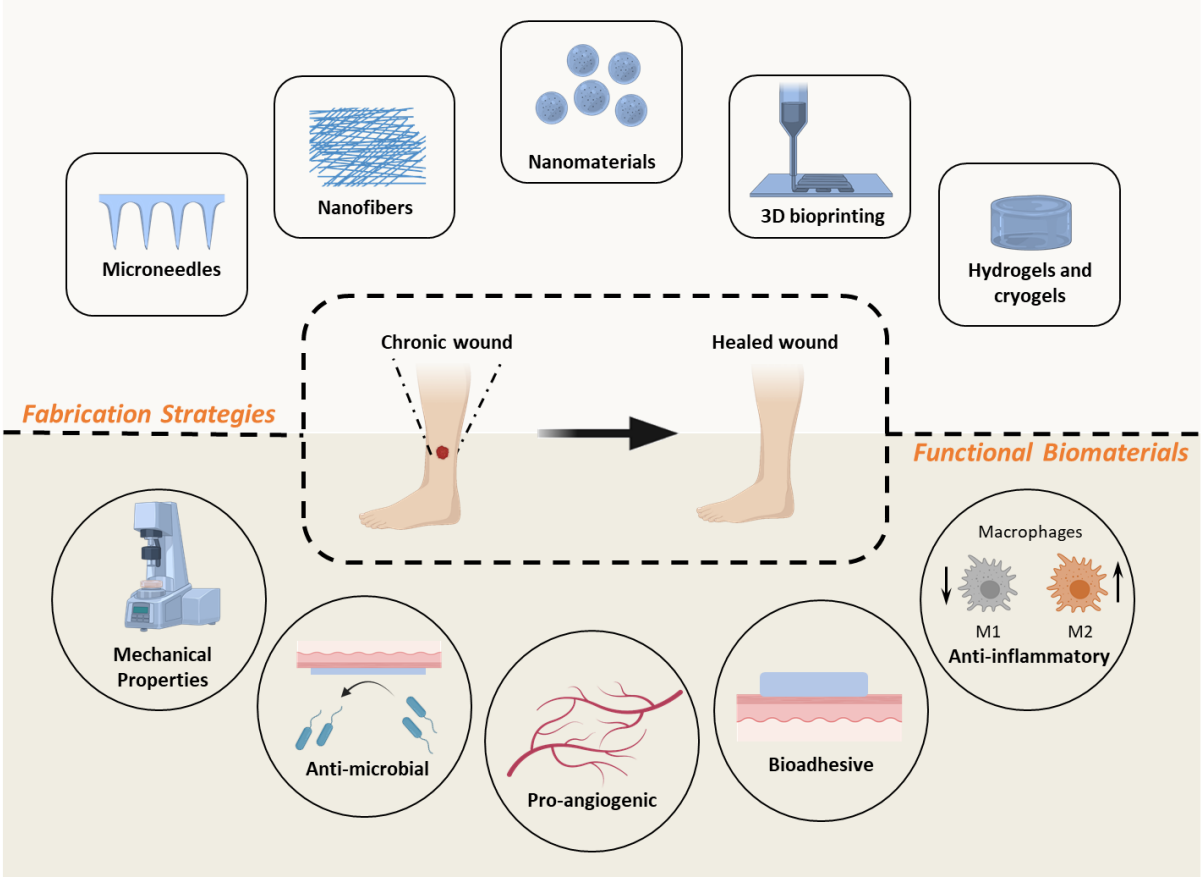


Figure 1: Overview of engineered biomaterial design functionalities along with the developed fabrication techniques to improve and enhance the wound healing process in patients with chronic wounds.

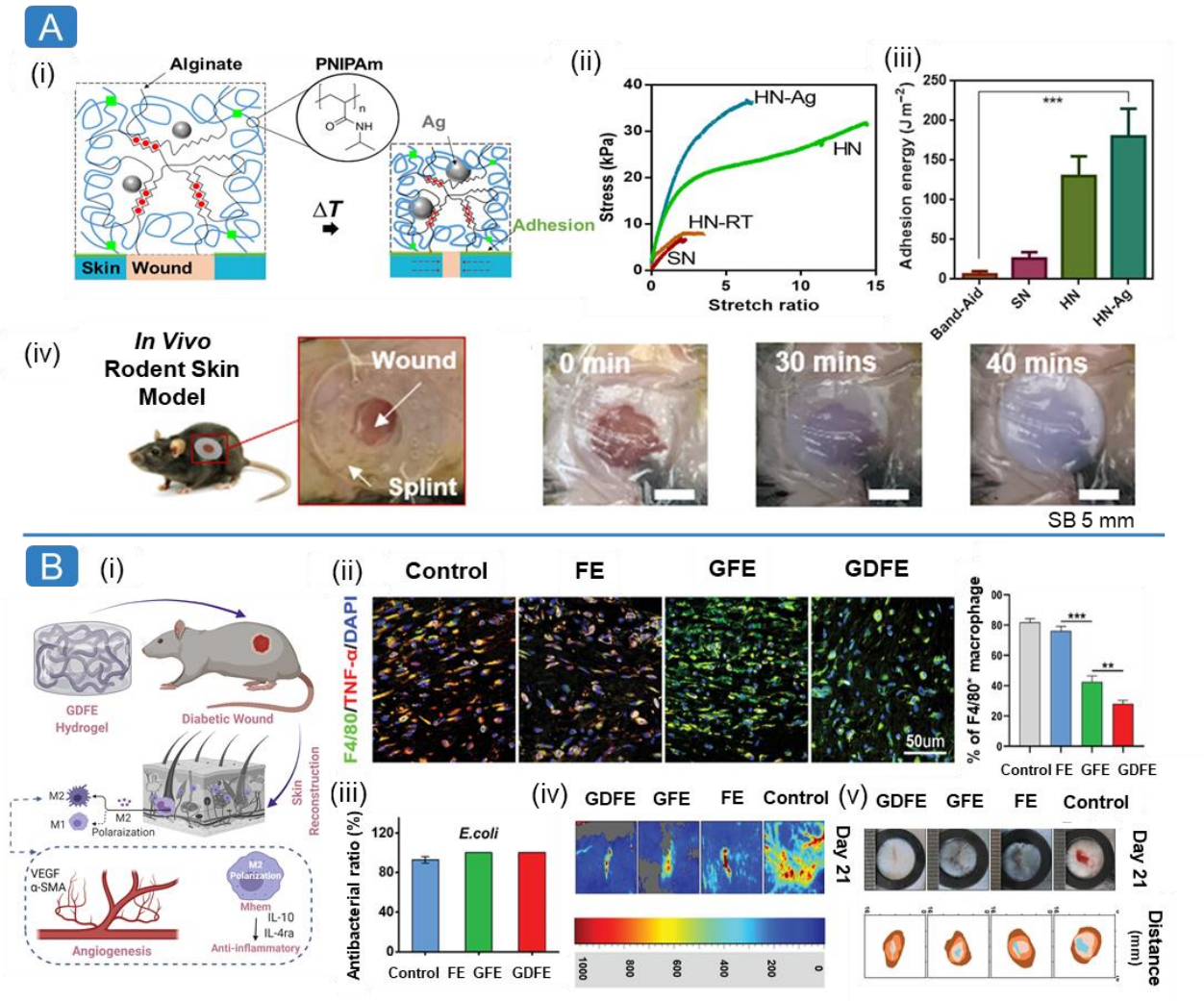


Figure 2: Schematics of highly adhesive hydrogels loaded with antimicrobial, anti-inflammatory, proangiogenic, and mechanical properties to accelerate chronic wound closure. A) Shows bioinspired active adhesive dressing; (i) Hydrogel designed with PNIPAm, alginate, and AgNPs illustrate wound contraction achieved by the firm adhesion of the hydrogel to the wound, which was triggered by the skin temperature; (ii-iii) Stress-strain curves of the designed hydrogel along with the graph of adhesion energy calculated on porcine skin revealed AgNP-laden hybrid hydrogel possessed strong adhesion energy compared to Band-Aid; (iv) *In vivo* results display that the skin temperature was triggering the adhesion of dressing to the wound which in turn accelerated the wound closure. Reproduced with permission [46] under permission of a creative commons license. B) (i) Displays polydopamine-modified GO (GDFE) hybrid hydrogel functionalized with proangiogenic, anti-inflammatory, and antimicrobial properties (recreated with BioRender.com); (ii) The developed GDFE hydrogel have reduced the inflammation and stimulated M2 polarization of macrophages on day 7 in diabetic wounds shown using F4/80 and TNF-α staining; (iii) Antimicrobial properties tested against *Escherichia coli* exhibited a broad spectrum of antibacterial activity of the hydrogels; (iv) Laser doppler scanned images of blood vessel flow and signal intensity on diabetic wound sites on day 21 shows that GDFE hydrogel possessed the highest level of blood flow among all groups; (v) *In vivo* results of diabetic induced mice model demonstrated accelerated wound contraction on day 21 with the GDFE hydrogel in comparison with the other groups. Reproduced with permission [60] Copyright 2021, Wiley-VCH GmbH.

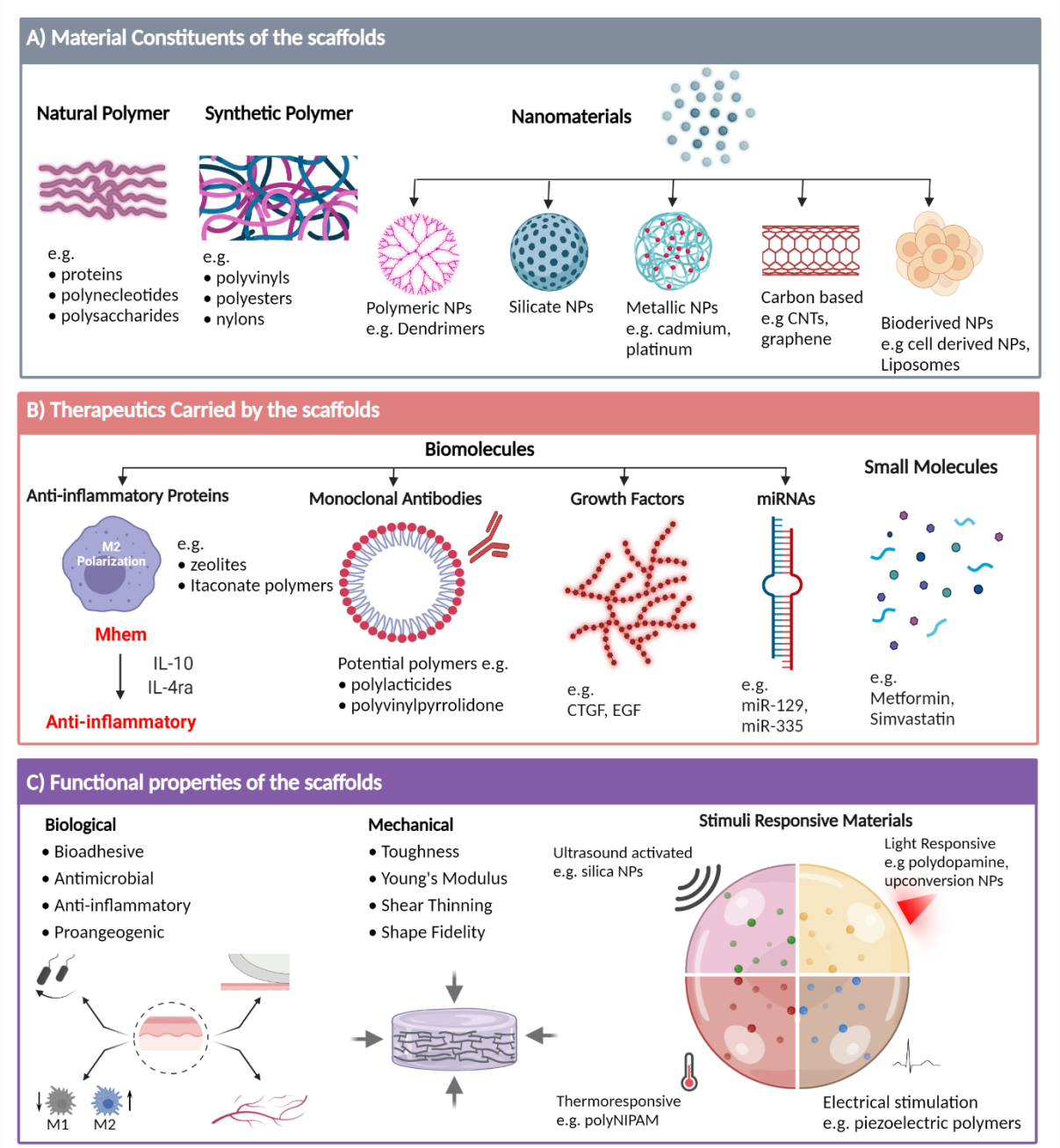


Figure 3: Simplified representation of material constituents, therapeutics, and the functional properties of the scaffolds. A) Wide range of natural and synthetic polymers and nanomaterials have been used as a constituent for developing wound healing scaffolds. B) Showcase various therapeutics such as multiple biomolecules and small molecules delivered through scaffolds. C) Functional properties of the scaffolds have been shown here, including biological, mechanical, and stimuli-responsive material characteristics specifically for chronic wound healing. Furthermore, various stimulants, such as light and ultrasound, among others, which are used for wound healing-based applications, have been highlighted here.

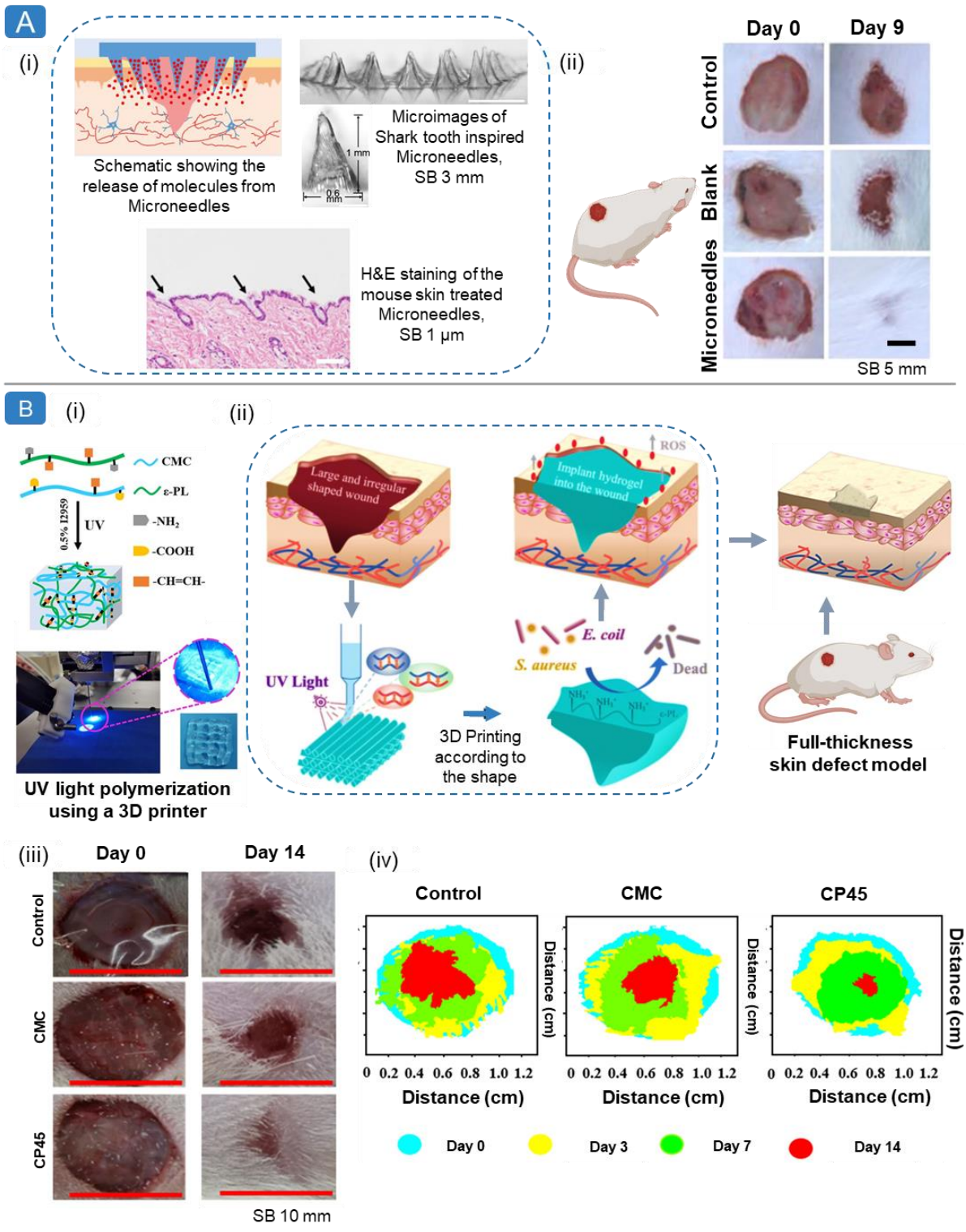


Figure 4: Examples of biomaterial-derived advanced wound healing techniques, including microneedles and 3D printed hydrogels. A) Shark tooth inspired microneedles were developed and integrated with an intelligent wound management system such as motion sensing, biochemical analysis, and healing rate; (i) Show microimages of the microneedles with the H&E staining picture of the mouse skin treated microneedles; (ii) *In vivo* results conducted on diabetic induced mouse model show the wound's complete recovery when treated with microneedles samples among other groups. Reproduced with permission [85] Copyright © 2021 American Chemical Society. B) (i-ii) 3D printed bionic hydrogel was fabricated using carboxymethyl cellulose/ε-polylysine (CP) cured via UV

irradiation; (iii) The developed hydrogels were applied to the rat skin model and visually observed the wound closure potential of Control (commercial dressing Tegaderm™ film), CMC, and CP45 hydrogels, scale bar: 10 mm. (iv) Further, authors have shown the graphical depiction of the same *in vivo* wound experiment to demonstrate the percentage of healing with the duration of time among their hydrogels. The CP45 hydrogel has shown an effective wound closure rate compared to the other groups, making it a promising biomaterial for chronic wound healing applications. Reproduced with permission [90]

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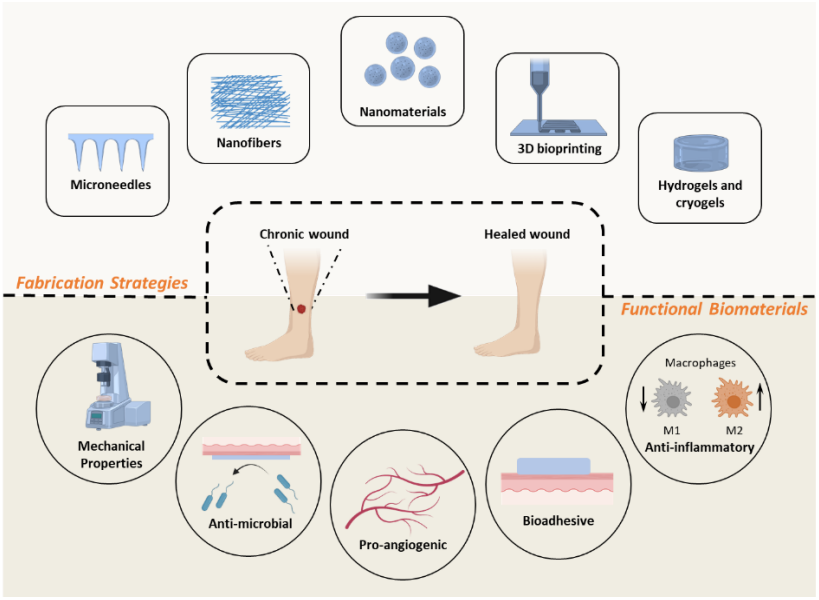

Table of Contents Entry: The graphic displays various biomaterial design functionalities along with the developed fabrication technologies to enhance the wound healing process in patients with chronic wounds.