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Review

3D printed drug loaded nanomaterials for wound healing applications

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ABSTRACT

Wounds are a stern healthcare concern in the growth of chronic disease conditions as they can increase healthcare costs and complicate internal and external health. Advancements in the current and newer management systems for wound healing should be in place to counter the health burden of wounds. Researchers discovered that two-dimensional (2D) media lacks appropriate real-life detection of cellular matter as these have highly complicated and diverse structures, compositions, and interactions. Hence, innovation towards three-dimensional (3D) media is called to conquer the high-level assessment and characterization *in vivo* using new technologies. The application of modern wound dressings prepared from a degenerated natural tissue, biodegradable biopolymer, synthetic polymer, or a composite of these materials in wound healing is currently an area of innovation in tissue regeneration medicine. Moreover, the integration of 3D printing and nanomaterial science is a promising approach with the potential for individualized, flexible, and precise technology for wound care approaches. This review encompasses the outcomes of various investigations on recent advances in 3D-printed drug-loaded natural, synthetic, and composite nanomaterials for wound healing. The challenges associated with their fabrication, clinical application progress, and future perspectives are also addressed.

Contents

Abbreviations: AFSs, amniotic fluid-derived stem cells; BLM, bilayer membrane; CACs, circulating angiogenic cells; CNTs, carbon nanotubes; CNFs, carbon nanofibers; ECM, extracellular matrix; EPCs, endothelial progenitor cells; FBMSC-CM, freeze-dried bone marrow mesenchymal stem cells conditioned medium; GelMA, gelatin methacrylol; HUCPVC, human umbilical cord perivascular cells; HUVECs, human umbilical vein endothelial cells; MBG, mesoporous bioactive glass; MSNs, mesoporous silica nanoparticles; NMs, nanomaterials; NPs, nanoparticles; PCL, polycaprolactone; PEDOT, poly(3,4-ethylene dioxythiophene); PEG, polyethylene glycol; PGA, polyglycolic acid; PNIPAAm, poly(Nisopropylacrylamide); PVA, polyvinyl alcohol; TESSs, tissue engineered skin substitutes.

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1. Introduction

1.1. Wound healing: clinical background

Wound is a defect or a rupture on part of the skin due to physical or thermal destruction or from a pathologic origin [1,2]. The type and extent of wounds differ based on their underlying causes, clinical presentations, healing mechanisms, or position of occurrence [3–5]. Whatever their nature, wounds are a stern healthcare concern in the growth of chronic disease conditions as they can increase healthcare costs and complicate internal and external health [6–8]. Wound healing encompasses various, organized molecular activities including hemostasis, inflammation, proliferation, and remodeling (Fig. 1) [3].

Even though the above molecular activities are involved in the physiologic wound healing process, huge and complex traumatic wounds resulted from accidents or chronic illnesses like obesity and type II diabetes are accompanied by unadorned skin loss with difficulty in regeneration [9–11]. Clinical wound care initially starts with offloading, treating the infection with antibiotic drugs, and managing with minor surgeries as necessary [12]. However, more aggressive therapeutic approaches such as debridement, biological intervention, or major surgical operations like amputation might be followed for severe and chronic wounds that failed to heal with initial care protocols. A model flow diagram of chronic wound management is presented in Fig. 2 [13].

Those chronic, non-regenerating, non-healing wounds result in damaging morbidity and mortality consequences such as compromised kinesis, amputation, and death [14,15]. Hence, advancements in the management of wound healing should be in place to counter the health burden of wounds [16,17]. Considering this, optimized pathophysiologic characterization with targeted drug delivery design is required. In addition, the variety of the wound environment in terms of enzymes, pH, and regeneration time scales should earnestly be considered during drug design [18,19]. Wound dressing, one of the commonest management approaches in wound healing, helps the course of healing either by providing a comfort zone for the healing process or by delivering loaded drugs to the wound site [20,21]. Moreover, wounds are often infected by microbes such as *S. aureus, S. epidermidis, P. aeruginosa, E. coli, Klebsiella, Enterococcus,* and *Candida* [22]. Hence, an effective wound dressing should exert maximal antimicrobial performance, provide acceptable biocompatibility and gas permeability, absorb wound exudates, and accelerate the healing process timely [23–25].

1.2. Traditional vs. modern wound dressing approaches

Traditionally, gauze, lint, plasters, bandages, and cotton have been used as primary or secondary dressings for preventing contamination of wounds [26,27]. However, their use is accompanied by several shortcomings such as the need of changing frequently, being suitable for superficial wounds only, lack of biologic activity, and lack of maintaining a moist environment for the healing process [28–30]. Hence, they are being replaced by modern and innovative dressings that can be used for prolonged duration, provide inherent biological action, carry, and release drugs. These categories are very effective especially for severe and complex wounds if the cost-effectiveness and regulatory issues can nearly be settled [31,32]. Modern wound dressings are devoid of the shortcomings of traditional dressings as they are designed to cover the demerits of conventional wound dressings [33,34] by

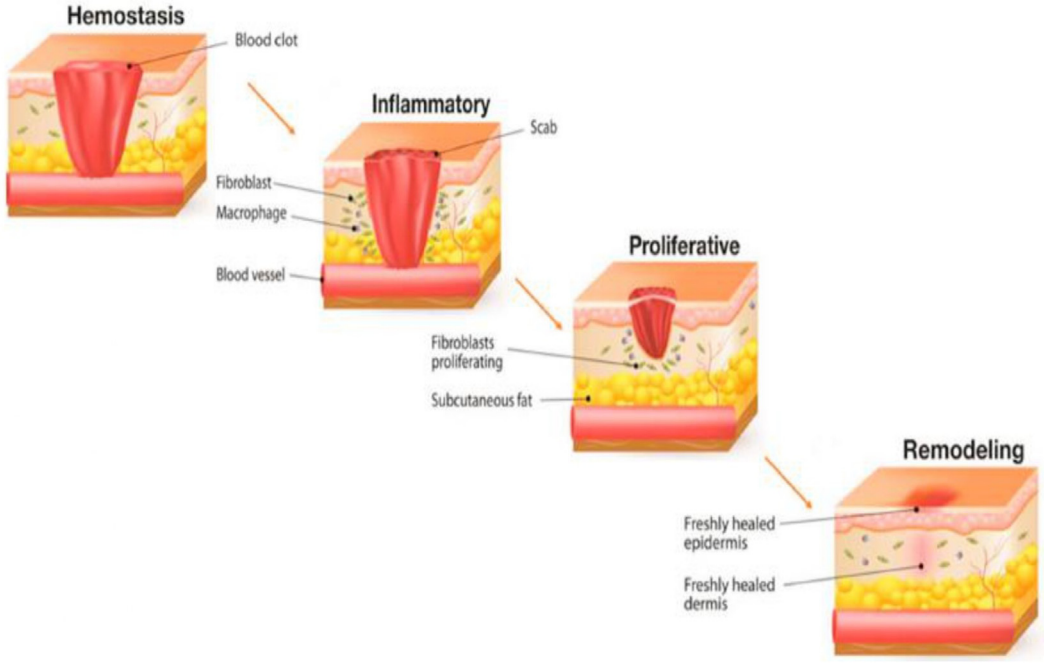

Fig. 1. Phases of wound healing [3].

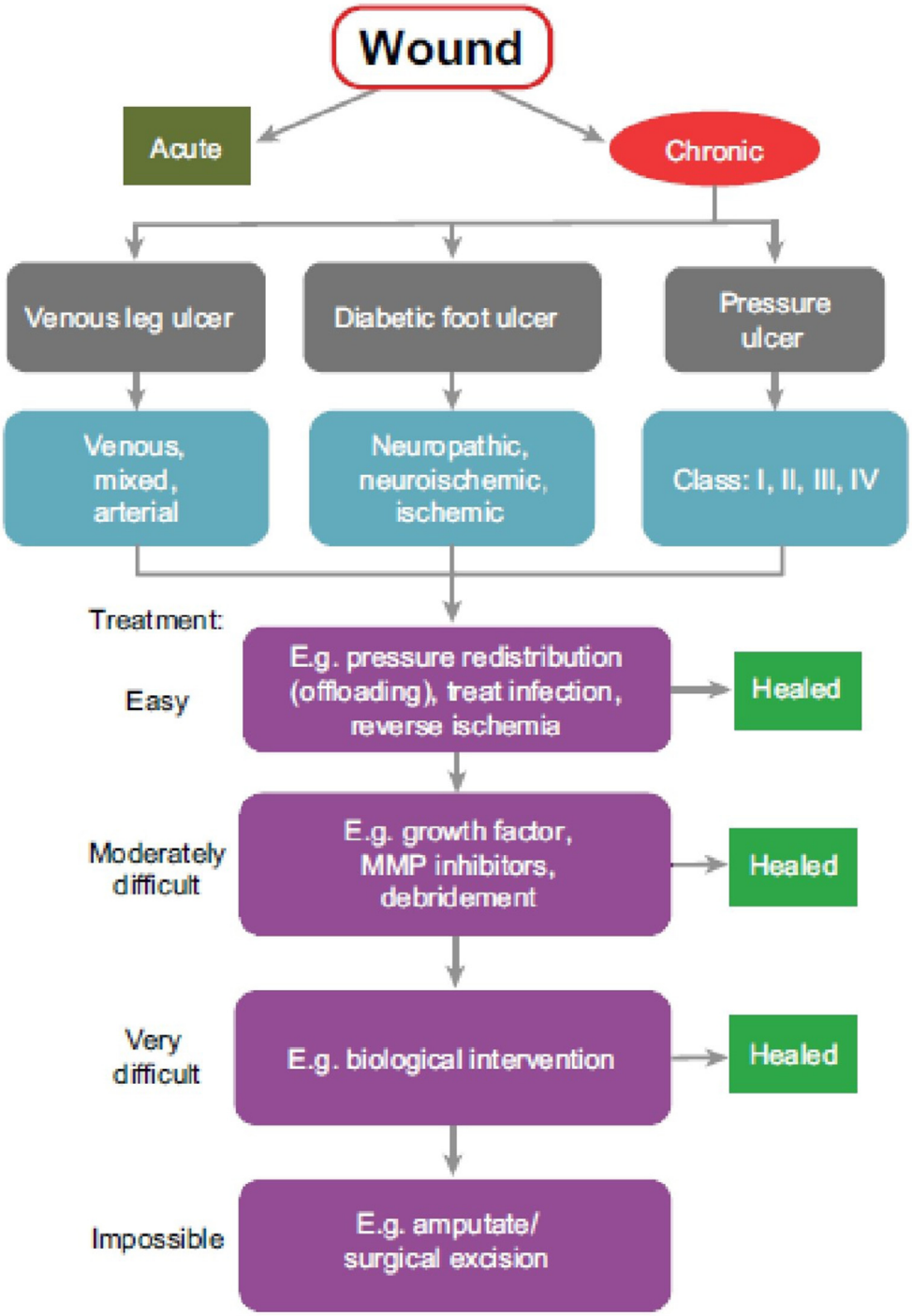

Fig. 2. Flow diagram of chronic wound management [13].

applying recent medical and engineering technology innovations. They are solely based on biocompatible natural, synthetic, or semisynthetic polymers with very flexible and breathable designs [35–37]. Natural inert and bioactive polymers such as cellulose, gelatin, polyurethane, polyethylene oxide, polyvinyl alcohol, hyaluronic acid, chitosan, and poly(L-lactide-*co*- ε-caprolactone) hydrogels, tissue-engineered skin substitutes (TESSs), alginate dressings, are among the commonly investigated advanced wound dressing materials [3].

1.3. 3D bioprinting technology for wound healing

Different polymeric scaffolds were used to create a multiparous and moist matrix around the wound to promote tissue regeneration. However, their single composition hindered to simulate the functions of the full-thickness skin [38,39]. Researchers discovered that 2D media lacks appropriate real-life detection of cellular matter as these have highly complicated and diverse structures, compositions, and interactions. Hence, innovation towards 3D

media is called to conquer the high-level assessment and characterization *in vivo* using new technologies [40,41]. These new technologies include advanced biomaterials and scaffolds prepared for the delivery of various therapeutic agents including cells, proteins, genes, and drugs [42]. The application of 3D printing for such therapeutics can not only maximize the therapeutic response but also advanced personalized treatment approaches [43].

Three-dimensional (3D) printing (sometimes called additive manufacturing) is an individualized, flexible, and precise technology for wound care approach [44,45]. *In vitro* 3D multiple-layer printed preparations can simulate the entire skin structure and layers [46–48]. It can upgrade pharmaceutical production for wound healing by providing personalized medicine, better feasibility, and complex geometries for resembling cellular structures [49,50]. 3D bioprinting is a layer-by-layer deposition of biomaterials by applying a combined principle of cell biology and materials science. It enables the manufacturing of new biological tools, patient-specific scaffolds, cell-mimicking tissue-engineered 3D scaffolds, and communication imitating extracellular matrix (ECM) products [51–53]. There are various 3D printing technologies utilized in customized medicines, such as stereolithography, selective laser sintering, fused deposition modeling, semi-solid extrusion, and powder-based printing [54,55]. The unique features, merits, and demerits of the commonly applied 3D printing technologies are summarized in Table 1.

3D porous structures fabricated from bioresorbable, biodegradable, bioactive, and mechanically robust biomaterials that induce cell ingrowth and proliferation, allow nutrient and oxygen transport, and promote new tissue creation became precisely promising for wound care applications [31,56,57]. These scaffolds can also bring numerous pharmaceutical advantages as they can enable personalized dose adjustment, drug combinations, and reduction of adverse effects [58–60]. Integration of 3D printing with nanotechnology can further advance drug solubility, stability, and targeting objectives [61,62]. This will intern lead to a perfect healing process, superior treatment outcome, faster healing time, and lower treatment costs [3,63,64].

3D printed scaffold wound dressings have several advantages, the major ones include the combination of various bioactive molecules and cells with polymers, the fabrication of complex scaffold designs, quicker healing times, and personalized wound dressings [65]. In addition, the dimensional properties (such as area, thickness, or pore size) of the dressing can easily be adjusted, drugs can be loaded easily, and there are plenty of natural and synthetic biomaterials available. Unlike conventional dressing, biomaterials, biomolecules, or cells can be used to form structures that can mimic the complexity of native tissues with the 3D printing method [66]. The technique also helps to overcome the limitations of traditional wound dressing manufacturing techniques; because, the structure is built layer by layer following a predetermined computer model, which offers better control of the wound dressings and skin applications architectures and geometries. Thus, it is possible to manufacture different modern wound dressings with different properties depending on the materials embedded inside the dressing [67]. Moreover, based on the patient's clinical needs, wound type, and metabolic characteristics it would be possible to generate more individualized treatments with better clinical efficacy with low treatment cost. The combination of stem cells, nanoparticles, and growth factors could also reduce healing times and costs [65,68].

One of the major requirements for 3D printing of tissue regenerative scaffolds is a bioink. Bioinks are a mixture of biomaterial (mostly hydrogels) and biological components such as cells. They provide an environment in which the cells can survive, grow, and multiply by giving the bioprinted tissue structure, support, and nourishment [69]. Bioinks are an important component of all bioprinting processes since they are utilized to produce the desired tissue structures' final shapes and are stabilized or cross-linked either during or right after bioprinting [70]. The most widely used materials for bioinks are gelatin methacrylol (GelMA), collagen, poly (ethylene glycol) (PEG), Pluronic®, alginate, and polymers based on decellularized ECM. Bioinks must satisfy the basic requirements for printability, desirable physicochemical properties (stiffness and viscosity), and biocompatibility. Hence, not only the printing techniques, the selection of the appropriate bioink should be emphasized during the 3D biomaterial preparations for wound healing and tissue engineering [71]. The important requirements for selecting a bioink for 3D printing in biomaterial aspects are illustrated in Fig. 3 [72].

2. 3D printed drug loaded nanomaterials for wound healing

Traditional approaches, like natural scaffolds or tissue donors, are unable to meet the rising demand for tissue engineering scaffolds. In this way, combining materials improves the qualities of the final product, such as biocompatibility, biodegradability, tensile strength, and design development for additional cell seeding [78]. Nanomaterial-based drug delivery systems and dressing scaffolds subsidized greatly to the advancements in wound healing and tissue regeneration [79,80]. They have demonstrated a promising healing outcome for the wound management of ulcers, trauma, chronic and severe wounds due to injury, burns, and infections, where wound care become more difficult and complex [42,81,82].

Nanomaterials applied for wound healing can be natural (originating from plants, animals, bacteria, etc.), synthetic, or composite systems. Alginate [83], Agaros [84], Carrageenan [85], Dextran [86], Cellulose [87], Chitosan [88], Chondroitin sulfate [89], Hyaluronic acid [90], Collagen [91], Gelatin [92], and Silk [61] are practically investigated examples of naturally originated 3D printed materials for wound healing. While, Polyacrylamide [93], Poly(N-isopropyl acrylamide) [94], Sodium polyacrylate [95], Polyethylene glycol (PEG) [96], and Poly(vinyl alcohol) (PVA) [97] are grouped under synthetic nanomaterials. Composites are formed by co-mixing both natural and synthetic materials with other cellular biomaterials [98]. A comparative view of natural, synthetic, and composite 3D materials is presented in Table 2. By providing adequate air and water vapor permeability, structure for macro- and microcirculation, support for cellular migration and proliferation, protection against microbial invasion, and resistance to external contamination, natural or synthetic, composite, or hybrid biomaterials represent suitable candidates for accelerated wound healing [99].

2.1. 3D bio printed natural biomaterials for wound healing

Natural polymers (collagen, agarose, gelatin, alginic acid, chitosan, etc.) have claimed central roles as bioinks for the 3D bioprinting of tissues and organs due to their ability to provide adapted scaffolding strategies for organizing cells structurally and functionally. All of these polymers are safe, biocompatible, and biodegradable, making them well adapted for several tissue engineering applications [105]. The origin of these materials makes them suitable for the substitution of natural ECM structural components and skin cellular background. Additionally, natural-derived polymers have a similar chemical structure with different groups that can be modified with some derivatives, leading to the development of adaptable materials fit for different tissue engineering necessities. Another key characteristic of natural

Table 1
Unique features, merits, and demerits of the major 3D bioprinting technologies [73–77].

Features	Laser-assisted Printing	Inkjet Printing	Extrusion Printing	Stereolithographic Printing
Physical Principle	A laser beam is guided toward sequential bioink droplets, resulting in heating them and, eventually, leading to their deposition on a surface, without requiring direct contact with this target area.	A method that does not require direct contact, utilizing piezoelectric, thermal, and electromagnetic sources to direct the ejection of multiple bioink droplets into different 3D shapes.	The most conventional 3D bioprinting technique, based on the use of varying pressure and temperature values to formulate bioprinted constructs of hierarchical architecture.	A technique that relies on the crosslinking of a photopolymerizable bioink solution, after its pouring into a mold with desired geometrical properties and its solidification under the irradiation from either a laser or UV light source.
Bioinks	Fibrinogen, Collagen, Gelatin Methacryloyl (GelMA)	Collagen, Poly (ethylene glycol), Dimethacrylate (PEGDMA), Fibrinogen, Alginate, GelMA	Gelatin, PCL, PEG, Alginate, Hyaluronic acid (HA), Polyamide (PA), Polydimethyl-siloxane (PDMS) dECM, Nanocellulose	PEGDA, PEGDMA, GelMA, dextran methachrylate (DexMA), assembly of cells
Resolution	1–50 μm	50–500 μm	>50 μm	<20 μm
Cell viability	97%	85–98%	80–96%	>80%
Cell density	10^8 cells/ml	<5x10^6 cells/ml	Cell spheroid	10 million cells/ml or a higher
Print speed	100–1600 μm/s	1000–5000 droplets/s	5e20 mm/s	25–300 μm/s
Target tissue	Skin, Vessel	Skin, Cartilage, Bone, Tumor, Liver	Skin, Cartilage, Vessel, Bone, Heart, Muscle, Tumor	Heart, Bone, Liver, Muscle, Breast, Adenocarcinoma cells
Merits	• High-speed printing • High resolution (10 μm) • High cell loading • No nozzle required which avoids clogging issues. • Suitable for in situ bioprinting purposes	• Low cost • High cell loading and viability. • High resolutions (up to 100 μm) • Suitable for scale-up activities • Allows direct printing of cells and other biologics. • Suitable for in situ bioprinting applications	• Low cost • Higher cell seeding • High cell viability • Moderate (300–600 μm) to high (200 μm) resolution • Suitable for large scale production • Allows direct printing of cells and other biologics. • Generally, requires low printing temperature and pressures. • Capable of printing high viscosity materials	• Low cost • High spatial resolution. • Use of predesigned molds enhances printing fidelity. • Speed of fabrication, • Higher quality • Creation of smooth surfaces • Better 3D integrity
Demerits	• Time-consuming preparation of the ribbon for printing • More expensive than inkjet- and extrusion based technologies. • Laser source is a potential disruption to cell viability	• Additional processing steps may be required (e.g., chemical crosslinking) • Polymer degradation has been associated with continuous inkjet bioprinting	• High temperatures may be required for high viscosity materials, ruling out the loading of biologics. • Additional processing steps may be required (e.g., chemical crosslinking)	• Slow process because it consists of two phases, • UV and laser irradiation can damage cells. • The dispersed nanophase can affect the extent of photopolymerization due to light scattering.

biopolymers is that when subjected to enzymatic degradation, they produce by-products that are generally well tolerated by living organisms without triggering toxic reactions. Undoubtedly, natural polymers have possessed difficulties to control due to their higher degradation rate or process [99].

Because of their biocompatibility, biodegradability, and similarity to macromolecules recognized by the human body, some natural polymers such as polysaccharides (alginates, chitin, chitosan, heparin, chondroitin), proteoglycans and proteins (collagen, gelatin, fibrin, keratin, silk fibroin, eggshell membrane) are extensively used in wounds and burns management [106]. Hydrogels engineered from polysaccharides through ionic and chemical means demonstrated high cell viability, cell binding affinity, and proliferation in wound healing applications, such as wound dressings and matrices for tissue repair and regeneration [107]. Chitosan-collagen cross-linked scaffolds also showed optimal porosity, reduced matrix degradation, and prolonged drug release with acceptable biocompatibility, enhanced cell development, and a prolonged release [108]. Chitosan can also be integrated with pectin and dextrin. Patches of such integration were investigated for wound healing with the incorporation of complexes of propolis extract. The bio printed scaffold showed *in vitro* antimicrobial and wound-healing activities [109]. Some natural products having emollient, demulcent, epithelializing, astringent, antimicrobial, anti-inflammatory, and antioxidant properties can improve the wound healing process [110]. Some of the practically studied 3D printed natural nanomaterials are presented in Table 3.

2.2. 3D bio printed synthetic biomaterials for wound healing

The use of polymers for potential improvement in controlling wound healing was a primarily anticipated innovation in wound treatment approaches. Nowadays, this application has been advanced towards 3D nano printed approaches as occlusive dressings [115]. A 3D printed wound dressing using antimicrobial metals (Zn, Cu, and Ag) incorporated into polycaprolactone (PCL) presented the strongest bactericidal potential against a common skin-infective bacterium, *S. aureus*. These metals with broad-spectrum antimicrobial properties improved the wound healing process [21]. Levofloxacin-loaded PCL scaffolds demonstrated excellent mechanical properties with sustained drug release when applied for antibiotic delivery to diabetic foot ulcer [55]. PEG based scaffolds have the characteristic nature to create an adequate biological environment and structural support with a mild inflammatory response and endothelial cell proliferation [34]. A PEG-polyglycolic acid (PGA) blend loaded with 3D printed PVA was applied to dermal wounds serving as a wound dressing. This synthetic extracellular matrix could deliver stem cells to the wound bed resulting in better regeneration and remodeling, bridging

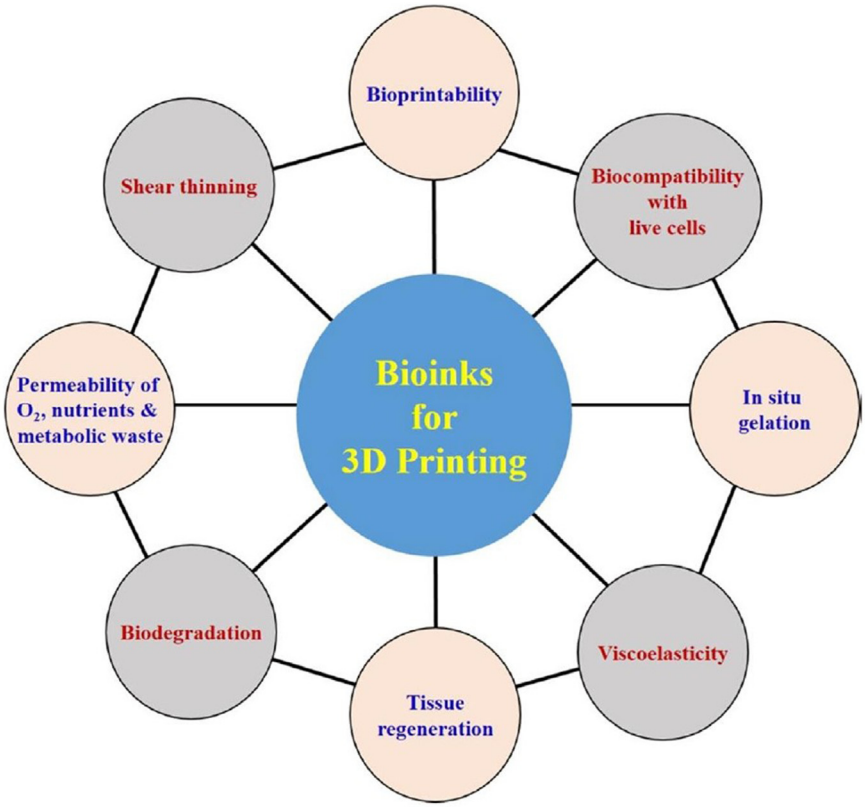

Fig. 3. Important requirements for selecting a bioink for 3D bioprinting [72].

Table 2
The merits and demerits of different materials used for 3D printed wound dressings.

Materials	Merit	Demerit	Commonly used Polymers	Reference
Natural	• Superior biological response • Good biocompatibility • Ecological safety • Biocompatibility and Non-toxicity • Easy availability • Cost-effective	• Poor mechanical properties • Low reproducibility due to variations in composition	Cellulose, Alginate, Agar, Chitin, Hyaluronic acid, Dextran, Starch, Collagen, Fibronectin, Gelatin, Elastin, Silk, Keratin, Fibrin	[99,100]
Synthetic	• Reproducible • Possess a defined chemical composition and • Tuneable properties according to the application requirements • Mechanically stable • Ease of modification • Consistent reproducibility due to uniform chemical composition	• Lack of cell adhesion sites • Less biocompatible • Expensive	Polyethylene glycol (PEG), Poly-β-hydroxybutyrate (PHB),Polypropylene fumarate (PPF),Polycaprolactone(PCL),Polyhydroxy ortho esters, Polyvinyl alcohol (PVA), Polyurethane (PU), Poly(methyl methacrylate) (PMMA), Polystyrene (PS), Polyethylene terephthalate (PET), Polyethersulfone (PES), Polyacrylic acid (PAA), Poly di ethylene glycol methyl ether methacrylate (PDEGMA)	[101,102]
Composite	• Increased mechanical strength. • Good tensile strength • Regulated biocompatibility, degradation rates, • cytotoxicity and thermostability	• Non-facile fabrication methods • Often require sophisticated Instruments • Expensive	PCL Collagen, PCL/Collagen/Titanium oxide, hEnSCs/PCL/Collagen,PEO/Chitosan/Collagen, PEO/Chitosan, PLLA/Chitosan, Pullulan/Collage, Collagen/elastin, Chitosan/Silk, Silk/Gelatin/Alginate, AgNPs/Chitosan, Carboxyethyl chitosan/PVA, Silk fibroin/hyaluronic acid/sodium alginate	[103,104]

the gap between injured and normal states. The construct was recommended for its great potential to be tailored or modified to include antimicrobial factors or possibly different factors to be released from each layer of the construct [11,116].

Metallic NPs, when applied as a 3D printed scaffold, have great, broad-spectrum antimicrobial properties that can improve the wound healing process [117–119]. A hydrogel of ZnO NPs utilized by 3D printing has shown increased healing progress in chronic

Table 3
Examples of 3D printed drug loaded natural nanomaterials for wound healing.

3D Scaffold	Product Description	Evaluation Outcomes	Reference
Chitin-covered CeNPs	Cerium NP-based wound dressing hydrogels covered by chitin	• an efficient fluid handling capacity and antimicrobial activity	[111].
RES-DOX–CS–CLG Cross-linked scaffold	emulsification and lyophilization based formulations of resveratrol microparticles (RES-GMS) loaded chitosan-collagen (CS-CLG) scaffold with doxycycline (DOX) on DWH	• optimal porosity, reduced matrix degradation, and prolonged drug release • promoted cell proliferation in the dermis by improving fibroblast function	[108]
CS-Pec-Dex Wound patch	propolis extract with beta cyclodextrin embedded with chitosan on pectin 3D-printed films using SSE.	• good *in vitro* antimicrobial activities • accelerated wound-healing effect	[109]
PhycoTrix™ bioink	a dual-network polysaccharide hydrogel 3D printed scaffold engineered through ionic and chemical means	• high cell viability, cell binding affinity, and proliferation compared to alginate studies • promising application as wound dressings and matrices for tissue repair and regeneration	[107]
Gentamycin Polyelectrolyte Multilayers	Conformal, consistent, inkjet printed coatings on a cotton substrate loaded with the antibiotic gentamicin.	• Significant antimicrobial activity of the gentamicin-releasing polyelectrolyte multilayer-coated cotton. • A burst gentamicin release, followed by steady release. • a low cost, scalable, versatile option for polyelectrolyte multilayer fabrication.	[112]
FBMSC-CMM 3D Membrane	freeze-dried bone marrow mesenchymal stem cells-conditioned medium membrane (FBMSC-CMM) for delivery of paracrine factors	• significantly accelerated wound healing • enhanced the neovascularization as well as epithelialization through strengthening the trophic factors in the wound bed	[113]
Osteopontin in collagen scaffold	A 3D scaffold fabricated from type 1 collagen for topical cell delivery of circulating angiogenic cells (CACs)	• Increased angiogenesis and increased percentage wound closure • a potential novel therapy for the treatment of non-healing diabetic foot ulcers in humans.	[114]

wounds due to its intrinsic antimicrobial properties, enhanced structure, and moisture retention properties. The scaffold was also capable of eliminating bacteria and allowing cell viability, all while being structurally and mechanically durable to maintain a chronic wound [120]. Mesoporous silica nanoparticles (MSNs) are highly promising drug carriers for controlled drug delivery due to their high specific surface areas, large pore volumes, high loading capacity, and favorable biocompatibility [121]. MSNs were utilized for a controlled co-administration of salicylic acid and ketoconazole to effectively treat highly resistant fungal infections. A rapid recovery from the fungal infection along with improved wound healing effectiveness and greater zone of inhibition was observed which should probably be due to improved bio adhesive and occlusive properties of MSNs. They additionally demonstrated a consistent controlled supply of medicaments at the target wound [122].

Metallic NPs are utilized for the delivery of antibiotics to the infection site, allowing reduced risks of toxicity related to systemic administration which requires high doses to reach adequate concentrations at the infection site. Moreover, they lower the risk of the growth of antibiotic-resistant bacterial strains [10,123]. Silver NPs, which are well known for their antimicrobial properties, were the most used nanomaterial in the preparation of 3D-printed forms [60]. The antimicrobial efficacy of these products was tested against several pathogens such as *S. aureus* which have great clinical relevance in the community- and hospital-acquired infections and their higher resistance and adaptability [60]. 3D printed antimicrobial loaded metallic nanoforms have quickly enabled the development of on-demand, patient-specific, targeted, controlled, and less-toxic antibiotic delivery which can be mediated by nanocarriers or from functionalized scaffolds [124,125]. Silver NPs loaded as an antibacterial agent in PLA, PVA, and PEA based 3D-printed antibacterial implant systems resulted in slow Ag NP release, forming a relatively constant antibacterial environment around the lesion area against methicillin-resistant *S. aureus* [MRSA], and preventing infection of the injured area [126]. A similar formulation with a 3D-printed responsive fever implant system also resulted in a thermosensitive release of the Ag NPs with effective inhibition of clinical bacteria such as *S. aureus, P. aeruginosa*, *Shigella* spp. and *E. coli* [127].

Titanium scaffolds covered by Ag NPs and $Ca_3(PO_4)_2$ NPs resulted in enhanced hydrophobicity and surface roughness at the nanoscale, interrupting bacterial adhesion, and preventing their growth. The synergistic effect of the NPs covering the surface of the 3D-printed scaffolds prevented biofilm formation [128]. Nanotitanium dioxide is reported to increase the mechanical properties of antimicrobial containing 3D nanocomposites in addition to their promising antibacterial effect against *E. coli* and *S. aureus* [58]. Wound healing scaffolds containing copper NPs showed a well-defined halo of inhibition and good antibacterial activity against *E. coli* and *S. aureus*, with an interesting potential for topical use [129,130]. Copper/zinc NPs-based scaffolds also showed improved mechanical properties, good porosity, and effective inhibition of bacterial growth of *S. aureus*. The histological evaluation revealed that the scaffolds containing copper and zinc-based zeolitic imidazolate nanoparticles drastically reduced the infiltration of inflammatory cells and mass of bacteria [131]. Some of the investigated synthetic materials for wound healing with 3D bioprinting applications are presented in Table 4.

2.3. Hybrid/composite 3D printed scaffolds for wound healing

The addition of small nanomaterials to the final product nanocomposite effectively enhances the mechanical and biological properties of polymeric and nonpolymeric scaffolds [123,139,140] (see Table 5). This route presents great versatility in the designing of new biomaterial compositions for 3D bioprinting, in which the integration of NPs can not only amplify the produced bioink biochemical response, but also improve the accuracy, fidelity, and reproducibility of the 3D printing process itself [141,142]. However, the presence of NPs can also lead to some adverse effects, such as reduced biocompatibility and slower degradation rates. The main reason for the advancement of 3D bioprinting technology is the

Table 4
Practical examples of 3D printed drug loaded synthetic nanomaterials for wound healing.

3D Scaffold	Product Description	Evaluation Outcomes	Reference
SA/KCZ-loaded MSNs	mesoporous silica nanoparticles (MSNs) for a controlled coadministration of salicylic acid (SA) and ketoconazole (KCZ)	• A rapid recovery from the fungal infection along with improved wound healing effectiveness • to improved bioadhesive and occlusive properties of MSNs and • a consistent controlled supply of medicaments at target wound.	[122]
CeNP nanogel (Ce-nGel)	wound bandages based on Cerium nanoparticle (CeNP)-loaded polyvinyl alcohol (PVA) nanogels.	• Broad spectrum antibacterial efficacy • rapid healing with less damage	[111]
PVA-CMC-polyethylene oxide membrane gel	ciprofloxacin, aloe vera, and curcumin loaded PVA-carboxymethyl cellulose-polyethylene oxide membranes	• effectively used to treat burn wounds, healing impaired ulcers, leprosy and other external wounds	[132,133]
PEG-HPM hybrid scaffold	degradable hybrid scaffold by mixing polyethylene glycol (PEG) acrylate and homogenized pericardium matrix (HPM)	• create an adequate biological environment and structural support • promote a mild inflammatory response and endothelial cell proliferation. • enhanced healing rate at the implantation site.	[34]
PGA-PEG blended scaffold	blend of polyglycolic acid (PGA) and polyethylene glycol (PEG) that incorporated 3D printed polyvinyl alcohol (PVA) sacrificial elements	• individualized medicine with effective delivery of stem cells to the wound bed • the sacrificial elements produce an internal void space for an injectable payload • effective incorporation of human mesenchymal stem cells (hMSCs) with maintained ability to differentiate	[11]
PCL based filament	antimicrobial metals (Zn, Cu, Ag) incorporated into polycaprolactone (PCL) to produce filaments	• strong bactericidal potential against a common skin-infective bacterium, *S. aureus* • customizable wound dressing fitting needs of individual patient	[21]
PCL-CaNP Scaffolds	covering PCL scaffold surface with biphasic calcium phosphate nanoparticles	• better *in vitro* osteoblast activity and mineralization of MG-63 cells • considerable improvement in calcium deposition and alkaline phosphatase activity • *in vivo* local treatment enhanced new bone production	[134]
1393@MBG 3D porous scaffold	Multiplexed drug delivery scaffold by coating mesoporous bioactive glass (MBG) on the surface of Silicate 1393 bioactive glass.	• excellent physical adsorption of various drugs without destroying the chemical activity • fantastic biodegradability and osteogenesis • better drug controlled release ability	[135]
AgMPs-PLA 3D coculture system	Polylactic acid (PLA) nanofibers loaded with highly porous silver microparticles (AgMPs) in simulated 3D coculture system	• steady silver ion release, at a greater rate of release • AgMPs overcomes concerns regarding the use of nanoparticles • great promise as skin substitutes or wound dressings for infected wound sites.	[136]
PCL-HA-Silica emulsified scaffold	W/O of PCL, modified hydroxyapatite and silica NPs loaded with ibuprofen	• Promising cytocompatibility with great bioactivity capacity • Prevention of severe inflammation induced from implantation of a synthetic scaffold. • release rate controlled by the amount of PCL in the scaffold.	[137]
HA-PLA-PEG-DEX 3D Scaffold	Dexamethasone-loaded matrix composed of nanohydroxyapatite, PLA and PEG.	• Effective local drug delivery with good bone regeneration and cytocompatibility • very slower dexamethasone release with unaltered anti-inflammatory effect • dexamethasone promoted osteoinduction and an osteogenic response, with an acceleration of the restoration process.	[138]
PLA-PVA-PEA-AgNP antibacterial implant	3D-printed antibacterial implant system using PLA filaments coated with polyvinyl alcohol, polyethylene acid (film-forming agent), and silver nanoparticles (antibacterial agent)	• formed a relatively constant antibacterial environment around the lesion area • the AgNPs were gradually released to kill the bacteria • prevented the infection of the injured area by methicillin-resistant *S. aureus* [MRSA]	[126]
PLA-AgNP-TDA responsive fever implant	3D-printed responsive fever implant loaded with AgNP and sealed by tetradecyl alcohol (thermosensitive material), with fluorescein isothiocyanate as a model drug	• antibacterial release at 39 °C, with responsiveness to fever • AgNP release allowed effective inhibition of clinical bacteria as *S. aureus, P. aeruginosa*, *Shigella* spp., *E. coli.*	[127]
Ti–Ag–$CaPO_3$ NP implant	titanium scaffolds covered by silver nanoparticles and calcium phosphate nanoparticles	• nanoparticles altered surface hydrophobicity and roughness, interrupting bacterial adhesion, and preventing their growth • the synergistic effect nanoparticles prevented biofilm formation	[128]

Table 4 (*continued*)

3D Scaffold	Product Description	Evaluation Outcomes	Reference
PLA-PCL-SilNP-enrofloxacin	3D printed PLA and PCL scaffolds stabilized by hydrophobically modified silica nanoparticles containing enrofloxacin	• crucially prevented bacterial infection at the bone implant site. • Good *in vitro* cytocompatibility • Enhanced cell growth induction. • Enrofloxacin was quickly released from the scaffold.	[112]
LFX-loaded PCL scaffold	3D-bioprinted PCL control scaffold for the delivery of an antibiotic (levofocixin) to diabetic foot ulcer (DFU).	• excellent mechanical properties for tissue engineering • sustained drug release for 4 weeks. • easily modified to the size of the wound. • simplified, low-cost alternative to current DFU treatment	[55]

goal of increasing its importance and possibly reducing its negative impact by improving the manufacturing process of bio-functional nanocomposites [75,143,144]. The NPs to be incorporated can be from carbon based NPs such as graphene, graphene oxide, carbon nanotubes, and carbon nanofibers; ceramic NPs such as silica-based nano biomaterials, bioactive glasses, and calcium phosphate NPs; biopolymeric nanoparticles, and various metallic NPs [145–148]. The various techniques and nanomaterials for nanocomposite fabrication are illustrated in Fig. 4 [75].

Nanoceramics can drive the growth of undistinguishable cells towards a specific tissue type, preserve good biocompatibility when utilized as nanocomposites in 3D printing, and advance the mechanical integrity and degradation profile of the scaffolds which they are included [149]. Carbon-based nanomaterials such as graphene, carbon nanotubes (CNTs), and carbon nanofibers (CNFs) type nanomaterials are very promising in nanocomposite applications as they possess particular electrical conductivity, large surface area, and mechanical strength. Their oxidized forms of graphene have acceptable cytocompatibility. The geometrical properties of CNTs (cylindrical folded) and CNFs (erratic stacking pattern) make them more favorable in tissue engineering applications as these properties ease the functionalization of medical devices [150–152].

Polymeric nanomaterial based nanoscale crystals and fibrils exhibit an excellent cytotoxicity profile with high thixotropic behavior with gelling the nanocomposite solution. The natural and synthetic biopolymers can be integrated for synergistic enhancement of properties and printability of the bioinks [153,154]. Polymers like poly (3,4-ethylene dioxythiophene) (PEDOT) have excellent electroconductivity which can be implied for tissue engineering applications that need bioelectric flow. Their highly hydrophobic nature can be minimized by mixing them with other hydrophilic biomaterials [155,156]. Metallic NPs also play an important role in nanocomposite preparation with their structural properties and biological activities. There are promising metallic NPs such as gold (Au) and silver (Ag) with acceptable biocompatibility, significant electroconductivity, and intrinsic antimicrobial activity. Even though biodegradability remains a challenge in their applicability, there are still numerous works suggesting their positive impacts on wound healing and tissue engineering used as composite systems [157–159].

Responsiveness to internal or external stimuli, including pH, temperature, ionic strength, and magnetism, is another promising means to improve the multifunctionality of smart scaffolds with on-demand delivery potential [160]. In recent years, smart/stimuli-responsive hydrogels have drawn tremendous attention for their varied applications, mainly in the biomedical field [161,162]. The hydrogels can be obtained from natural or synthetic sources though they can be composite using organic or nano organic fillers. The basic role of smart hydrogels depends on their swelling, shaping, hydrophilicity, and bioactivity in response to external stimuli such as temperature, pH, magnetic field, electromagnetic radiation, and biological molecules [1,163]. Smart hydrogels have opened a new horizon for scientists to fabricate biomimetic customized biomaterials for different applications including wound dressing, and controlled release of bioactive substances/drugs [53]. A 3D-printed bio-composite hydrogel formulated with small molecules, metal NPs, and proteins resulted in controlled release at the wound site and improved granulation tissue formation and differential levels of vascular density, depending on the growth factor's release rate [33].

The clinical trials of a hydrogel composed of ciprofloxacin, aloe vera, and curcumin loaded PVA-carboxymethyl cellulose-polyethylene oxide membranes confirmed that such gels can be effectively used to treat burn wounds, healing impaired ulcers, leprosy, and other external wounds [132]. 3D printed thermo-responsive hydrogel-based wound dressings containing an antibacterial ingredient in a novel printable ink containing poly(N-isopropylacrylamide) (PNIPAAm) precursors, sodium alginate, and methylcellulose possess accurate printability and shape fidelity with a sustained antibacterial release [164]. High surface area metallic silver NPs and microparticles (MPs) in PLA nanofibers containing highly porous exhibited steady silver ion release. The replacement of AgNPs with the newly introduced AgMPs overcomes concerns regarding the use of NPs and holds great promise as skin substitutes or dressings for infected wound sites [136]. Flexible dressings printed by using a combination of chitosan/PVP/PEG/PVA exhibited complete wound healing and re-epithelialization during *in vivo* studies [165].

The delivery of stem cells in combination with 3D scaffolds has been a promising approach in the field of regenerative medicine. For instance, bone marrow mesenchymal stem cells, human umbilical cord perivascular cells (HUCPVC), amniotic fluid-derived stem cells (AFSs), endothelial progenitor cells (EPCs), and circulating angiogenic cells (CACs) are commonly investigated. Early EPCs, often referred to as CACs, are extracted from the mononuclear cell fraction of peripheral blood and may be used topically to treat nonhealing diabetic foot ulcers. Increased angiogenesis and an increased percentage of wound closure were observed from a scaffold fabricated by collagen for topical cell delivery of CACs to a diabetic rabbit ear wound (alloxan-induced ulcer) [166]. A 3D membrane scaffold prepared from a freeze-dried bone marrow mesenchymal stem cells conditioned medium (FBMSC-CM) significantly accelerated wound healing and enhance neovascularization as well as epithelialization through strengthening the trophic factors in the wound bed [113].

A 3D scaffold dressing composed of mesoporous bioactive glass (MBG) and exosomes also permitted sustained release of bioactive exosomes. The MBG-Exosome hydrogel scaffolds possess a good 3D structure with a suitable porosity, biocompatibility, and hemostasis ability, which could promote the proliferation, migration, and

Table 5
Examples of 3D printed drug loaded hybrid & nanocomposite materials for wound healing.

3D Scaffold	Product Description	Evaluation Outcomes	Reference
ZnO Hydrogel	printed alginate + ZnO NP gels	• enhanced structure and retention of moisture • structurally and mechanically durable • capable of eliminating bacteria and allowing cell viability	[120]
Stimuli-responsive hydrogel	smart and automated flexible wound dressing with temperature and pH sensors built onto flexible bandages	• personalized treatment • adaptable, intelligent wound dressing system	[167]
PCL-based vessel-like composite hydrogel	vessel-like constructions made of Poly (-caprolactone) (PCL), low molecular weight chitosan (CS), and alginate-hyaluronic acid-collagen type I hydrogel	• overcome the issues associated with past use of traditional grafts • biocompatible, biodegradable, and nonimmunogenic hydrogel • effective for the development of functioning blood vessels.	[169]
SIS/MBG@Exos hydrogel scaffold	decellularized small intestinal submucosa (SIS) combined with mesoporous bioactive glass (MBG) and exosomes to fabricate a 3D scaffold dressing	• suitable porosity, biocompatibility and hemostasis ability • permits sustained release of bioactive exosomes • promote the proliferation, migration and angiogenesis of Human umbilical vein endothelial cells (HUVECs) • promote granulation tissue formation, well-organized collagen fiber deposition, functional new blood vessel growth	[170]
PLGA-ALG BLM Scaffold	bilayer membrane (BLM) scaffold of an outer poly (lactic-*co*-glycolic acid) (PLGA) membrane and a lower alginate hydrogel layer, respectively mimicking skin epidermis and dermis	• promoted cell adhesion and proliferation *in vitro* • minimized bacterial invasion and maintained moisture content • highest levels of best skin regeneration by increasing neovascularization and boosting collagen I/III deposition • ultimately accelerated wound healing	[168]
CS-PVP-PEG Flexible dressing	Flexible dressings using a combination of chitosan/polyvinyl pyrrolidone/polyethylene glycol on the cotton fabric	• exhibited complete wound healing and reepithelialization during *in vivo* studies.	[165]
TiO_2-PEEK PMMA composite	Polymethyl methacrylate (PMMA) composite with different titanium dioxide:polyetheretherketone (PEEK) ratios	• best possible mechanical and antimicrobial properties against *E. coli* and *S. aureus* at optimized TiO_2:PEEK ratio	[171]
CuNP-Alginate/Bacterial Cellulose Composite	3D-printed alginate/bacterial-cellulose hydrogels with in situ-synthesized copper nanostructures	• improved printability with a simple route for the production of alginate/cellulose inks • improved antimicrobial behavior against *E. coli* and *S. aureus* strains	[129]

angiogenesis of human umbilical vein endothelial cells (HUVECs). The results of a diabetic wound study *in vivo* indicated that the hydrogel scaffolds accelerated diabetic wound healing by increasing the blood flow of wounds and stimulating the angiogenesis process of the diabetic wound. The scaffolds also promoted granulation tissue formation, well-organized collagen fiber deposition, functional new blood vessel growth, and factors promoting wound healing [165].

Wound bandage composites based on cerium NPs (CeNP) loaded in PVA nanogels resulted in the sustained release profile of the cerium from the bandage with good antibacterial efficacy against gram-positive and negative microorganisms. *In vivo* healing evaluation of skin wounds showed that rapid healing was perceived in the nanocomposite-treated wound with less damage [111]. A wound dressing with an electronically controlled flexible heater and a stimuli-responsive drug-releasing system comprised of a hydrogel loaded with thermo-responsive drug carriers was designed to release the medications on-demand by Huang et al., 2020. This adaptable, intelligent wound dressing system demonstrated the potential to change the way chronic wounds are currently treated towards a personalized treatment system [167].

A bilayer membrane (BLM) scaffold consisting of an outer PLGA membrane and a lower alginate hydrogel layer, which respectively mimicked the epidermis and dermis (Fig. 5) promoted cell adhesion and proliferation *in vitro*. While the PLGA membrane prevented bacterial invasion and maintained the moisture content of the hydrogel. The application of BLM scaffold resulted in the highest levels of best skin regeneration by increasing neovascularization and boosting collagen I/III deposition and ultimately accelerated wound healing [168].

3. Challenges & future perspectives

3.1. Challenges

After much advancement in the field, the technology growth is limited due to the unavailability of material for 3D printed medicines, limitations in quality control and accuracy, clinically unacceptable defects, and low yield [172]. Scientific investigations for upgrading the advancements in 3D bioprinting are still in need to overcome their limitations and related challenges. The main challenges of 3D bioprinting are the suitable material and nutrient supply to the cells that stunted the process of this technology for several years [173,174]. Reduced mechanical strength over time, inability to completely promote skin regeneration, lack of fully stimulating the exact skin structure are reported deficiencies from these scaffolds [3,175]. A perfect degree of precision with an accurate hierarchical structure mimicking the skin's nature is yet to

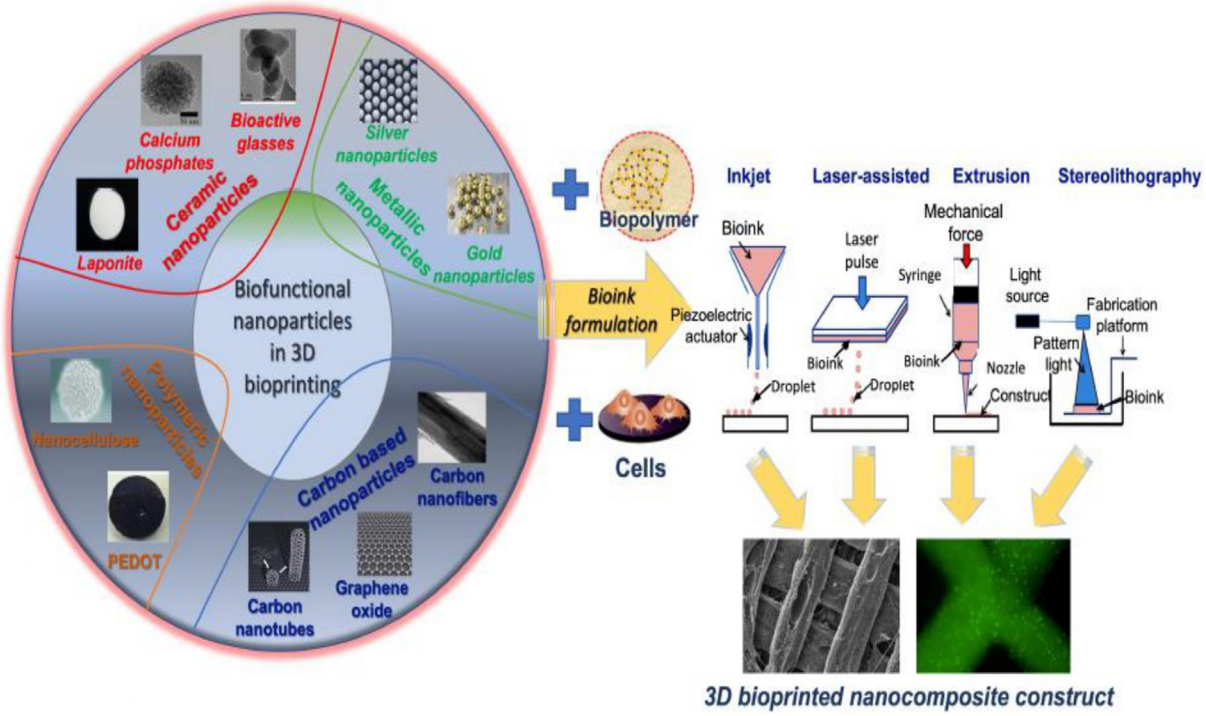

Fig. 4. 3D bioprinted nanocomposite constructing approaches [75].

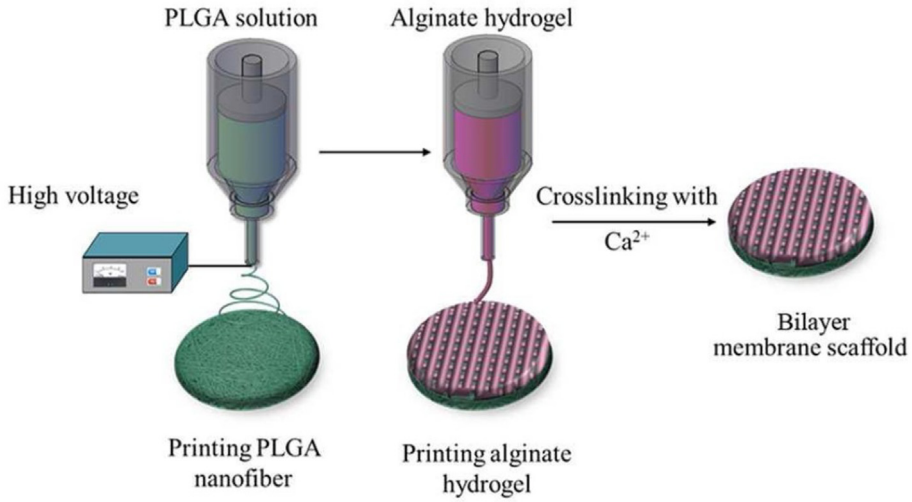

Fig. 5. Schematic diagram of bilayer membrane scaffold by 3D printing [168].

be achieved. Moreover, protocols and nomenclature systems of printing techniques are not identical and universally accepted [60,176].

There is a long way to achieve successful integration of required outcomes in terms of cell density, viability, and resolution [177]. In addition, scalability, consistency, traceability, and other acceptable regulatory issues need to be settled [98,178,179]. The speed of bioprinting, optimum level of resolutions, source scarcity (limited range) in material choice, biocompatibility, and safety issues are still considerable challenges of 3D printing [22,180,181]. Even though treatment individualization is a great advantage of such preparations, the manufacturers may neglect them as they provide suitable production of niche products or orphan drug products where the conventional large-scale production is not cost-effective [120,179]. By comparing the *in vitro–in vivo* correlation one can establish its product in the market, but it could be very challenging for the manufacturer to get regulatory approval. A satisfactory level of international regulatory agreement should be in practice regarding 3D printing for health applications [182].

3.2. Future perspectives

The better structural integrity of bioinks with improved hardening or gelation, for example by using bio-composites, is required to optimize the applicability of 3D printed biomaterials. Advanced technological innovations for the synthesis of adequately biocompatible biopolymers should be implemented. Mechanisms to reduce healing cost and time, such as combination with stem cells, nanoparticles, and growth factors should be outlined [3,116]. Research should be conducted on bringing high speed bioprinting with appropriate resolution [63,126,183]. Ways to revolutionize the pharmaceutical market regarding wound care and bring wound healing drug delivery and manufacturing closer to the patient is one critical agenda in maximizing 3D bioprinting application [184–186]. Parallel to their mechanical strength, scaffolds with enhanced cell adhesion and proliferation are required [60,187]. Integration of nanostructures as carriers with biomaterials for 3D bioprinting and investigating them with clinical trials may bring new achievements with extraordinary new applications. Multidisciplinary research and integrative participation are required to succeed in the achievements and have agreed scientific protocols of fabrication [60,188]. Antimicrobial-loaded implants with sustained, controlled, or dual release nature can be prepared using nanotechnology [60].

Imminent guidelines would interestingly be outlined regarding multi-layered scaffolds that bring dual administration by incorporation of drugs, cells, or other biologics [55]. The possible toxicity of organic linkers, metal ions, solvents, and chemical residues is a big challenge in this area that should be addressed in more detail [189]. The development of novel biocompatible and biodegradable nanomaterials (NMs), which can correct all phases of wound healing, can be a future goal for researchers working in this area. Further investigations and future perspectives should progress into the application of 4D printing systems which comprises “3D printing plus time” [53,190]. Extra dynamism and proficiency are needed for innovating the drug delivery system using multifunctional 4D printing technologies by working on its accompanying drawbacks like lower mechanical strength of the material and a longer response time to stimuli, resulting in a slower shape change rate [191]. Before considering a new generation of 3D printed nanomaterials and skin substitutes being translated to the clinical and commercial setting, gaps in the current regulatory framework towards the previously investigated approaches and nanomedicine systems need to be addressed soon [30]. Integrating theranostic constituents with wound scaffolds for monitoring the prognosis of wound healing will be the upcoming research area in 3D applications. This may be achieved by syndicating interactive and bioactive materials with therapeutic and diagnostic agents loaded into a solo scaffold [99].

4. Conclusion

3D nano printing has brought modern and innovative wound treatment applications including dressings that can be used for prolonged duration, provide inherent biological action, carry, and release bioactive components such as drugs with a controlled and sustained release pattern. Natural inert and bioactive polymers, hydrogels, tissue engineered skin substitutes, alginate dressings, polymers such as cellulose, gelatin, polyurethane, polyethylene oxide, polyvinyl alcohol, hyaluronic acid, chitosan and poly(L-lactide-*co*- ε-caprolactone) are among the commonly experimented advanced wound dressing materials. 3D printed nanomaterials are also applied to deliver antimicrobials, anti-inflammatory drugs, anti-coagulants, and cellular components. *In vitro* and *in vivo* evaluations confirmed the suitability of various 3D printed nanomaterials for improved wound healing processes based on cytocompatibility, biodegradability, resolution and viability, tissue regeneration, drug loading and release efficiency, moisture absorption capacity, and synergistic anti-infective responses. The future of these nanomaterials towards an effective clinical application for wound healing is grounded on the integrative and multidisciplinary effort of nanomedicine, materials science, and other respective bodies on their scalability, consistency, traceability, and other acceptable regulatory issues.

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