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Recent perspective of polymeric biomaterial in tissue engineering– a review

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ABSTRACT

Tissue engineering represents an advanced approach to treating patients who have suffered tissue or organ loss or failure, with the ultimate goals of tissue restoration and extended life expectancy. Polymeric biomaterials are increasingly favored in tissue engineering applications due to their advantageous qualities and characteristics, such as adaptable structure, exceptional flexibility, inherent biocompatibility, physiological activity, strong mechanical strength, and favorable biological environment. The latest advancements in tissue repair and regeneration using biomaterials and fabrication techniques for various tissue engineering applications, including dermal, muscle, bone, neural, vascular, oral, corneal, cardiac, and hepatic applications, are effectively demonstrated. Furthermore, the technical challenges and untapped potential of bioactive materials are highlighted to provide a comprehensive understanding of tissue engineering. Therefore, the recent development of polymeric and ceramics for the fabrication of different biomaterials for various tissue engineering applications. This review provides a state-of-the-art biomaterial critical analysis and comparative perspectives from polymers and ceramics and their applications for advanced tissue engineering. The critical analysis and comparative perspectives to stimulate further in-depth research on bioactive materials have been discussed that expand the new horizons in polymer chemistry, material science, and their fundamental applications in tissue engineering. It also provides substantial awareness about polymeric biomaterials and discusses important challenges and future perspectives that highlight future research with advanced progress in tissue engineering.

1. Introduction

Researchers worldwide seek alternative solutions to address the growing demand for treatment and replacement of damaged or defective organs using nanotechnology, material science, polymer chemistry, and tissue engineering [1,2]. To overcome these limitations, the engineered polymeric biomaterials must be biocompatible and biodegradable for tissue regeneration to develop polymeric biomaterials [3]. Biomaterials have different and distinctive hybrid, composite, and nanomaterials classes that replicate the characteristics of various tissues and organs [4,5]. They work by incorporating cells into their structure, eventually degraded to leave only normal tissue behind. Polymeric biomaterials have recently gained tremendous attraction due to their capacity to maintain a high water content, maintain a porous structure, and adapt to various sol-gel conditions [6,7]. The structural characteristics of polymeric biomaterials enable their use as tissue scaffolds in the body by promoting the influx of cell metabolic pathways and the eradication of cell wastes via their pores [8] (see Tables 1 and 2).

Polymeric biomaterials have several applications in tissue engineering and have attracted more interest over the past few decades [37].

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Polymeric biomaterials are either crosslinked or processed materials that may have water-soluble, covalently bonded structures [38]. They have several physicochemical interactions due to large polymeric chains, strong van der Waals interaction or hydrogen bonding, or crystallites that bring more than two macromolecular chains together [39]. Polymeric biomaterials can be developed from natural and synthetic polymers. They also can be categorized depending on various parameters, including fabrication method, mechanical, structural, physicochemical, and biological characteristics. These have potential properties and responsiveness such as temperature, pH, ions nature, etc., with potential tissue engineering applications [24,40,41]. The structural classification can be amorphous, hydrocolloid, hydrogen-bonded, and semicrystalline. Polymeric biomaterials have several applications in tissue engineering, including bone, cardiac, dermal, muscular, neural, oral, and vascular [42,43]. Researchers are working to find alternative solutions for increased organ demands due to the lack of donors and other medical limitations for transplantation. Highly biocompatible yet delicate biomaterials for tissue regeneration have been engineered to these limitations and other medical problems [44]. Therefore, biocompatible and biodegradable biomaterials are required, which can serve as a scaffold for treating and repairing different body issues [45].

Therefore, it is necessary to use advanced methods to develop advanced biomaterials such as hydrogels [46], scaffolds [47], nanofibers [48], microstructures [49], and nanostructures [50]. The ideal and best polymeric biomaterials must meet minimum standards for vascularization, host integration, and cell proliferation [51]. The engineered polymeric biomaterials should naturally degrade during or immediately following the healing process. However, incorporating these polymeric biomaterials still presents broad applications in biomedical engineering to address medical challenges [52]. The various biological and pathological transformations occur constantly and consistently in the human body, and the properties of polymeric biomaterials must be compatible with the biological systems [53]. Therefore, there is still a need to find appropriate hydrogel systems to encourage effective tissue regeneration for various biomedical applications [54,55].

Recently, there has been rapid progress in polymeric biomaterials in different applications of tissue engineering. Though several review articles address either protein, carbohydrate, synthetic or ceramic-based biomaterials, there is still a need for a comprehensive review article that is dedicated to polymeric biomaterials for tissue engineering. The literature review provides the recent developments and advances in polymeric biomaterials in tissue engineering. This review article focuses on frequently used materials and biomaterials in developing and assessing their fundamental properties in tissue regeneration, and the fabrication of different biomaterials via fabrication techniques has been summarized. The challenges and future perspectives of biomaterials in tissue engineering also have been discussed. In repairing and regenerating damaged tissue while maintaining the biological microenvironment and properties, significant challenges must be overcome in developing biofabrication techniques and biological environments. It also provided possible challenges and future perspectives and would help and guide the reader for future research by offering critical insight and ideas.

2. Materials of choice in tissue engineering

2.1. Polymers

Polymers have gained popularity in tissue engineering over the past decade because of their structural characteristics and similarities to ECM. Biomedical applications have made extensive use of both synthetic and natural polymers. We review recent literature on well-known synthetic and natural polymers used in biomedical applications.

2.1.1. Biopolymers

Natural polymers have received considerable attention in fabricating biomaterial in tissue engineering for recent decades. The material is selected based on its solubility, structure, wettability, surface morphology, swelling, biodegradation, and biocompatibility. The inherent characteristics of polymeric scaffolds provide high surface area, porosity, pore size, bio-friendly, and mechanical behavior and gained increasing interest in tissue engineering [56]. Natural polymers were used to fabricate biomaterials to assist tissues such as bone, bladder, cartilage, corneas, heart valves, nerves, pancreas, and skin are among those being developed by material scientists and biomedical engineers [57]. Natural polymer-based products are controlled biodegradable and tunable physicomechanical behavior with desirable architecture and construction in tissue engineering applications. Synthetic polymers are famous in tissue engineering in several biomedical applications due to their controlled and optimize properties such as mechanical, surface, pore size, and volume porosities. However, synthetic polymers have fewer options than natural polymers as they can support and maintain the micro-environment of the host biomedical site [58]. Natural polymers engineer most biodegradable and biocompatible biomaterials, and

Table 1
We have summarized the basic properties of polymeric materials in tissue engineering with basic tissue engineering applications.

Natural polymer	Synthetic polymer	Additives	Additive benefits	Applications	Reference
Chitosan	Polylactic acid	Hydroxyapatite	Bioactivity, Biocompatibility, Osteoconductive	Dentistry	[9]
Nanocellulose	Polyvinyl alcohol	Bioglass	Biomineralization Hemocompatibility Material architecture	Orthopedic	[10]
Gelatin	Polycaprolactone	Bioglass	Degradation Mechanical Biocompatibility	Orthopedic	[11]
Sodium alginate	Polycaprolactone	Bioactive glass	Biomineralization Degradation Osteoconductive	Orthopedic	[12]
Silk	Poly(lactide-co-glycolide)	–	Anti-inflammation Mechanical Biocompatible	Skin tissue	[13]
Chitosan	Polyvinyl alcohol	Zinc oxide	Antibacterial Hemocompatibility Mechanical Osteogenesis	Orthopedic	[14]
Cellulose acetate	–	Hydroxyapatite	Cell adherence Mechanical Material architecture	Wound healing	[15]
Collagen	Polyvinyl alcohol	Hydroxyapatite	Biocompatibility Osteoinductive Osteoconductive	Orthopedic	[16]

Table 2
In the study, we have summarized different fabrication techniques, biomaterials, and bioactive molecules in tissue engineering.

Fabrication techniques	Materials	Functional properties	Biological models	Applications	Ref.
Electrospinning	HAp/alginate	Enhanced mechanical behavior. Osteoblast proliferation.	Osteoblast (In vitro)	Bone tissue	[17]
	PCL/calcium lactate	Enhanced biomineralization. Cell infiltration and proliferation.	MC3T3-E1 (In vitro)	Bone tissue	[18]
	PCL/polystyrene/gelatin	Antibacterial active. Water adsorption and robust mechanical properties. Improved cell adherence. Cell proliferation, migration, and cell growth.	NIH/3T3 (In vitro)	Wound healing	[19]
	Pluronic F-127/MWCNTs/PLLA	Enhanced cell proliferation. Osteogenic differentiation. Hydrophilic, mechanical, and piezoelectric.	MC3T3-E1 (In vitro) and mice model (in vivo)	Bone tissue	[20]
	PCL/gelatin	Antibacterial adhesion. Increased mechanical properties, wettability, and permeability. Improved cell viability, proliferation, migration, and angiogenesis. Wound closure.	HSF and HUVECs (In vitro) and STZ rat model (in vivo)	Wound healing	[21]
	PLGA/decellularized/ methacrylate	Enhanced cellular orientation and myotube formation.	hMPCs (In vitro)	Muscle tissue	[22]
	PLA/PEG/polyaniline	Increased thermal and electrical properties. Cell proliferation and adherence. Increased cytocompatibility and biocompatibility.	NRK and MG-63 (In vitro)	Cardiac tissue	[23]
Freeze drying	nHAp/GO/arabinoxylan/acrylic acid	Excellent antibacterial activity. Improved mechanical properties. Enhanced cell adherence, viability, and proliferation.	MC3T3-E1 (In vitro)	Bone tissue	[24]
	GO/Bacterial cellulose/β-glucan	Antibacterial activities. Increased mechanical strength, swelling, degradation, and wettability. Improved cell adherence, proliferation, and biocompatibility.	MC3T3-E1 (In vitro)	Bone tissue	[25]
	Cellulose acetate/collagen	Improved antimicrobial activities. High porosity, swelling, and stability. Increased cell adherence and proliferation.	HaCaTs and 3T3 (In vitro)	Skin tissue	[26]
	CaO_2/polycaprolactone	Improved mechanical strength, swelling, and degradation. Enhanced cell viability, proliferation, noncytotoxic and metabolic activities.	Cardiomyocytes (In vitro)	Cardiac tissue	[27]
	Chitosan/silk fibroin/cellulose acetate	Increased surface roughness, enlarged pore size, and mechanical strength. Cell adherence, proliferation, infiltration, and gene expression.	HaCaTs and 3T3 (In vitro)	Smooth muscle tissue	[28]
	PEL/Gelatin/PEG	Supported swelling and porosity. Cell proliferation, gene expression, growth, and differentiation.	HaCaTs and 3T3 (In vitro)	Cartilage Tissue	[29]
3D-Bioprinting	Nanocellulose/Chitosan	Printability and enhanced mechanical properties. Cell viability, proliferation, and osteogenic differentiation. Excellent biomineralization, phosphate alkaline activity, and formation of ECM.	MC3T3-E1 (In vitro)	Bone tissue	[30]
	GelMA/Hyaluronic acid/ Dopamine	Printability, Shape fidelity, and microporosity. Cell viability, encapsulation, and wound healing. Tissue adhesion, self-healing	L929 (In vitro)	Wound healing	[31]
	Gelatin methacryloyl/hyaluronic acid methacryloyl	Promoted neovascularization, collagen secretion, and remodeling. Wettability, degradable, and cytocompatible	ADSCs (In vitro) and Nude mouse model (In vivo)	Skin tissue	[32]
	PMMA/Polyethylene oxide/ Chitosan	Porous architecture and controlled degradations and swelling. Printability, reproducibility, thermal stability. Water absorption, self-healing, bioink interaction with DNA,	Human Skin (In vivo)	Skin tissue	[33]
Solvent casting	PCL/graphene oxide	Scaffold architecture and porosity. Improved degradation studies. Cell adherence, proliferation, viability, and differentiation.	mBMSCs (In vitro)	Cartilage tissue	[34]
	PMMA/polyurethane	Interconnected porosity and controlled pore size. Increased mechanical	HS-5 (In vitro)	Bone tissue	[35]
	HAp/PLGA/polyaniline	Enhanced antibacterial activities and hemocompatibility. Increased mechanical strength, swelling ratio, and delayed biodegradation.	MC3T3-E1 (In vitro)	Bone tissue	[36]

synthetic polymers with filler can be added to control and optimize the engineering, structural and mechanical properties. Natural polymers provide excellent bioactive properties that promote biomaterial-cell interaction and improve cellular efficiency in the biological system [59]. The famous natural polymers have been detailed by putting light on synthetic and bioactive ceramic materials.

2.1.1.1. Alginate. Alginate belongs to an anionic polymer that usually originates from brown seaweeds. It has gained popularity due to potential qualities like biocompatibility, cytocompatibility, antibacterial activity, and gelation. It has received extensive research and is applied in various biomedical applications [60]. Alginate hydrogels can be produced via different cross-linking techniques because they possess structural similarities with ECM found in biological tissues. Its gels enable numerous applications in transplanting cells, tissue engineering, wound treatment, and delivery of bioactive substances, including protein molecules, small-molecule drugs, and nanoparticles [61]. It promotes tissue healing by preserving a physiologic microenvironment of moisture and reducing bacterial growth at the injured tissue site. Alginate gels can also be injected with very little invasiveness or given orally. These techniques make its numerous applications in tissue engineering and pharmaceuticals possible [62].

2.1.1.2. Cellulose. The fabricated biomaterials from cellulose and its derivative have essential biomedical properties that increase their significance over natural and synthetic polymers [63]. Cellulose and cellulose-based biomaterials have been extensively used in biomedical applications such as tissue engineering, wound healing, and drug delivery system. Its tunable, physicochemical, and biomechanical properties make it a more promising and adaptable material for biomedical applications [64]. It is a biopolymer with versatile properties due to its functionalization, modification, and optimization, making it a potential material in biomedical applications to develop biomaterials that resemble the natural ECM. Biofabrication cellulose-based biomaterials are required essential expertise and knowledge in tissue engineering with basic features and optimization of cellulose in biomedical applications [65]. It develops a bio-friendly local cellular micro-environment that encourages cell adherence, proliferation, migration, and differentiation. It may regulate and functionalize the tissues without causing any host reaction at the host tissue site [65,66]. The micromechanics and other biomedical properties of cellulose-based biomaterials make it a promising natural polymer with several important applications in biomedical engineering [67,68].

2.1.1.3. Chitosan. Chitosan is a well-known polysaccharide derived from chitin and contains N-acetyl-D-glucosamine and D-glucosamine. Crustaceans, insects, and a few fungi all have exoskeletons rich in chitin [56,69]. De-acetylation is a process used to separate chitosan from chitin, which entails treating the chitin to remove the acetyl group, and it typically occurs in an inert environment to avoid unfavorable side effects [70]. Chitosan has several hydroxyl (-OH) groups like glucose and an additional amine (-NH_2) group. It finds extensive use in various industries due to its highly valuable properties, including biodegradable, biocompatible, and soluble in aqueous solution [71]. Chitosan has minimal toxicity and various biological properties, including innate antibacterial activity, bioactivity, immunogenicity, and miscibility with other polymers. These qualities led to its multiple applications in biomedical including wound healing, medication delivery, biomedical implants, and tissue engineering [72].

2.1.1.4. Collagen. Collagen type I collagen is found in many important tissues and organs, including skin, bone, blood vessels, and heart tissue, and is frequently employed in tissue engineering, reconstruction, and repair. Collagen is present in large amounts in the ECM, which contributes to intracellular scaffolding and has a unique fibrillar molecular structure as an alternative to ECM [73]. Collagen possesses properties to control cell shape, adhesion, migration, and differentiation, including poor immunogenicity, a structure with significant permeability, porous superior biocompatibility, and biodegradability. It is a suitable biomaterial for tissue engineering scaffolds based on its excellent results [74]. Although collagen scaffolds are hydrated, they lose their mechanical durability and structural stability, which affects the tissues for which they can be used. Physicochemical techniques can be used to physically or chemically cross-link collagen molecules, enhancing the mechanical characteristics of the scaffold. However, numerous collagen-based biomaterials have been fabricated and engineered by incorporating other substances to increase the mechanical durability of collagen scaffolds [75].

2.1.1.5. Gelatin. Animal collagen is used to produce gelatin and has a structural resemblance with collagen with water solubility. The tissues from swine, fish, and bovine animals were employed to produce gelatin, mostly used for tissue engineering [76]. The parameters such as pH, temperature, and extraction rate during collagen processing can affect gelatin-produced quality [77]. The gelatin interacts with ECM proteins and receptors on the cell surface for cell adherence, and fibronectin is a fantastic substrate. Furthermore, collagenase can digest gelatin matrices, allowing for in vivo matrix remodeling driven by biological processes [78,79]. Gelatin-based biomaterials have exceptional transparency because they contain more water, making them perfect for tissue engineering regeneration and repair. Regularly using gelatin in certain applications can increase protein hypersensitivity [80]. Immune reactivity has been shown to differ depending on the molecular weight of the gelatin. Therefore, the practical translation of tissue-engineered structures will require considering the processing method and gelatin type in tissue engineering applications [81].

2.1.1.6. Hyaluronic acid. Hyaluronic acid (HA) is a glycosaminoglycan present in extracellular tissue and has several potential biomedical, including cell culture substrates and cosmetic products [82]. Its physical and biological characteristics, whether in solutions or hydrogels form, are alluring for diverse biomedical applications in tissue repair and regeneration. It is gaining interest in biomedical applications due to its functionality, mechanism of action, and ability to build suitable structuring biomaterial [83]. Previous assessments of HA have concentrated on chemical alterations, biological processes, and medical uses such as visco-supplementation, wound treatment, drug targeting and delivery, and tissue engineering [84].

2.1.1.7. Silk. Silk has been utilized as a suture within the healthcare and med-textile industries for a long time. The macromolecular protein polymer known as silk is produced by epithelial cells in specialized glands produced by several Lepidopteran larvae [85]. The basic protein, fibroin, is surrounded by a glue-like coating made of a second protein, sericin, which together make up the spun fiber. Non-biocompatibility issues with silkworm silk are well documented due to residual sericin contamination [86]. Sericin-free fibroin fiber demonstrated high biocompatibility and cytocompatibility when used in biomedical applications. The pair of proteins with little weight and massive chains comprise the fibroin that makes up silk fibers bridged by solitary disulfide connection [87]. Hydrophobic and hydrophilic building blocks make up that naturally occurring amphiphilic block copolymer known as silk fibroin, and these factors increase its elasticity and hardness [88]. Silk fibroin has been researched for biomedical applications more and more during the past several years due to its good biocompatibility and predictable degradation rates. When formed into various shapes, these qualities may have extraordinary mechanical properties that last for hours to years [89]. Additionally, the option to precisely control the molecular, structural, morphological, and modification of the surface alternatives. It has increased the protein's usefulness in various

biological applications, including tissue engineering and the delivery of drugs, proteins, and genes [90].

2.1.2. Synthetic polymers

Several synthetic and biodegradable polymers have been employed to fabricate biomaterials with excellent biomedical properties in various biomedical and tissue engineering applications because of their controlled degradation. Biodegradable and biocompatible polymers are used in tissue engineering, drug delivery, and medical devices.

2.1.2.1. Polyurethane. Polyurethane (PU) is a flexible polymer in various biomedical applications, including bone regeneration. Polymeric materials with desirable mechanical and biocompatible properties make bone tissue engineering suitable. The porous scaffolds with optimized pore sizes and porosity can be fabricated from polyurethane, and it may provide an active biological environment that supports bone regeneration [91]. The porous scaffolds all the exchange of nutrients and waste products with enhanced bone tissue regeneration with optimum mechanical properties. The scaffold must bear mechanical load during healing, and the mechanical properties and PU-based scaffolds can be modified to get optimized properties [92]. The polyurethane biodegrades progressively to eliminate the need for a second surgical procedure to remove the implant. It may not possess osteoconductive properties, but its surface-modified or combined with bioactive substances to enhance its ability to interact with bone cells and promote the formation of new bone tissue. Polyurethane can be incorporated into more complex tissue engineering, and it combines with other cell types, biomolecules, and materials in advanced bone tissue systems that promote bone regeneration [93]. Zhang et al. have reported the development of the polymeric composite from polyurethane and calcium phosphate (including hydroxyapatite and tricalcium phosphate) with improved mechanical behavior and other biomedical properties. They have observed that the PU/HAp-based polymeric composite materials offer antibacterial, bioactive, and osteogenic characteristics and would be excellent polymeric composite biomaterials for bone repair and regeneration [94]. Jingjing Du et al. reported the synthesis of polymeric composite materials to develop highly resilient porous scaffolds from PU/whitlockite. They observed that the scaffolds exhibit remarkable mechanical behavior, wettability, and cytocompatibility (like cell viability and proliferation). They have suggested that polymeric composite scaffolds would be promising biomaterials to repair and regenerate fractured and defective bones in tissue engineering [95].

2.1.2.2. Polyethylene glycol. Polyethylene glycol (PEG), a synthetic and biodegradable polymer, is extensively studied for potential applications in several biomedical, tissue engineering, and regenerative medicines. It is a well-known biomaterial due to its exceptional characteristics, including its remarkable flexibility, biocompatibility, hydrophilicity, and water solubility [96]. These properties give it more potential in tissue engineering and other biomedical applications. The fabrication of three-dimensional scaffolds that facilitate bone cell adhesion, proliferation, and differentiation can be achieved using PEG-based hydrogels. The hydrogels can replicate the composition and structure of the extracellular matrix found in bone tissue, facilitating cellular interactions with the scaffold to facilitate tissue regeneration [85]. The cells-encapsulated hydrogels can generate bioactive molecules and facilitate the process of bone tissue repair. Polyethylene glycol-based coatings can be utilized in medical implants and orthopedic devices. These coatings enhance their biocompatibility and mitigate the likelihood of immune responses and other associated problems [97]. PEG hydrogels can be incorporated with various substances, such as polymers or ceramics, to produce composite scaffolds with enhanced biological and mechanical functionality. Its scaffold materials possessed considerable mineralization to augment their efficacy in facilitating the regeneration of bone tissue. It is important to note that PEG-based materials can have a wide range of molecular weights, crosslinking densities, and other properties that support the bone repair and regeneration [98].

2.1.2.3. Polyvinyl alcohol. Several biomedical applications of the synthetic polymer polyvinyl alcohol (PVA) have been reported in biomedical and tissue engineering applications due to its exceptional properties. The featured biomedical characteristics are biocompatibility, biodegradability, cytocompatibility, and controlled physicochemical, making it exceptional synthetic material in bone restoration and regeneration [99]. It is a potential polymer in tissue engineering applications due to its water solubility and ability to produce hydrogels. These provide a moist and supportive bioactive environment for bone cells to adhere, proliferate, and differentiate into new bone tissue. PVA-based hydrogels can be engineered for significant mechanical properties by adjusting crosslinking density and polymer concentration [100]. The biodegradability of PVA can be altered, allowing the substance to degrade gradually as new bone tissue develops. Numerous factors, including molecular weight, degree of crosslinking, and incorporation of bioactive compounds, can alter the PVA-based properties of hydrogels. These modifications impact the behavior of the hydrogel for the repair and regeneration of bone tissues [101]. Khan and co-workers have developed nanocomposite film from PVA/chitosan/Nano-hydroxyapatite doped with TiO2 with mechanical properties to address bone repairing and regeneration applications. They have reported that increasing TiO2-nHAp increased mechanical tensile and elasticity by offering cytocompatibility behavior against osteoblasts like MG-63 cell lines [102].

2.1.2.4. Poly(lactic-co-glycolic acid). The biodegradable copolymer poly (lactic-co-glycolic acid), also known as PLGA, has received considerable attention in bone tissue engineering. It is a combined form of lactic acid and glycolic acid to fabricate porous scaffolds. They have controlled mechanical properties and degradation rates that may serve as a temporary foundation for bone cells to adhere, proliferate, and generate new tissue [103]. It degrades very slowly, and the scaffold can be gradually degraded and to form newly bone tissue. Biodegradability is one of the primary advantages of PLGA, and during degradation, lactic acid and glycolic acid are produced as by-products that are released naturally to metabolized body system [104]. It can be combined with hydroxyapatite or natural polymers to produce composite structures with improved mechanical and biological properties. These composites can more closely resemble the composition of natural bone tissue. The biocompatibility, adaptability, and degradation of PLGA have led to its extensive use in bone tissue engineering applications [105]. Hossein et al. have reported the synthesis of polymeric composite from PLGA/-TiO2 to fabricate the bioactive scaffold for bone regeneration and evaluated in vitro and in vivo activities. They observed that the scaffolds exhibit increased mechanical porosity with desirable porosity, hydrophilicity, degradation, and new bone formation. They concluded the newly developed polymeric composite would be potential biomaterials for bone tissue engineering [106].

2.1.2.5. Polycaprolactone. Polycaprolactone (PCL), a synthetic biodegradable polymer, has attracted considerable interest in bone regeneration and tissue engineering due to its biodegradable and biocompatible properties. PCL has been extensively utilized in biomedical applications, in addition to scaffolds, implants, and drug delivery systems for bone repair and regeneration [107]. The fabrication of porous scaffolds with controlled pore diameters, mechanical properties, and degradation rates can be fabricated by PCL. These scaffolds provide a three-dimensional framework that facilitates the adhesion, multiplication, and differentiation of bone-forming osteoblasts and tissue regeneration [108]. PCL-based scaffolds are often incorporated with other materials (polymers, metallic nanoparticles, and ceramic) to enhance their

biomechanical and physicochemical properties. Its rigidity and tensile strength can be adjusted to satisfy the mechanical requirements of the target bone tissue [109]. It can be combined with other materials, such as natural polymers or bioactive ceramics, to develop composite structures with enhanced mechanical and biological properties. These composites are intended to resemble the composition and characteristics of actual bone tissue more closely. PCL can encapsulate stem or osteoblast cells, resulting in structures rich in cells that promote tissue regeneration [110]. Lee et al. have synthesized printable polymeric composite material from PLA/β-tricalcium phosphate to fabricate a 3D scaffold for bone tissue engineering. They have reported that the fabricated scaffold would be promising biomaterials for bone tissue engineering [111].

2.1.2.6. Poly(glycolic acid). Poly(glycolic acid) (PGA) is a synthetic and biodegradable polymer with potential bone regeneration and repair applications. It has been the subject of extensive research and usage in biomedical and tissue engineering applications. It is regularly combined with other materials (polymers and ceramics) to enhance the properties of PGA. It can be applied to fabricate porous scaffolds with controlled pore sizes and mechanical properties [112]. These scaffolds provide a temporary scaffold for bone cells to adhere to, grow, and form new tissue and control degradation to produce glycolic acid as a by-product. Although PGA is very brittle, its mechanical characteristics can be tailored by incorporating other materials to synthesized composites that resemble the properties of natural bone tissue [113]. These composite materials are implanted to promote the bioactive environment necessary for bone repair and regeneration. It has been used for cell therapy to encapsulate osteoblast cells and be injected into defect areas to encourage tissue regeneration [114]. Shuai et al. fabricated a bioactive scaffold from the PGA/HAP/poly-L-lactic acid (PLLA) with enhanced degradation, bioactivity, and osteogenesis. They also reported that the scaffolds supported the biomineralization, cell viability and proliferation, and potential materials for bone regeneration and bone-related applications [115].

2.2. Bioactive ceramic

Fabricating biomaterials for tissue engineering, including soft and hard tissues, involves the active reaction of bioactive ceramics. The bioactive ceramic interacts with biofluids to promote physiological interactions with increased cellular activities [116,117]. The frequently used bioactive materials are hydroxyapatite (HAp), tricalcium phosphate (TCP), glass ceramics, and bioactive glasses like silicate and phosphate glasses [56,118]. Their frequently inadequate biocompatibility and biodegradability nevertheless constrain their potential for application in clinical settings. These difficulties can be resolved by combining polymers or employing composite materials that enhance the scaffold's properties and enable regulated degradation and biological compatibility in tissue engineering applications [119,120]. The method for achieving engineered and biological efficacy in hard tissue and soft tissues is fabricating polymeric composites using natural polymers and inorganic bioactive ceramics [116,121].

3. Essential tissue engineering properties

3.1. Biocompatibility

Biomaterials used in tissue engineering should be biocompatible and encourage cell adhesion, biofunctionality, proliferation, differentiation, and migration [122]. The prepared biomaterials interact with cells on the surface of implanted biomaterials to regenerate tissue. The engineered biomaterials should elicit a bio-friendly environment for supporting damaged tissue [123]. The host immune response should be absent or minimal and not cause a strong inflammatory response that could hinder healing or tissue regeneration [124].

3.2. Biodegradability

The ultimate objective of tissue engineering is that the body's cells subsequently substitute the implanted biomaterials for tissue engineering. Biomaterials are substances that are not meant to be long-term implants [125]. Therefore, the biomaterials should be biodegradable for cells to generate their extracellular structure. It is capable of to be eliminated the body without harming host tissue. The process combines an inflammatory reaction with the carefully controlled infusion of cells that includes macrophages [126]. It is necessary to permit degradation to occur while tissues are regenerated, and tissue engineering techniques are used more frequently in medical applications. The study of immunology is becoming more significant in tissue engineering research [127].

3.3. Material architecture

Material design, architecture, geometry, and engineering are important factors in biomaterial engineering. The biomaterials should have an interconnected, highly porous structure to ensure cellular performance. Additionally, the porous, interconnected architecture is needed to exchange nutrients and waste products of the biomaterials [128]. It should not affect the regeneration during the degradation of implanted biomaterials. Degradation results from a deficiency of waste disposal and vascularization are two major issues in tissue engineering [129]. Specifically, controlled porosity and pore size of biomaterials are crucial as cells primarily communicate with biomaterials through available functional groups on the surface. Incorporating functional groups that encourage protein adsorption, increasing functional group density, and increasing the surface area are necessary parameters [130]. The average pore size of biomaterials determines the surface area within the pore to which cells adhere. The engineered material promotes cell migration into the porous biomaterials without compromising cellular behavior and eventually binds to the ligands in the biomaterials [131]. The minimum ligand density is essential because of the specific surface area needed to bind sufficient cells to the biomaterials efficiently. Thus, the essential range of pores in biomaterials may vary depending on the specific cell type and engineered tissue [132].

3.4. Mechanical behavior

The designed biomaterial should aid the damaged tissue site and support mechanically to normalize the mechanical properties. Mechanically stable biomaterials must be used in all tissues because applying them in bone and cardiac tissue fields can be challenging [5]. Developing biomaterials with sufficient porosity and mechanical characteristics to support the host-damaged tissue for bone tissue engineering is still challenging [133]. The implanted biomaterials must have enough mechanical strength for tissues to function properly from implantation to transformation, especially for bone tissues. Another challenge in bone tissue is that the healing and regeneration rate changes with age, which is another challenge. The healing rate is higher among young people than older people [134]. Subsequently, efforts have been concentrated on developing scaffolds with mechanical characteristics akin to bone and cartilage. Several materials have been designed that have desirable mechanical characteristics, but they lack porosity and pore size. The ideal scaffold would have a balance between its mechanical attributes and a porous design that would allow for cell migration and vascularization [135].

4. Biomaterials in tissue engineering

Bioengineering allows the processing of polymers to produce various morphologies using synthetic and natural polymers. These biomaterials, which come in various morphologies and bioengineered shapes, can be applied to tissue engineering (including membranes/films, nanofiber

mats, hydrogels, artificial fibers, sponges, and 3D bioprinting) (see Fig. 1).

4.1. Membranes

Fabricating polymeric membranes or thin films involves spin coating and vertical deposition with different tissue engineering applications [136]. The polymeric solution and methanol are alternately coated onto glass substrates when the spin coating is used [137]. The alcohol has an important impact on enhancing the surface characteristics of the thin film. After ethanol treatment, the fibroin film transforms into a jelly-like substance with a hydrated hydrogel covering most of its surface [138]. Ethanol-treated thin film has a rougher surface texture. A study found that different methanol treatments can affect surface properties [139] because it results from the flow of the particulate suspended deposits of agglomerates that have already been formed under the influence of evaporation of the solvent [140,141]. In biomedical applications, thin films have been thoroughly studied and have exceptional use in medical implants [142,143], tissue engineering [144], and drug delivery systems [145,146]. The thin films have tunable surface morphology, biodegradability, and biocompatibility, encouraging cell adherence, growth, and differentiation [147]. Canran Wang et al. fabricated flexible and printable hydrogel membranes from methacrylate alginate and silver nanowire with enhanced antibacterial activities for wound healing applications (Fig. 2A–C). They have reported enhanced epithelization, angiogenesis, and antibacterial microenvironment to promote cell proliferation and differentiation due to electrical stimulation. Rapid wound closure was observed in 7 days in vivo rat model as compared to normal healing process in 20 days [148].

4.2. Hydrogels

The hydrogels are three-dimensional polymer networks and exhibit swelling properties on the absorption of vast amounts of water and have several important applications in tissue engineering [150,151]. They offer a variety of methods for delivering therapeutic agents and different types of cells [152,153]. They have the benefit of being injectable, making them useful for cell seeding and encapsulating for tissue engineering applications. The prepared hydrogels are particularly well-suited for clinical and tissue engineering applications [154]. The profitability and growth of cells were discovered to be enhanced. The hydrogel can be developed by chemical or physical crosslinking and stabilized during gelation [77,155]. It causes structural changes in the polymers during biodegradation, and chain interaction leads to the three-dimensional configuration of a hydrogel. The hydrogels support cell adherence, differential proliferation, and migration to facilitate tissue formation or regeneration [156,157]. Gang Tao et al. fabricated the antibacterial hydrogel from silk sericin and sodium alginate incorporated with silver nanoparticles for wound healing application (Fig. 2D and E). They have reported that the fabricated hybrid hydrogel has desirable swelling and enhanced antibacterial activities with promoted cytocompatibility. The wound contraction was found to be 99 % after 12 days and would be promising wound dressing material for wound healing applications [149].

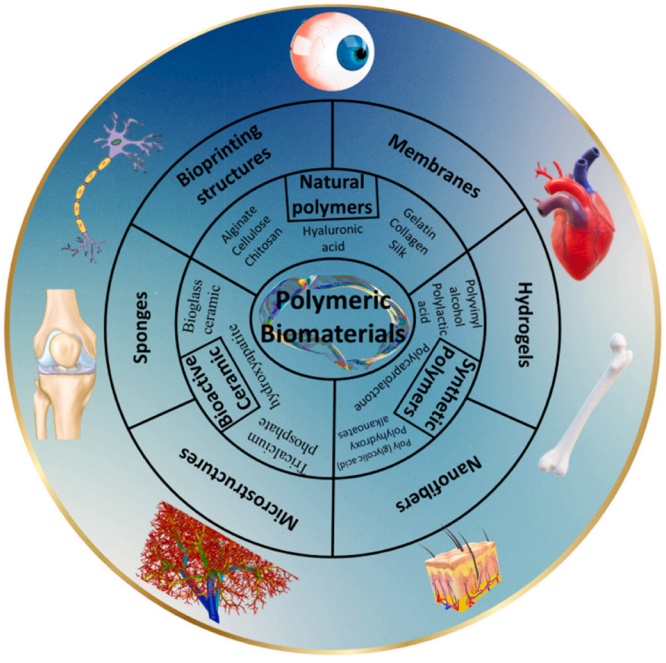

Fig. 1. The image presents the different biomaterials, their form, and their applications in tissue engineering.

4.3. Nanofiber

Different fiber spinning techniques were used to fabricate nanofibers mate, including electrospinning [158,159], wet spinning [160], and dry spinning [161] from polymeric solutions. The nanofibrous scaffolds can be fabricated via the electrospinning strategy [162] that mimics the ECM of natural fibers. The fiber-spinning approach is continuously improving to have more control over the process and its results [163,164]. The nanofiber mats are useful in tissue engineering and promote cell seeding due to their high surface area, porosity, and interconnectedness [165,166]. In the past, nonwoven nanofiber mats were created by spinning polymeric solutions at high voltages between 2 and 30 kV [167,168]. However, polymeric fibers fabricating via wet spinning is another option to produce high-quality nanofibers with tunable structural and mechanical properties [169]. In contrast, fabricating nanofiber from electrospinning is possible at the micrometer scale. Wet spinning allows for customizing fiber morphological, structural, and other characteristics, enabling the mixing of various polymeric solutions with other biomolecules during fabrication [170]. Before and during the wet-spinning process, the polymeric solutions can be modified using various physicochemical techniques to improve structural, morphological, and mechanical behavior of nanofibers. However, the wet-spinning method produces high production efficiency with minimal waste, and the complex spinning procedure cannot support large-scale production [171]. The study showed that high-quality fibers could be spun using a straightforward wet-spinning technique from relatively small-sized recombinant spider silk. Dry-spinning is more environmentally friendly than the earlier methods because it doesn't require organic solvents or coagulation baths [172]. Modern techniques for spinning polymeric nanofibers include centrifugal electrospinning [173]. It is more structurally and thermally stable than fibrous mats produced through standard electrospinning and centrifugal electrospinning, but centrifugal electrospinning allows for a higher and more affordable production rate [173]. Ying Wang and coworkers have fabricated the VEGF-loaded ECM-modified and electrospun silk fibrin bioscaffold with enhanced angiogenesis for bladder tissue repair and regeneration (Fig. 3A and B). They reported that the bioscaffolds have promoted the pro-angiogenesis and would be promising material for bladder repair and regeneration applications [174].

4.4. Micro-structures

Cellular behavior is influenced by the complex micro/nanoscale topologies and morphologies that comprise the ECM [176]. Therefore, it is essential to make an effort to simulate as many of these topologies as possible to guarantee the desired cellular behavior. The micro-patterning structure of polymeric materials has been shown to affect cell adhesion, proliferation, and migration [177]. Several improvements and developments have been introduced in

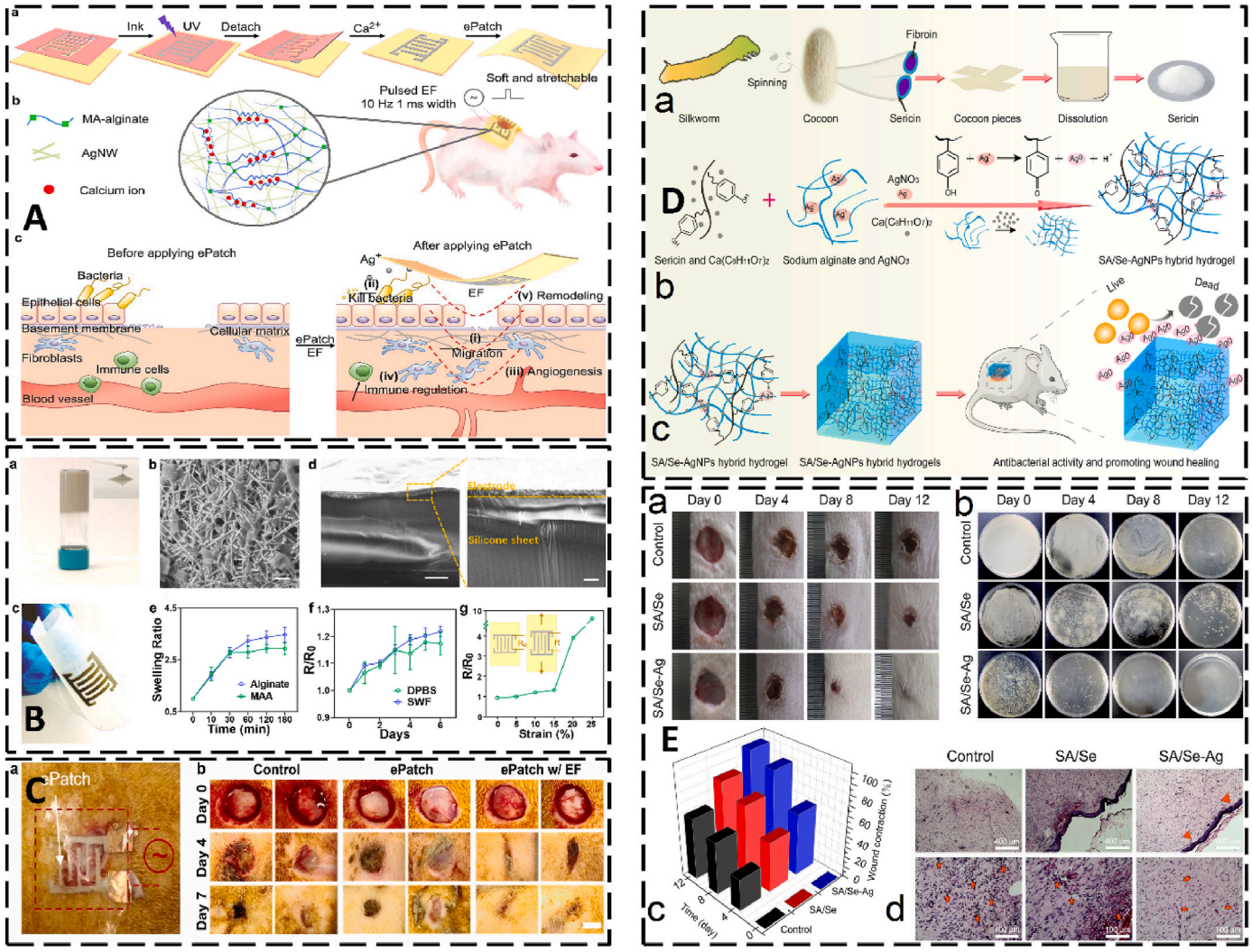

Fig. 2. The membrane and hydrogel-based biomaterials for tissue engineering applications. (**A**) Schematic preparation of synthesis of conductive hydrogel to fabricate e-patch and application of e-patch before and after for wound healing to enhance wound healing by cell migration and proliferation, antibacterial, angiogenesis, remolding, and epithelization, (**B**) Silver incorporated BioInk, crosslinked SEM morphology, e-patch, crosslinked SEM morphology, swelling and electrode resistance, (**C**) e-Patch on rat model and wound healing of optical images [148], with permission from Elsevier. (**D**) Schematic diagram of fabrication and in vivo rat model, (**E**) Open wound healing model, exudates culture, wound contraction ratio, and histological evaluation [149], with permission from Elsevier.

micro-patterning technologies that allow for spatial control of cell behavior [178]. Lithography is a well-established method for micro-patterning proteins onto substrates and includes an ultraviolet, soft, scanning probe, and electron beam lithography. Soft lithography is a quick, easy, and affordable method. It allows for manipulating surfaces' molecular makeup and patterning complex molecular configurations with biological relevance [179]. It develops channel structures appropriate for microfluidics to manipulate cells with spin-coating polymeric as a positive photoresist. An ultraviolet image is created on a silica substrate by exposing it to the argon laser beam through a pattern-covered chromium mask [180]. After cleaning the exposed areas with deionized water, patterned polymeric films exhibit diffracted color with a minimum line width of 1 μm. There are fewer steps, and polymers are used in this water-based approach rather than photo-initiators [181]. Inkjet printing offers an economical micro-patterning technique that accurately patterns complex geometries. Additionally, since inkjet printing employs a non-contact process, there is a markedly reduced risk of product contamination. The self-assembled peptide nanofiber patterns have been used to control cell growth on polymeric surfaces using inkjet printing [182,183]. Gang He and coworkers have fabricated a microneedle array loaded with 5-aminolevulinic acid, catalase, and Cu-doped-$CaPO_4$ nanoparticle encapsulated for photodynamic tumor therapy (Fig. 3C and D). In vivo, the mice model was used to evaluate the intratumor O_2 saturation and metabolic kinetics. They also observed that this approach helps optimize therapeutic biofactors to treat different cancers by releasing calcium and copper ions for promising clinical applications [175].

4.5. Sponges

The porous scaffolds are made up of sponges that closely resemble the physiological environments of living things. These facilitate nutrient and waste transport via perfusion or diffusion in a closed environment. Their 3D porous structure enables cell attachment, proliferation, and migration [77,184]. Salt leaching (porogen), gas foaming, or freeze-drying techniques can be used to develop pores of various sizes. Different processing parameters can control polymer degradation in aqueous or organic solvents [185]. Scaffolds composed of crosslinked, interconnected polymeric biomaterials are comparatively slow under in vivo degradation. Polymers are typically dispersed by an organic solvent in a typical procedure. The porogen, particulates of sodium chloride, or ammonium bicarbonate are added to optimize porosity with highly

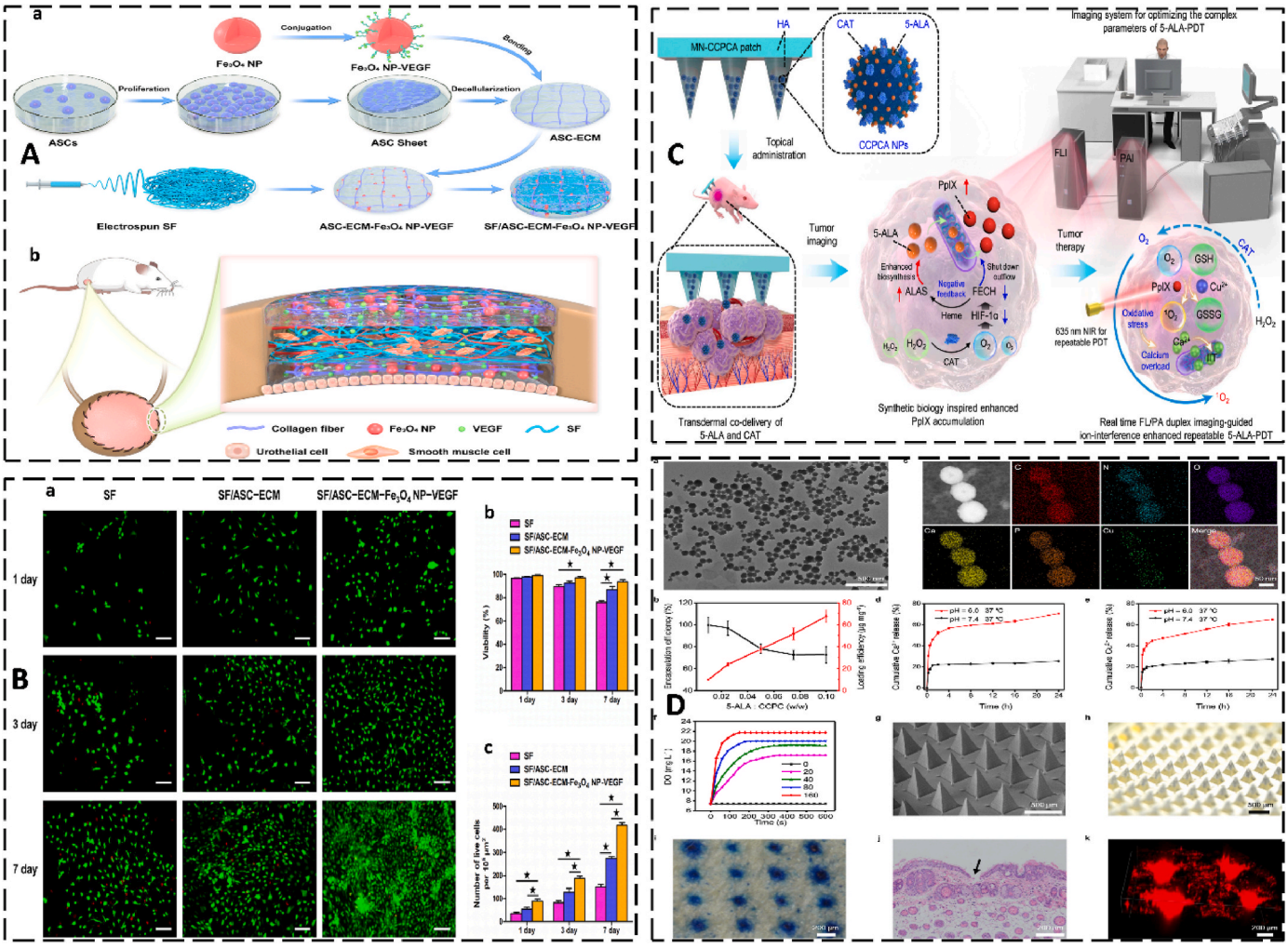

Fig. 3. The applications of nanofibrous and microstructure-based biomaterials in tissue engineering. (**A**) Schematic diagram to fabricate VEGF-loaded ECM-modified bioscaffold for bladder repair and regeneration in the rat model. (**B**) Live/dead assay to evaluate cell viability and the number of alive cells [174], with permission from Nature Publishing Group. (**C**) On-site tumor transdermal sustained therapeutic efficacy for tumor by microneedle array with real-time PpIX and biosafety. (**D**) The images of TEM, Loading and encapsulating efficiency, elemental analysis, dissolved oxygen at different concentrations, and SEM of the microneedle array. The MB staining images, mouse skin applied microneedle H&E staining images, and 3D reconstructed images of RhB FL on nude mice [175], with permission from Nature Publishing Group.

uniform pore size distribution as long as porogenic materials are uniform [186]. Freeze drying is another method to fabricate pore size, influenced by the polymeric solution's freeze-drying temperature, fibroin concentration, and pH [187,188]. Gas foaming methods with desirable pore size and porosity can develop porogenic biomaterials [189,190]. In hot water, ammonium bicarbonate sublimates when added to polymer solutions by forming porous sponge structures [191, 192].

4.6. Bioprinted structures

Complex and high-definition structures can be produced using bottom-up additive fabrication and bioprinting methods using computer-aided design and software. Three-dimensional (3D) bioprinting is an advanced technique over conventional tissue engineering by integrating architectural geometry [193]. 3D bioprinting technology comprises biological inks (bioinks), which control tissues' structural and functional properties to promote cellular behavior such as proliferation and differentiation. Although tissue engineering has used 3D bioprinting, many obstacles remain to be overcome [194]. Limited material and cell type options are challenging due to biocompatibility, biodegradability, and mechanical properties. However, polymorphic scaffolds can be fabricated to enhance mechanical behavior. The physicochemical and biomechanical properties can be enhanced by incorporating nanoparticles, additives, and polymeric-based inks to get 3D biomaterials with optimum porosity and pore size [195,196]. The polymer can undergo chemical modification to create printable bioink using a digital light processing 3D printer [197,198]. It can print complex structures (such as the brain, nose, and ears). Because of their robust mechanical and structural characteristics, the resulting 3D scaffolds can be used for cartilage and other bone tissue applications [199–201].

5. Tissue engineering applications

5.1. Bone tissue engineering

Bone tissue engineering is an emerging field that protects soft body organs from injury by supporting movement. Defected or fractured bone causes extreme patient discomfort and increases their risk of disability. Bone defects cause significant financial and medical pressures on patients and can increase the probability of bone deformity and even disability in extreme situations [202,203]. The need for clinical treatment of bone defects and fractures can be addressed by fabricating and engineering scaffolds using different techniques or methodologies. The

current clinical procedures commonly treat microfracture, tissue grafting, and bone replacement. However, these treatments have many drawbacks, including a lack of donors, insufficient compatibility, and inadequate resemblance with host bone tissue and surrounding area [204,205]. In the past few decades, hydrogels have been raised as the materials of choice for bone tissue regeneration with incorporations with other ceramic or metallic and other materials [206,207]. The researchers have fabricated scaffolds that significantly promote cellular proliferation and cell adherence that promote the healing of fractured bone [205,208]. Efforts were made to increase biological capabilities with the host bone and surrounding area. Khan et al. developed scaffolds for bone tissue from polymeric-incorporated HAp via freeze-drying methods to treat fractured bone. They reported that fabricated scaffolds are biocompatible with desirable physicochemical properties for load-bearing applications [203]. Shaheen et al. have reported synthesizing scaffolds from chitosan/alginate/HAp/cellulose scaffolds for bone tissue engineering via dicationic crosslinking using calcium chloride. They also observed the scaffolds' improved swelling and mechanical behavior with appropriate porosity than other already reported biomaterials for bone tissue engineering. They also found prolonged cell adherence and viability of fibroblast cell lines [209]. Anuj et al. reported the synthesis of composite hydrogels from polyacrylamide, poly (vinyl alcohol), bioactive glass, and halloysite nanotubes to fabricate hydrogel scaffolds for bone tissue engineering. The prepared hydrogels have structural and morphological with desirable mechanical properties to support bone tissue. They also reported that the fabricated hydrogels had enhanced biomineralization, cell adherence, and cytocompatibility. These would be promising materials to treat defective bones [101]. Nader et al. reported the fabrication of a scaffold reinforced with electrospun chitosan and hydroxyapatite nanofibers. Increased mechanical compression and reduced swelling were observed as an increased crosslinker. It was further observed that the scaffold enhanced biological activities such as MG-63 cell viability and biomineralization [210]. Peng et al. fabricated the silk fibroin composite scaffolds and modified them by coating them with polydopamine to improve biomineralization and biocompatibility for bone tissue engineering. They have observed different effects on porosity, swelling, hydrophilicity, mechanical behavior, and mineralization. The increased polydopamine coating

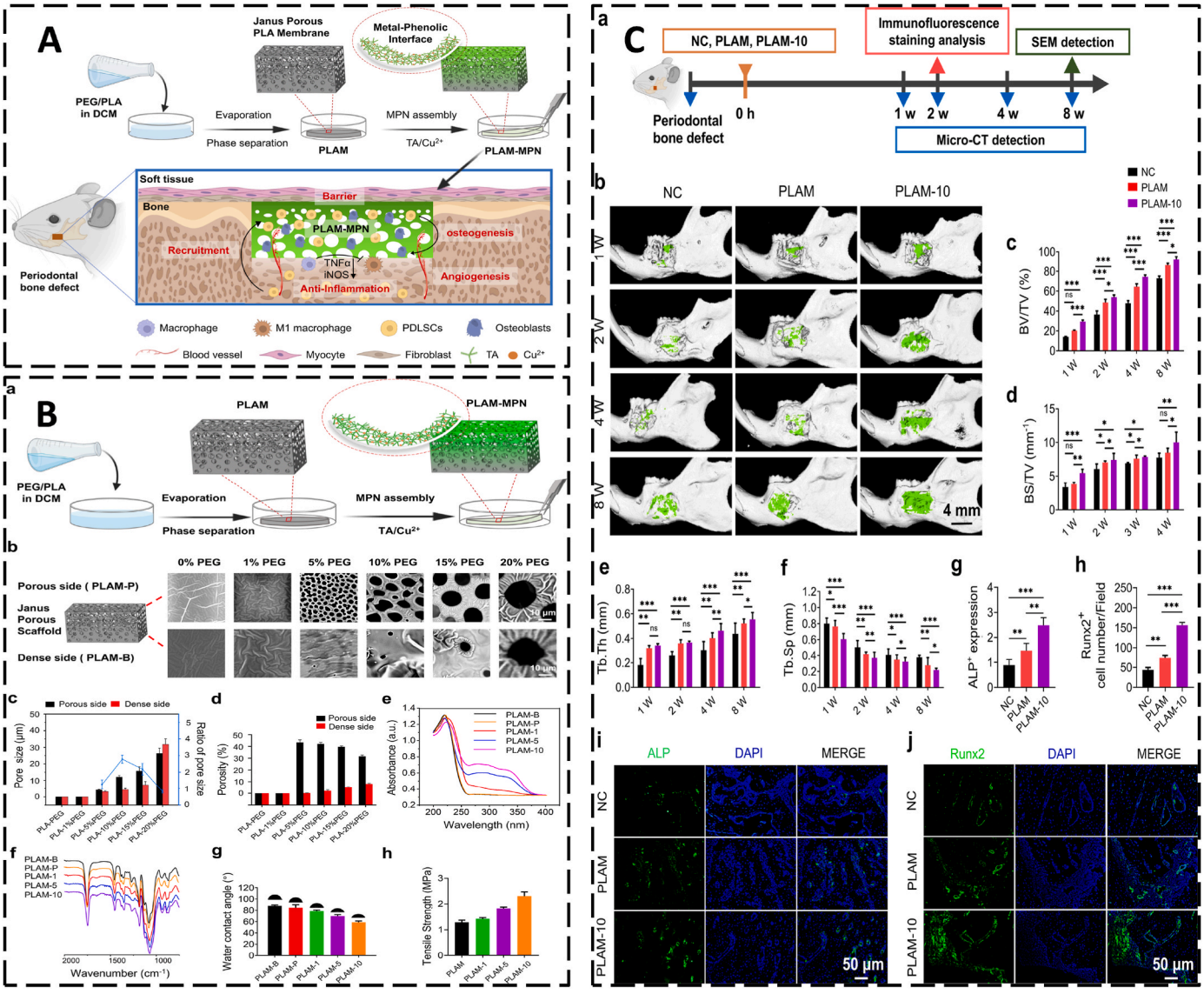

Fig. 4. Synthesis and application of composite materials for bone tissue engineering. (A)Schematic illustration of fabrication and bone regeneration, (**B**) Fabrication process, FTIR, SEM, wetting analysis, pore size and porosity, UV–vis spectra, and mechanical testing of PLAM and PLAM-MPN scaffolds. (**C**) Schematic diagram, Micro-CT images, Quantitative analysis of representative immunofluorescence staining images and quantitative analysis of mandibular bone defects, ALP staining, Runx2 staining [212], with permission from Nature Publishing Group.

enhanced the cell viability of MC3T3-E1 with excellent bioactivity [211]. Yaping Zhang et al. and co-workers have reported the fabrications of Janus PLA membrane by combined unidirectional evaporation-induced pore formation and self-assembly of metal–phenolic network (MPN) nanointerface (Fig. 4 (A-C)). The fabricated nanointerface has exhibited exceptional in vitro angiogenesis and enhanced cell adherence, migration, and differentiation against human umbilical vein endothelial cells (HUVECs) and human periodontal ligament stem cells (hPDLSCs), respectively. The implantation of nanointerface has promoted bone repair and regeneration in rat models and would be a potential membrane for clinical applications [212].

5.2. Cardiac tissue engineering

Myocardial infarction (MI) continues to be the leading cause of death and illness, and it is notoriously difficult to treat successfully in medical facilities. When an infarction affects a significant portion of tissue, it is frequently necessary to undergo clinically appropriate surgical intervention [213]. Although conventional methods have high importance for enhancing the life expectancy ratio of sufferers, any attempt to alter the structure of the cardiac tissues will always cause more damage to the vulnerable myocardium. This trauma can result from ventricular wall shortening, injured tissue, and heart failure [214,215]. According to earlier research findings, the epicardial patch can reduce the size of the damaged area of the myocardium. Bing et al. have developed injectable gallium-based self-setting glass-alginate composite hydrogels for cardiac tissue engineering. It was observed that the stiffness is comparable with cardiac tissue, and the optimum gelation rate makes it a desirable candidate for minimally-invasive intravascular injection. However, the composite hydrogel can be modified to deliver essential ions to the local cardiac environment without platelet adherence and affecting vascular cell viability [216]. Yong et al. reported synthesizing composite hydrogels from alginate with controlled release of VRGF and BMP9 to address myocardial infections. They observed the quick release of VEGF initially for a few days and sustained release of BMP9 for a few days, facilitating the angiogenesis with inhibition of myocardial fibrosis [217]. Finklea and coworkers have engineered the production of cardiac tissue microspheres by direct differentiation of hydrogel-encapsulated human pluripotent stem cells. They have observed that cells form cell-cell junctions with aligned myofibril fibers. These microspheres were kept in culture media for 36 months, and quick formation of cardiac microsphere tissues is not accessible by including biosynthesis with injectable and regenerative therapies [218].

5.3. Cartilage tissue engineering

Avascular and aneural chondrogenic density are almost negligible, and water content is high (70 %) in cartilaginous tissue. It is a useful, highly hydrated heterogeneous tissue that gives diarthrosis joints a load-bearing, wear-resistant exterior that reduces friction for effective joint movement [219,220]. Elastic cartilage, which has elastic fibers present in the ECM, is one of three classes of cartilage tissue that can be classified based on the composition of the ECM. The matrix of the fibrous cartilage is abundant in collagenous fibers. The matrix of hyaline cartilage is primarily made of glycosaminoglycans (GAGs). From a microscopic perspective, human cartilage comprises a hydrated ECM composed of proteoglycans with a core protein and covalently attached GAGs [221,222]. It is primarily chondroitin sulfate and collagen type II fibrils responsible for the cartilage's ability to sustain high compressive loads. It offers its high tensile strength and ability to withstand shear stresses. Because cartilage can't repair itself due to its avascularity and the low rate of chondrocyte proliferation, trauma, accidents, or other infections may result in cartilage loss [223,224]. Many possible therapies for chondral injuries include autograft transplantation, periosteal grafts, mosaicplasty, and microfracture. The clinical studies did not show long-term fixes and reliable regular fibrocartilage production. The formation structure of native tissue, which includes regions with various cell morphologies and arrangements and ECM arrangements, constituents, and distribution, makes it challenging to produce functional articular cartilage. The introduction of 3D bioprinting in tissue engineering has achieved notable progress in simulating the anatomy of articular cartilage tissue. Researchers claim this method can create constructs resembling cartilage by combining various hydrogels. However, simultaneous thermoplastic polymer deposition using multiple dispenser systems has been the most successful technique. While structural materials can maintain mechanical load, hydrogels serve as cell carriers. Researchers have also altered the properties of bioinks, including their printability, mechanical properties, and degradability. Chen et al. developed hydrogel from modified hyaluronic acid to facilitate the adhesion to host tissue and promote cartilage tissue regeneration. They have found an increased mechanical behavior with desirable cell proliferation and migration in rat osteochondral-defected models [225]. Li et al. have reported the fabrication of 3D hydrogel scaffolds with different porosity from silk and gelatin with cell seed for cartilage regeneration strategy. They have observed that the hydrogel exhibited excellent physicochemical and mechanical with desirable biodegradation to support cartilage regeneration.

In vivo, the rabbit model has presented the articular cartilage regeneration after 12–16 weeks [226]. Zhiyi Lui et al. and coworkers have studied the early stage of OA and destabilized medial meniscus surgery by developing two-photon excited fluorescence and second harmonic generation (Fig. 4 (A-C)). They observed substantial collagen fibers development and crosslink changes after one week of surgery. It was followed by high dynamic behavior in cellular metabolism with enhanced oxidative phosphorylation to promote glycolysis after ten weeks in the mouse model [227]. Jianjun Wu et al. and coworkers have fabricated ROS-responsive nanofibrous membranes via electrospinning for sustained Fucoxanthin release with antioxidative and anti-inflammatory activities against IL-1β-induced chondrocytes by exhibiting low cytocompatibility (Fig. 5 (D-F)). The nanofibrous membrane has in vitro logger and sustained drug delivery behavior for 66 days in an H_2O_2 environment. They confirmed that smart ROS-responsive nanofibrous membranes are biocompatible and biodegradable, promising for Osteoarthritis therapies under arthroscopy [228].

5.4. Corneal tissue engineering

The cornea is the anterior section of the eye's protective covering that resembles a dome-shaped structure and is transparent. It helps focus light and shields the eye's sensitive intraocular nerve endings and sensory organs [229]. Scarring and stromal shrinkage of the cornea due to injury or disease can cause irreversible visual impairment because of the cornea's extreme fragility. The preferred techniques for repairing damaged corneal tissue in the clinic include endothelial keratoplasty, corneal transplantation, and cyanoacrylate glue [230,231]. Despite these strategies' successes, corneal impairment care is still inadequate because of inherent problems such as donor scarcity, immunological rejection, insufficient integration, and low performance. An advanced strategy for treating damaged corneas is desperately needed, especially considering the scope of the issue [232]. Polymeric biomaterials offer a potential approach to treating injured corneal tissue, and they can significantly heal microincisions without any stitches or cuts. It enables increased bio-integration between the hydrogel and the native tissues of the cornea [233]. Therefore, the hydrogel can mimic several biological properties of native corneal tissue, such as optical clarity, water-holding capacity, and structural stability. These characteristics and hydrogel's ability to imitate them make regenerating and restoring corneal tissue possible [233,234]. Feng et al. have developed a biomimetic thermo-gelling scaffold from dendronized chitosan for corneal tissue engineering. It deep-filled corneal stromal irregular injuries and supports tissue regeneration. The thermos-gelling hydrogel has offered

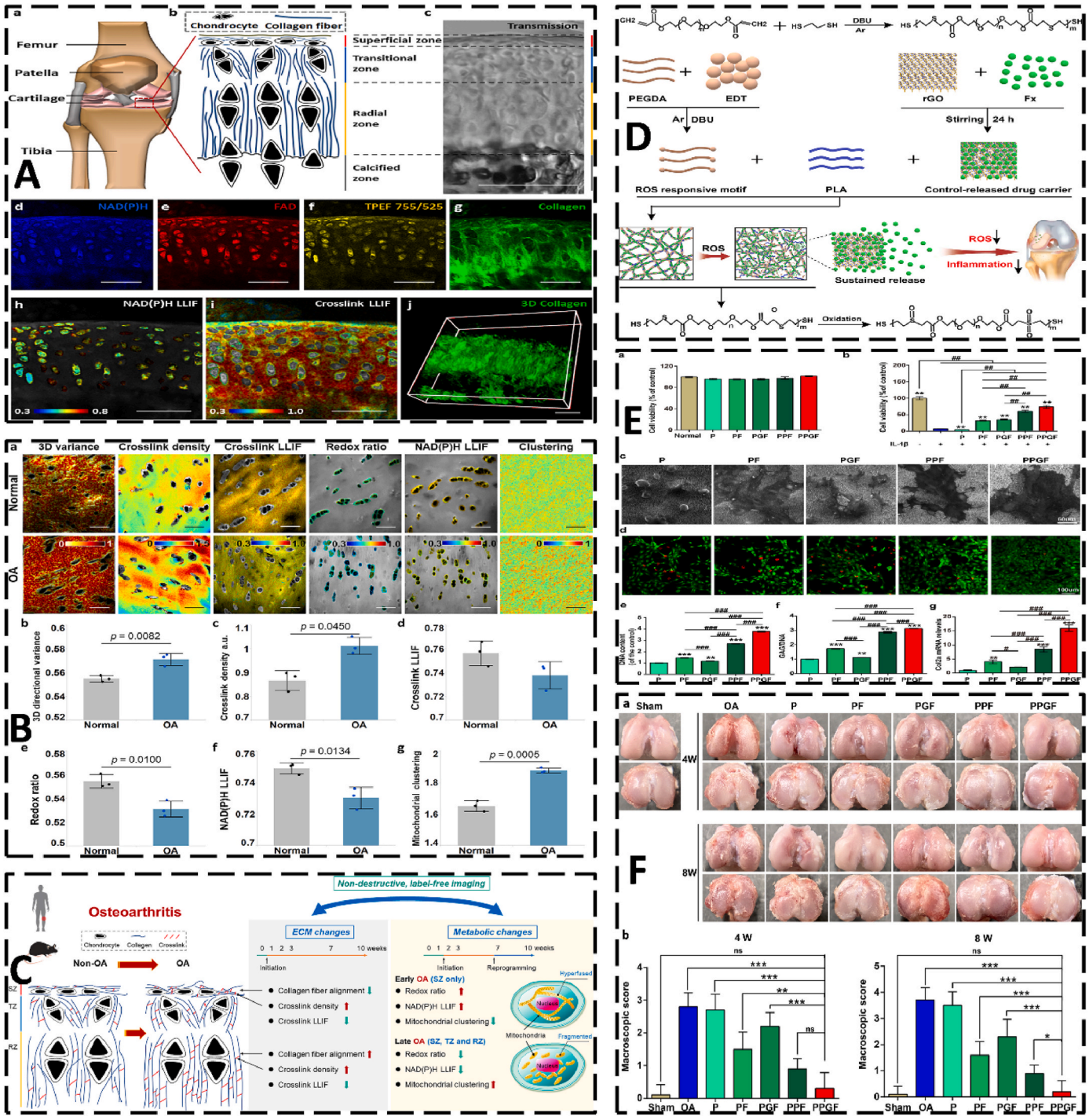

Fig. 5. The synthesis of polymeric-based biomaterials for cartilage repair applications. **(A)** Schematic illustration of cartilage composition, transmission image of mouse knee cryosection, and other analysis for evaluations of collagen fiber in a 3D context. **(B)** Mapping, 3D directional variance, crosslinking density, and mitochondrial clustering of normal and OA samples. **(C)** Superficial, Transition, and Radial zones [227], with permission from Nature Publishing Group. **(D)** Schematic diagram of nanofibrous membrane for sustained release of Fucoxanthin for OA therapy. **(E)** Cell viability, adherence, live/dead assay, DNA and GAG contents, mRNA expression on nanofibrous membranes in the stimulation with or without IL-1β. **(F)** The Fucoxanthin concentrations after nanofibrous membrane plantation in the cartilage, macroscopic analysis, and articular from the distal femur and tibial plateau after treatment [228], with permission from Nature Publishing Group.

exceptional cell viability, proliferation, and migration of keratocytes. However, tissue regeneration was observed in a rabbit in vivo model [235]. Arica et al. fabricated a composite electrospun matrix from gelatin methacryloyl by electrospinning technique and was crosslinked with poly (hydroxymethyl methacrylate). They have reported that the composite electrospun matrix was hemocompatible against red blood cells with desirable protein and cell adherence with cell growth [236]. Chen et al. reported the synthesis of hyaluronate-collagen to treat and repair corneal defects. They have studied the light transmittance of the biorthogonal and observed that the light transmittance is 79 % greater than water. The capability of the crosslinked hyaluronate-collagen hydrogel was investigated using several studies, including those on

mechanical behavior, morphology, refractive index, biocompatibility, and epithelialization. The results obtained from in vitro, in vivo, and ex vivo present that bio-orthogonal crosslinked hyaluronate-collagen hydrogel is a potential biomaterial to repair and treat the cornea [237]. Aung Than et al. have reported safe drug delivery to treat ocular disease and infection by microneedle array patches that penetrate surface tissue (Fig. 6 (A-C)). They have employed a corneal neovascularization disease model to study the sustained anti-angiogenic monoclonal antibody (DC101) release by reducing the neovascular area. The fast release of diclofenac as an anti-inflammatory with sustained

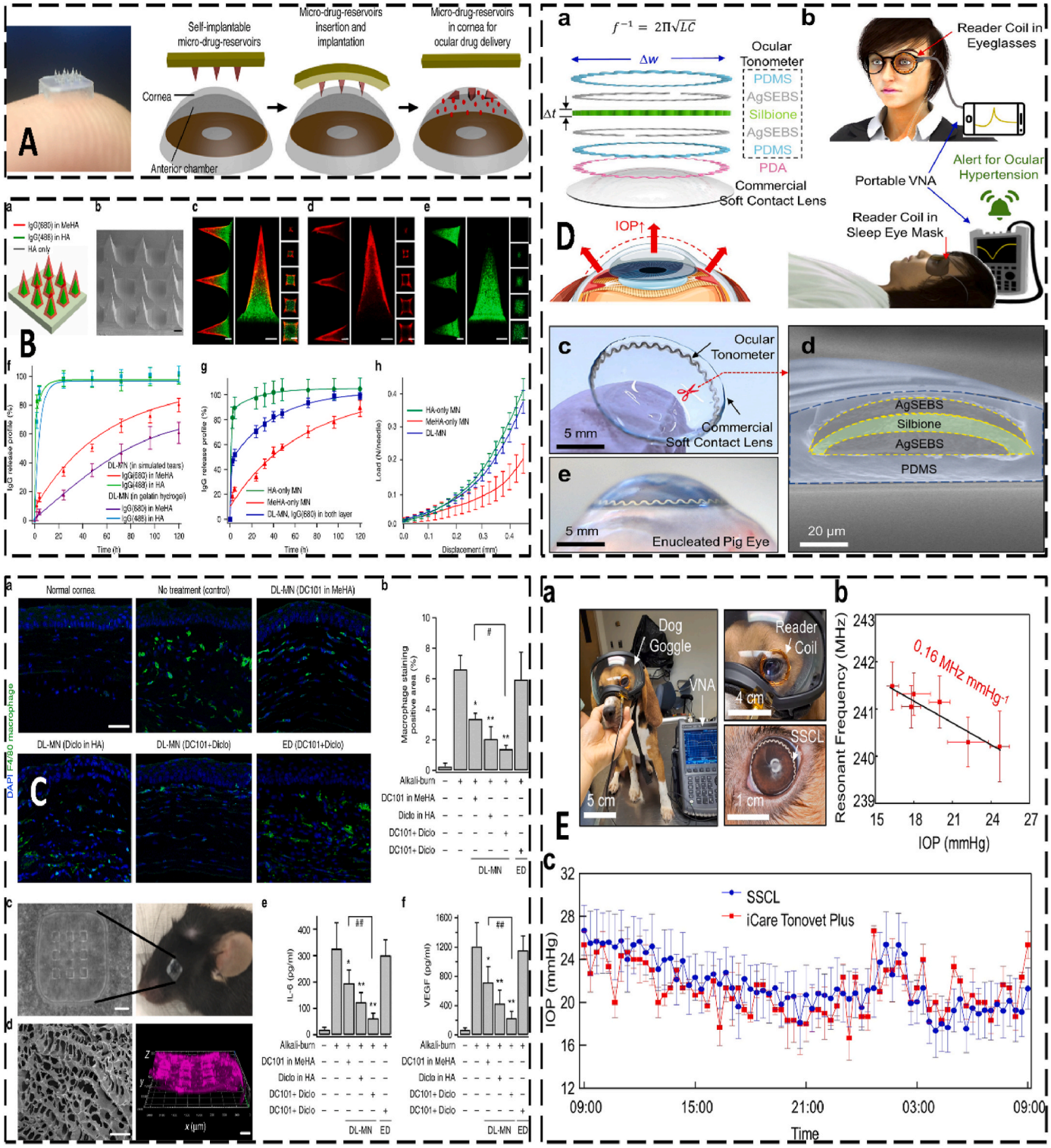

Fig. 6. Synthesis and design of polymeric materials for corneal applications. **(A)** Schematic diagram of microneedle-based drug delivery for ocular. (**B**) Characterizations of microneedles array by SEM and confocal analysis and loading and release of therapeutic agents. **(C)** Anti-inflammation evaluation by microneedle patch using mouse eyes model, immunohistochemical staining, quantitative macrophage accumulation, cytokine concentrations, SEM analysis microneedles soaked in PBS [238], with permission from Nature Publishing Group. **(D)** Schematic view of smart contact lens and monitoring at day-time and night-time with photographs and SEM analysis. **(E)** The reader coil is embedded with the goggles of a dog to study the resonant frequency [239], with permission from Nature Publishing Group.

release of DC101 promotes the synergistic therapeutic effects for ocular disease and infections [238]. Jinyuan Zhang et al. and coworkers have introduced a smart contact lense with inherent properties including biocompatibility, wettability, transparent, softness, and O_2 permeability to monitor ocular pressure for 24 h (Fig. 6 (D-E)). They have conducted in vivo assays against rabbit, dog, and human models to measure the designed smart lens's accuracy and comfortability with the glaucoma care's effectiveness [239].

5.5. Lungs tissue engineering

Globally, lung illness is one of the leading causes of morbidity and mortality. Medical issues, including lung cancer, cystic fibrosis, and pulmonary hypertension, are a few of the major illnesses. Currently, the only effective treatment available is a cadaveric lung transplant; however, organ transplantation is limited due to low success rates, the need for lifelong immunosuppression, and global limitations of suitable donors [240,241]. The lung parenchyma presents the interface between the air in the lungs and the blood in the circulatory system, providing a suitable surface for efficient gas exchange. Air is inhaled by the mouth, passing through the trachea, bronchioles, and finally, the alveoli, the smallest functional units of the lung. Here, gas exchange takes place between a thin layer of extracellular matrix (ECM), a monolayer of type I and type II pneumocytes, and, depending on the location, the endothelial layer or interstitium of a blood artery [242]. Type I collagen, which is mechanically dominating, and type III collagen, which provides structural integrity, comprise most of the parenchymal extracellular matrix. The essential components of the pulmonary extracellular matrix are proteoglycans and elastin. In order for lung tissue to perform mechanically, elastin is essential. Research has demonstrated that both collagen and elastin are responsible for the macroscopic elastic and dissipative characteristics of alveolar tissue [243]. Furthermore, it has been shown that, for small lung volumes, elastin plays the primary role in determining recoil, while collagen begins to take over as the capacity increases. Because of their complimentary roles in the biomechanical behavior of healthy lung tissue, collagen and elastin are, therefore, of great interest [244].

5.6. Skin tissue engineering

The human skin is the biggest organ in the human body and performs several essential physiological processes, such as sensation, absorption, secretion, metabolism, and protection. It serves as the initial external shield of the human body and is the most susceptible body part to damage [245]. The human body will initiate cellular reactions to complete the complex wound repair process. The damaged skin is due to exposure to external environmental effects. Fundamental factors will significantly slow down wound healing, for instance: age, sexual hormones, mental anxiety, and inadequate blood flow in the local area [246,247]. Patients with extensive skin injuries have various consequences and are in danger of getting sick or infected. These may cause limb amputation sometimes, and these reasons sometimes lead to death [248,249]. As a result, healing skin wounds presents a complex medical issue, and developing efficient and quick wound treatment procedures is essential. Dressings are frequently used in treatment to have an optimal microenvironment for wound healing [250,251]. Polymeric materials are promising new materials for wound treatments because they accelerate wound healing. The autolytic debridement of trauma wounds, humidity regulation, infection prevention, and localized stress reduction are all enhanced by polymeric biomaterials [252].

The hydrogel with desirable adhesion strength can function as an inhibitor or hemostatic substance to prevent fluid loss in the host area. It is significant for specialized emergency skin tissue applications [253,254]. Ting et al. fabricated the agarose-polydopamine hydrogels scaffold for skin wound healing to determine the effect of polydopamine on mechanical behavior, water holding, and cell adherence. They have reported exceptional cell viability, proliferation, and angiogenesis and accelerated healing of full-thickness skin wound-model with increased deposition of collagen [255]. Jie et al. have prepared the biologically functionalized hybrid scaffold hydrogels decellularized matrix, chitosan, and gelatin with enhanced biocompatible and antimicrobial activities for skin tissue engineering. The interconnected structure and exceptional porosity were observed that help cell migration. They also reported that the hydrogel scaffolds have desirable water and protein adsorption behavior to avoid bacterial infection with cell proliferation and cytocompatibility [256]. Movahedi et al. fabricated the core-shell electrospun nanofibers from polyurethane, hyaluronic acid, and starch for skin tissue engineering. They have observed an increased porosity with average nanofiber diameter that promotes cell adherence, morphology, and adherence of L929 fibroblast cell lines for wound healing and skin tissue engineering [257]. Hao Chen and coworkers have fabricated hydrogel coordination crosslinking of thiolated polyethylene glycol and $AgNO_3$ (Fig. 7 (A-D)). The fabricated injectable hydrogel has enhanced self-healing, angiogenesis, and antibacterial characteristics that are potential bioactive materials for diabetic wound healing. They further reported that multifunctional hydrogel could be desirable biomaterials for repairing and regenerating exposed and open wounds without any host reaction under high bacterial infection and mechanically stable under external irritation [258].

5.7. Neural tissue engineering

The healing of trauma-related spinal cord, brain injuries, and other severe nerve damage is currently the most challenging medical problem like stroke, Alzheimer, Parkinson, neurodegenerative, and Huntington neurological disorders [259]. Among the most suitable techniques for reconstructing damaged nervous tissues is the improvement of 3D models of nerves that mimic the native ECM. Generally speaking, the neural model should meet specific criteria, such as neuro-compatibility, which permits attachment and nerve cell proliferation. The elastic behavior of the micro-engineered biomaterials produces electroconductivity. It resembles the ECM of native nervous tissue mechanical and physicochemical characteristics [260]. Because it can process a wide variety of materials, EBB, one of the 3D bioprinting techniques, excels at developing the idea of neural tissue. It usually includes suspensions, cell-filled hydrogels, solutions, thermoplastics, thermosets, and elastomers. There are comparatively fewer reports on using EBB in neural regeneration, which may be due to the lack of suitable neural bioinks. These can accurately mimic the mechanical/chemical properties of the native ECM. Xiaowei et al. fabricated the composite from nanofiber and hydrogel to determine the effects of repairing and regeneration on neural tissue in the contused spinal cord. They have reported the desirable mechanical behavior, porosity, and positive neural tissue regeneration effect in a rat model after 28 days [261].

5.8. Vascular tissue engineering

Vascularization is essential for angiogenesis for the pancreas, spleen, heart, and kidneys as they remove waste materials and regulate oxygen and nutrient distribution [262,263]. The vascular-like networks with great success by conventional fabrication methods have developed. Designed tissue substitutes can be developed from the well-structured, optimized physicomechanical biomaterial produced using 3D bioprinting [264,265]. The multiscale, branched vascularization system for appropriate advective transport is essential in vascular engineering. The bioprinting methods can also assist in producing vascular networks that would be developed within the scaffolds by removing sacrificial layers for tissue repair and regeneration strategies [266,267]. The vascularized tissue depends on ECM-related materials like elastin and collagen deposition. It is promising to address challenges for scaffold-based vasculature alternatives with a small diameter with desirable mechanical properties for native vascular tissue [267,268]. The mechanical

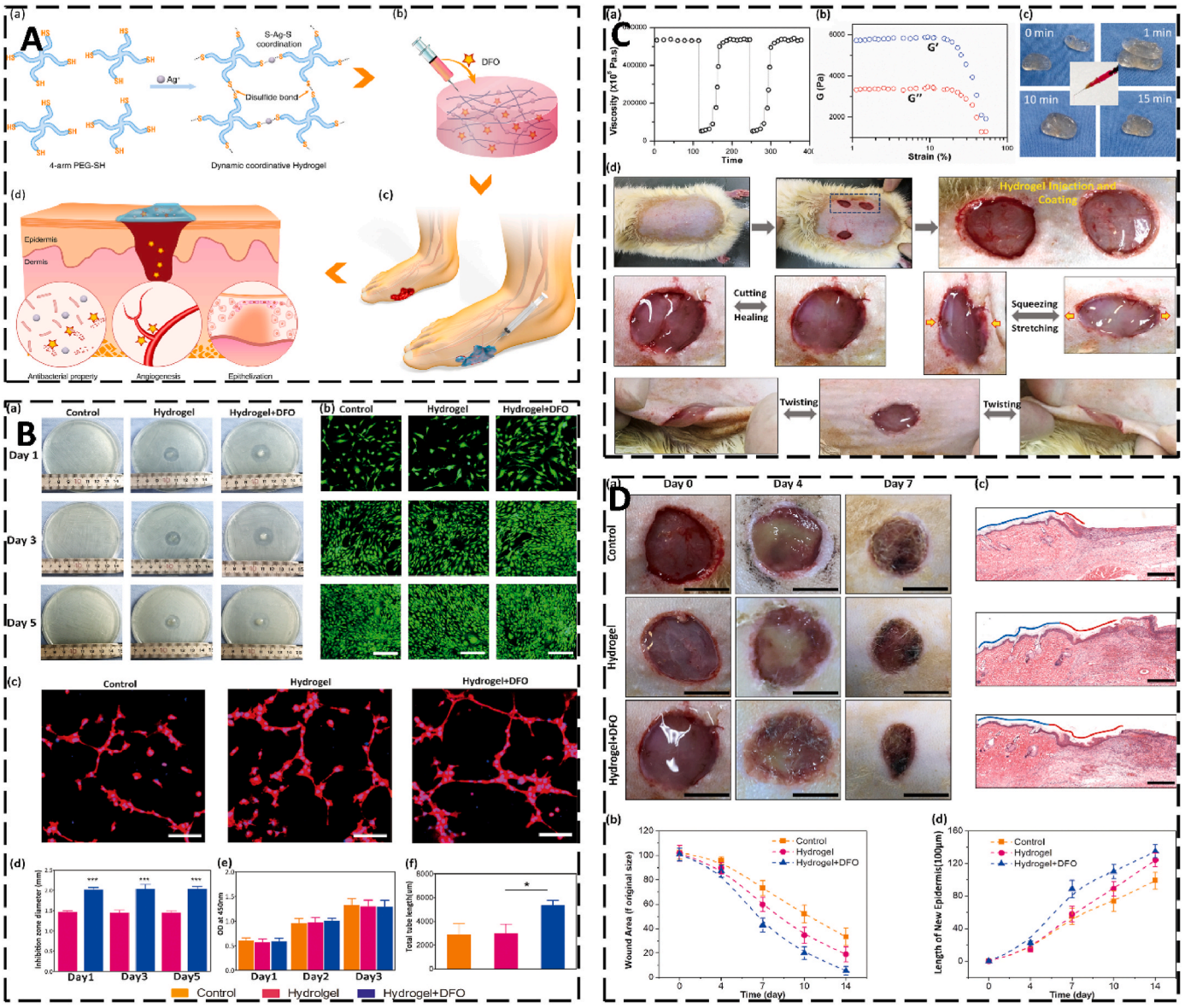

Fig. 7. The fabrication, characterization, and application of biopolymeric injectable hydrogel for wound healing applications. (A) Schematic diagram of Ag(I)-thiol and (Au–S) synthesis, desferrioxamine loading with self-healing, antibacterial, and angiogenic activities for type I diabetic foot ulcer with skin regeneration via injectable hydrogel. (B) Antibacterial activities, cell viability, proliferation, Live and dead, and cell quantification assays with the angiogenic assay in vitro and fluorescence images. (C) Viscosity, mechanical properties, self-healing behavior, and shape retention of hydrogel in a full thickness rat model of a rat model. (D) Hydrogel injected images, quantitative wound closure, growth of new epithelial layer captured digitally, and quantitative analysis of new epidermis layer by ImageJ [258], with permission from Nature Publishing Group.

properties of the hydrogel are low, so applying hydrogel-based scaffolds is an additional challenge that reduces the mechanical properties of tissue-engineered vascular substitutes [269,270]. Additionally, the polymeric biomaterials produce by-products during biodegradation that may alter cellular characteristics and interfere with the vascular wall. These problems can be addressed by developing scaffold-free bioprinting using cellular microspheres by self-assembly method [271, 272].

6. Commercialization of biomaterials

Commercializing biomaterials can be a complicated and drawn-out process. Still, if done right, it can result in essential breakthroughs in tissue engineering, medicine, and other fields that use biomaterial-based products. Businesses taking part in this process should strive to assemble a multidisciplinary team with knowledge in biology, materials science, regulatory affairs, and business development, among other areas. Commercialization of biomaterials is introducing innovative technologies and goods based on biomaterials to the market for a range of uses in tissue engineering, regenerative medicine, healthcare, and other industrial sectors. Biomaterials are materials that have been developed to communicate with biological systems in a therapeutic or medical capacity [273]. The following are the fundamental aspects of commercialization of the biomaterials.

6.1. Research and development

The design, characterization, and use of biomaterials that interact with biological systems are all part of the multidisciplinary field of biomaterials research and development (R&D). These materials find extensive use in tissue engineering, drug delivery systems, medical implants, and other areas. Numerous materials, such as composites, metals,

polymers, and ceramics, can be used to develop biomaterials. Researchers carefully choose and create materials based on variables, including mechanical characteristics, degradation rate, biocompatibility, and intended use. It is essential to ensure that it is biocompatible to avoid negative responses when a biomaterial interacts with live tissues. It entails assessing the material's suitability for harm-free integration with biological systems. Researchers study the physical, chemical, and biological characteristics of biomaterials [274]. Different methods are used to produce biomaterials with specific compositions and characteristics. These may involve surface modification, 3D printing, electrospinning, and polymer synthesis. Drugs and other therapeutic substances are frequently transported via biomaterials. It entails creating systems that can release drugs in a targeted, regulated manner to increase treatment effectiveness and decrease adverse effects. In tissue engineering, biomaterials are essential because they are utilized to make scaffolds that promote tissue growth and regeneration. This field of study aims to create functional organ and tissue substitutes for diseased or damaged ones. Materials with unique qualities are made through the application of nanotechnology and nanoscale biomaterials, giving precise control over interactions with biological systems [275]. Comprehending the gradual degradation of biomaterials in the body is crucial for applications whereby the material must be absorbed or substituted with native tissue. Researchers study degradation rates and mechanisms to ensure they are compatible with biological systems. It evaluates elements such as proliferation, tissue integration, and cell adhesion. As they develop biomaterials for clinical use, researchers have to consider safety standards and regulatory requirements. It entails taking care of concerns with sterility, biocompatibility, and possible harmful effects. Collaboration between specialists in a variety of disciplines, such as materials science, biology, chemistry, engineering, and medicine, is frequently necessary for successful biomaterials R&D. Biomaterials research and development is a fast-paced, constantly-evolving field with enormous potential to advance healthcare and other industries [276]. It necessitates a multidisciplinary strategy, a solid grounding in scientific principles, and a commitment to solving challenging problems at the interface of biology and materials.

6.2. Regulatory compliances

In the context of biomaterials, regulatory compliance means abiding by the rules, regulations, and laws that control the creation, production, testing, and distribution of goods derived from biomaterials. For biomaterials to be proven safe, effective, and high-quality—especially when they are meant to be used in medical applications—compliance is essential. To guarantee the efficacy and safety of medical devices, including biomaterials, the Food and Drug Administration (FDA) regulates them [277]. Good manufacturing practice (GMP) regulations guarantee that biomaterials are manufactured and managed consistently to fulfill quality requirements. Manufacturing facilities must adhere to GMP to preserve the quality and safety of their products. Regulatory bodies frequently demand comprehensive biocompatibility testing to evaluate how biomaterials interact with biological systems. Biomaterials often go through preclinical testing in animal models to determine their safety and efficacy before being used in humans. It contributes to the evidence supporting the safety and performance profile of the biomaterial [278]. Clinical trials are performed on biomaterials meant for medical applications to assess their human performance. Safety, efficacy, and patient outcomes are among the variables that these trials evaluate. Manufacturers must conduct risk assessments mandated by regulatory bodies to pinpoint possible risks related to biomaterials and put preventive measures in place to lessen those risks. Proper labeling is crucial for healthcare professionals and end users to receive accurate and precise information regarding the use, indications, and possible risks of biomaterial-based products. It is frequently mandatory for manufacturers to oversee the functionality of biomaterials following their commercialization. Reporting adverse events and carrying out post-market research are part of this to guarantee ongoing efficacy and safety. Companies engaged in the research, development, and marketing of biomaterials should collaborate closely with regulatory affairs specialists who are skilled in negotiating the intricate regulatory compliance environment [279].

6.3. Scaling up production

Increasing the production of biomaterials entails moving from small-scale laboratory experiments to larger-scale manufacturing to satisfy market demand. Careful planning, optimization, and validation are necessary during this process to guarantee the biomaterials' consistent performance and quality. It could entail modifying variables like the conditions of the reaction, the composition of the materials, and the processing methods. It could involve more giant reactors, mixing tanks, extruders, and other specialty machinery. Establish trustworthy sources for raw materials and carry out exhaustive quality inspections to guarantee purity and consistency [280]. Studies on process performance qualification and qualification may fall under this category. Verify that all applicable regulations have scaled up the production process. Recognize the obstacles and limitations involved in scaling up specific biomaterial processes. Certain procedures have built-in scale limitations because of heat transfer or reaction kinetics. Install monitoring systems to keep an eye on important process metrics instantly. It guarantees that the process stays within predetermined operating limits and permits timely adjustments. Before beginning full-scale production, conduct pilot-scale production runs to confirm the process's viability and find any possible obstacles. Develop and maintain up-to-date comprehensive documentation, such as batch records, protocols, and SOPs, to guarantee consistency and repeatability in the manufacturing process [281]. Determine and evaluate the possible risks connected to increased production volume, then implement mitigation plans. Keep an eye out for opportunities to optimize efficiency, cut costs, and improve quality by regularly monitoring and assessing the production process. Increasing the production of biomaterials is intricate and calls for meticulous planning, verification, and observance of quality guidelines. A multidisciplinary team comprising professionals from the domains of materials science, engineering, quality assurance, and regulatory affairs is crucial for this undertaking [282].

6.4. Quality control and assurance

A vital component of producing and utilizing biomaterials is quality control and assurance, which guarantees that the materials fulfill predetermined performance, safety, and efficacy requirements. Maintaining consistency and dependability in producing biomaterials is facilitated by implementing robust quality control and assurance procedures. Take action to guarantee the sterility of biomaterials meant for implantation. Develop and update standard operating procedures (SOPs) for every step of the processes involved in quality assurance and control [283]. These documents offer precise guidelines for analysis, testing, and decision-making. Keep thorough records of every quality control test, including the initial data, the outcomes, and any deviations from the requirements. It could entail recording the occurrence, taking remedial action, and looking into the underlying cause. Incorporating new technologies, best practices, and insights from past production runs into your quality control and assurance processes requires regular reviews and updates. Ensuring that biomaterials consistently meet safety, efficacy, and performance standards is critical for their successful application in a variety of industries, including tissue engineering and healthcare [284].

6.5. Post-market surveillance

After biomaterial-based products are commercialized and used by healthcare providers or end users, post-market surveillance of

biomaterials entails tracking and assessing the efficacy, safety, and quality. If problems or unfavorable events occur when the biomaterials are used in a real-world clinical setting, finding and fixing them through continued monitoring will be imperative. Ensure you have a system to gather and record reports of any adverse events or mishaps involving biomaterials. Surveys or studies should be conducted to gather more clinical information about the biomaterial's performance and safety in actual clinical settings [285]. Make any necessary updates to product labeling, such as cautions, warnings, or usage guidelines based on post-market surveillance results that may interest consumers. As the law requires, notify the relevant regulatory authorities of any significant adverse events or incidents. Whenever a paramount safety concern is discovered, remove impacted products from the market and fix the problem through a recall or other field corrective action. Ensure all post-market surveillance activities are meticulously documented, including adverse event reports, complaints, inquiries, and necessary steps. Provide updates on the safety profile of the biomaterials and any pertinent post-market surveillance results in Periodic safety update reports (PSURs) that are prepared and submitted to regulatory agencies [286]. Apply the knowledge acquired from post-market surveillance to ongoing quality assurance initiatives, design upgrades, and product improvements. Maintaining products' continued efficacy and safety based on biomaterials requires post-market surveillance. Ultimately, it enables manufacturers to provide the highest quality and safety for patients and users while maintaining regulatory compliance and responding to emerging issues.

6.6. Market assessment

Assessing the biomaterials market entails determining the competitive landscape, market trends, and potential demand for products derived from biomaterials. This evaluation offers businesses aiming to create and market biomaterials. Give a clear explanation of the market assessment's objectives, including particular targets to be reached, client needs to be comprehended, and competition to be assessed. Identify the sectors and uses in which biomaterials can be used, such as drug delivery, tissue engineering, healthcare (implants, medical devices), and other specialized fields. Examine past growth patterns and forecast growth in the future by taking into account variables such as new applications, regulations, and technology developments [287]. Determine the major trends driving the biomaterials market, including the advancements in materials science, the rise in demand for treatments in regenerative medicine, and the changing needs of the healthcare industry. Examine the current players in the biomaterials industry, such as significant producers, upstarts, and academic institutions. Evaluate their offerings, market portion, means of distribution, and edge over competitors. Determine and describe possible consumers or product end users that use biomaterials. Manufacturers of medical devices, research institutes, healthcare providers, and other stakeholders may fall under this category. Choose the best approaches to break into the biomaterials market: joint ventures, license contracts, direct sales, or other channels of distribution [288]. Describe the advantages and unique selling points of biomaterial-based products over competing products. It could involve elements like enhanced functionality, affordability, or better performance. A thorough market analysis offers insightful information that can direct decision-making during the development and commercialization process of biomaterials.

6.7. Intellectual property protection

Protecting legal rights to developments, procedures, developments, or other forms of biomaterial-related intellectual property is part of safeguarding biomaterials through intellectual property (IP). Patents grant inventors the sole authority to produce, utilize, and market their inventions for a predetermined time. Patents covering utility features shield functional aspects of inventions, including particular compositions of biomaterials, synthesis techniques, and special uses in medicine delivery or tissue engineering. Patents on designs safeguard a product's decorative or artistic elements. These may apply to products with distinctive forms or surface patterns made of biomaterials, even though they are less common in biomaterials [289]. Trademarks are helpful for marketing and branding biomaterial-based products, even though they are not usually used for the biomaterial. Trade secrets may be maintained regarding certain facets of the development of biomaterials, such as exclusive formulations or manufacturing techniques. Though they are more frequently linked to artistic and literary creations, copyright laws can also cover some biomaterial-related products, such as educational materials or software used in biomaterial research. Intellectual property related to biomaterials can also be safeguarded through the use of confidentiality agreements, licensing agreements, and non-disclosure agreements (NDAs) [290]. The conditions that govern information sharing and use are outlined in these contracts. Formal agreements can aid in determining ownership and rights to any intellectual property created through collaboration when several parties are involved in biomaterial research. After a person is granted rights to their intellectual property, it is crucial to keep an eye out for any unauthorized use or infringement and, if needed, take legal action. It might be required to look for intellectual property protection in several nations using tools like international patents, depending on the market and global reach of products based on biomaterials [291].

7. Current challenges and future perspectives

Cell transplantation and polymeric-based tissue repair and regeneration are common techniques in tissue engineering and biomedical applications. The adaptive response of cells and the host organ in vivo determines the morphology of tissue structures to regulate essential biological and physiological behavior [292]. The capacity for developing tissues in a lab by tissue engineering techniques is beneficial. After transplantation, necessary procedures to promote regeneration by maintaining a desirable microenvironment for complex tissue and organs are still big challenges and beyond our control [293]. Here, biomaterials produce endovascular systems that can repair and regenerate organ function over time. Biomaterials aim to address challenges in developing transcutaneous organ restoration systems. Before transplantation, the crucial tissue systems needed to be maintained, assembled, cultured, and transformed. Before transplantation, the characteristics of engineered organ systems must preferably be developed [294]. In vivo, methods are frequently considered more biologically accurate and appear sufficiently reasonable. Although in vivo methods are frequently preferable for tissue engineering, this is not always true. The inability to regenerate anything but fibrous tissues is a major challenge of in vivo methods for tissue engineering research [295]. Recently, it was established that fibroblasts and inflammatory cells are the living body's most quickly proliferating cells by consuming additional nutrients and oxygen to produce energy for cell proliferation with metabolic activities [296]. Therefore, the transplanted cells cannot survive with insufficient blood supply to supply essential nutrients and remove waste products. The ideal tissues or organ systems can be grown without profibrogenic surroundings outside the body [297].

Consequently, more effective in vitro techniques are required to guide, establish, and promote cells in immune-privileged 3D signal transduction pathways so that cultured cells maintain their distinctive functions. Bioprinting is the only opportunity with a controlled biomechanical for cell proliferation and migration to repair and regenerate new tissue [298]. For example, an environment with high or low oxygen tension, irregular growth factors, and exposure to medications with high pharmacological activity can all be used to incubate biofabricated tissue. It is impossible to control such incubating parameters in vivo due to adverse effects on the recipients [299]. Therefore, an endovascular system is appealing clinically, and advanced endovascular procedures are necessary for biofabrication studies. Such processes might make it

possible to control precise time and space at will without negatively affecting the patients [300]. The biofabrication and materials engineering goals are another challenge in tissue regeneration to develop novel extracorporeal processes [301]. The biomaterial can't function naturally to replace the lost tissue or organ after implantation, which is another challenge. Therefore, biofabrication is extracorporeal organ engineering that supports tissue repair and regeneration [302]. According to the research, various polymeric biomaterials offer excellent physicochemical, biomechanical, and physiological properties that allow them to simulate natural biological systems successfully. The future of tissue engineering for biomedical applications lies in using polymeric biomaterials and 4D bioprinting technology [303]. Studying and developing advanced biofabrication techniques to fabricate multifunctional and bio-responsive polymeric biomaterials by synthesized, engineering, and functional modification. Engineering and design of polymeric biomaterials using cutting-edge methods and empirical modeling. The development of biocompatible materials, tissue interlinks, and the introduction of commercial 4D bioprinting [304].

8. Conclusions

Biomedical science has invested much time and energy in developing new methods for fabricating biomaterials from biocompatible and natural resources with advanced technologies. Natural polymers can be modified and tailored with desirable structural, morphological, and mechanical properties for tissue engineering applications as they are biocompatible and biodegradable behavior. These can fabricate soft and hard and other tissue engineering systems from polymeric materials to repair and regenerate tissue. The biodegradable and biocompatible materials do not allow additional medical procedures for surgical removal after implantation. Natural polymers have distinct advantages compared to other material types, making it possible to design and fabricate more intricate structures to mimic the dynamics of living tissues and organs. Biofabrication methods are constantly being improved and are now combined with established methods for advanced approaches. Th biomaterials with different shapes and morphologies by advanced techniques using natural polymers and materials are fabricated. Hence, it is necessary to choose proper materials with multifunctional properties other than their chemical, mechanical, and biological characteristics. The biofabrication of biomaterials using advanced techniques can be synthesized methods to target damaged tissue in tissue engineering applications.

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CRediT authorship contribution statement

Muhammad Umar Aslam Khan: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Visualization, Writing - original draft, Writing - review & editing. **Muhammad Azhar Aslam:** Formal analysis, Data curation, Methodology, Software, Visualization, Writing - original draft, Writing - review & editing. **Mohd Faizal Bin Abdullah:** Data curation, Funding acquisition, Methodology, Project administration, Validation. **Anwarul Hasan:** Methodology, Validation. **Saqlain A. Shah:** Investigation, Project administration, Validation. **Goran M. Stojanović:** Funding acquisition, Investigation, Resources, Supervision, Validation, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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