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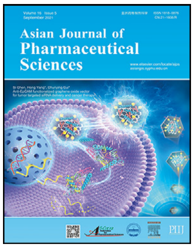

Review

Additive manufacturing of sustainable biomaterials for biomedical applications

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ABSTRACT

Biopolymers are promising environmentally benign materials applicable in multifarious applications. They are especially favorable in implantable biomedical devices thanks to their excellent unique properties, including bioactivity, renewability, bioresorbability, biocompatibility, biodegradability and hydrophilicity. Additive manufacturing (AM) is a flexible and intricate manufacturing technology, which is widely used to fabricate biopolymer-based customized products and structures for advanced healthcare systems. Three-dimensional (3D) printing of these sustainable materials is applied in functional clinical settings including wound dressing, drug delivery systems, medical implants and tissue engineering. The present review highlights recent advancements in different types of biopolymers, such as proteins and polysaccharides, which are employed to develop different biomedical products by using extrusion, vat polymerization, laser and inkjet 3D printing techniques in addition to normal bioprinting and four-dimensional (4D) bioprinting techniques. This review also incorporates the influence of nanoparticles on the biological and mechanical performances of 3D-printed tissue scaffolds. This work also addresses current challenges as well as future developments of environmentally friendly polymeric materials manufactured through the AM techniques. Ideally, there is a need for more focused research on the adequate blending of these biodegradable biopolymers for achieving useful results in targeted biomedical areas. We envision that biopolymer-based

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3D-printed composites have the potential to revolutionize the biomedical sector in the near future.

1. Introduction

Scientific progresses in novel manufacturing approaches especially in the additive manufacturing (AM), alias three-dimensional (3D) printing areas, have laid the foundations for many engineering and biomedical applications thanks to its efficiency, precision and accuracy [1], as illustrated in Fig. 1. The AM technology uses imaging techniques or computer-aided design (CAD) software to fabricate 3D customized objects like patient-specific implants, without the need for molds or machining [2–4]. This technology is highly appropriate to develop intricate structures by using different materials, in contrast to conventional manufacturing processes [5–7]. Over the years, this technology has found its potential in myriad manufacturing areas including, but not limited to, automotive, aerospace, construction, rapid prototyping, jewelry and biomedical fields [8–11].

Since the beginning of the 21st century, the 3D printing technique has been extensively applied in the biomedical sector for developing personalized prosthetics, dental implants, organ and tissue fabrications, anatomical models, and pharmaceutical products [12–14]. Some studies also illustrate the utilization of this novel technology for producing exoskeletons, ears, stem cells, bones and microvascular networks [15–17]. The technology utilizes different biomaterials including metals, powders, liquids, ceramics, polymers and living cells to develop intricate structures with excellent mechanical characteristics, which cannot be attained through conventional manufacturing techniques [18–20]. Biomaterials used for the development of such implants and human organs can be classified into three types of materials, i.e., metals, polymers and ceramics [21]. Despite the high strength, hardness, fracture toughness and corrosion resistance of inert metallic implants such as stainless steel (SS), these 3D-printed components may adversely impact on the human body because of their non-biodegradability [22–25]. However, metallic implants exhibit high elastic moduli that result in stress shielding. Furthermore, toxic effects appeared due to the release of ions from the metallic implants limiting their use in biomedical applications [26].

Other non-biodegradable alloy scaffolds such as chromium-cobalt(Cr–Co) alloys also exhibit limited advantages, e.g., they can support tissues but simultaneously cause inflammation and allergic reactions at the implantation sites [27]. Most of these alloys contain free ions in their structures, which are responsible for these problems. It is worth mentioning that these are relatively expensive materials as well. To circumvent the aforementioned drawbacks, sustainable biomaterials have been formulated for a wide range of applications [28].

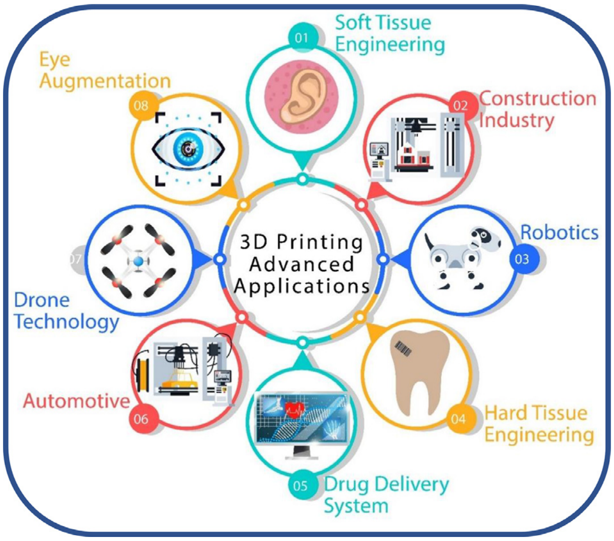


Fig. 1 – Recent scientific progresses in various fields of engineering.

Renewable resources are the most attractive sources of raw material in terms of green environment and planetary health. Sustainable materials are acquired from renewable natural resources, recycling or other low-carbon feedstock, which are managed through biodegradation and recycling approaches [29]. These materials including natural, synthetic or modified bio-based polymers, are sustainable, renewable and extraordinary materials with low carbon footprints and low embodied energy levels, compared to the existing traditional stabilizers. Carbon dioxide released at the end of service time, due to biodegradation is reabsorbed by fauna and flora, which makes them carbon neutral [30]. Biopolymers follow a circular economy model, which helps their recycling at the end of life. Additionally, the accumulated plastic waste has triggered the use of these environmentally benign polymers in different industrial sectors including biomedical engineering/science [31].

Sustainable biopolymers provide an interrelationship between renewable natural resources and biomaterials, and the world has considered the development of novel and sustainable biopolymer-based biomaterials as a feedstock for the AM technology, as illustrated in Fig. 2, thanks to their biodegradability, biocompatibility and renewability [32–34]. These types of feedstock materials promote the sustainability within the AM technology itself [35]. Sustainable biopolymers including bio-based polymers are viable raw materials, which upon formulation and modification into resins and inks offer sustainable AM solutions [36]. These polymers provide AM users the environmentally benign manufacturing options [37].

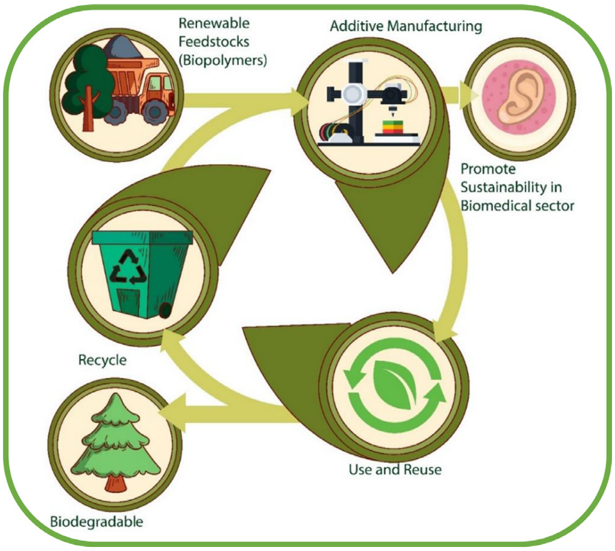


Fig. 2 – Biopolymer-based biomaterials, as feedstock materials for AM technology to promote sustainable environment. (Figure modified from [38]).

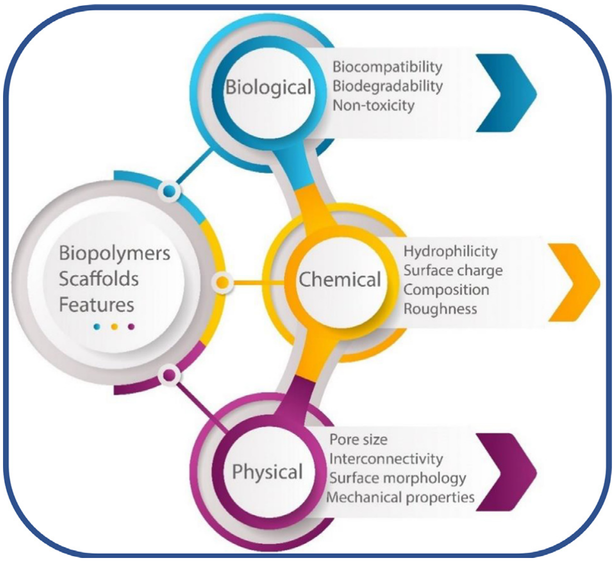


Fig. 4 – Characteristics of 3D-printed biopolymer scaffolds (Figure drawn through the information provided by [46]).

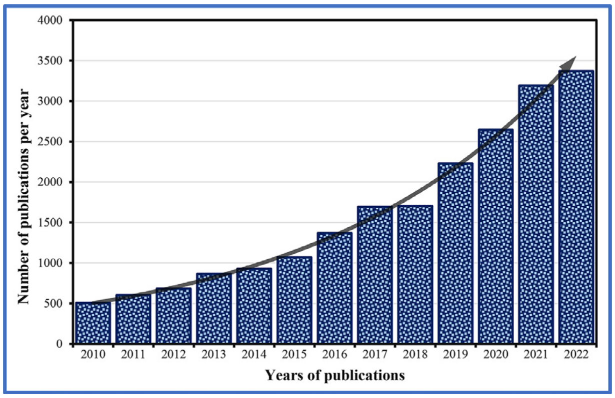


Fig. 3 – Number of publications related to biopolymer-based biomaterials from 2010 to 2022. (Figure drawn by using both "Biopolymers" and "Biomedical" as keywords from Scopus database).

Bio-based polymeric materials like proteins, polysaccharides and aliphatic polyesters are produced from plants, animals or microbial synthesis [39]. These polymers are different from other biopolymers and can exist as biodegradable (like starch) or non-biodegradable (like bio-polyethylene) [40]. Especially polycaprolactone (PCL) and polylactide (PLA) have been vastly explored in AM to generate biodegradable and biocompatible scaffolds for the biomedical sector [41]. The applications of these biopolymer-based sustainable biomaterials have increased quite dramatically in the last decade, compared to traditional materials, as illustrated in Fig. 3. The decomposition can be adjusted precisely by developing harmless components upon the implantation of sustainable materials [42–44]. The unique features can assist constructing hard and soft tissues simultaneously by using a selected array of synthetic and natural biopolymers [45]. Furthermore, these biopolymeric materials are less costly and have matching chemical, physical and biological characteristics, as shown in Fig. 4, which are similar to certain living cells and tissues.

Fig. 5 depicts the socio-economic and environmental factors for evaluating the sustainability performance of biopolymeric composites. Sustainable materials have shown huge potentials in the 3D printing sector [38]. Soft biomaterials are vastly applied in different biomedical applications including tissue engineering (TE), lab-on-chip, scaffold design, nerve grating, microvascular network, wound healing and drug carrier applications [47–51], to mention a few. The 3D printing of biopolymeric materials is further revolutionizing healthcare systems by fabricating on-demand drug-released medical devices [52]. Different novel formulations including multi-drug combinations, controlled-release, novel design, orally disintegrating,and pediatric-friendly formulations have also been reported in the literatures [53–55].

Amid the coronavirus disease 2019 (COVID-19) pandemic, the estimated market size of AM in the healthcare system was $1.45 billion in 2021 [57]. It is predicted that the economic growth of 3D-printed medical models and devices in the healthcare market will reach $6.21 billion by 2030 [58]. Due to enormous interest in biopolymers for the AM, it is necessary to highlight the recent progresses and the role of environmentally sustainable biomaterials in advanced healthcare systems. Herein, we highlight some of the recent advancements in 3D printing biopolymeric materials including their potential applications in the field.

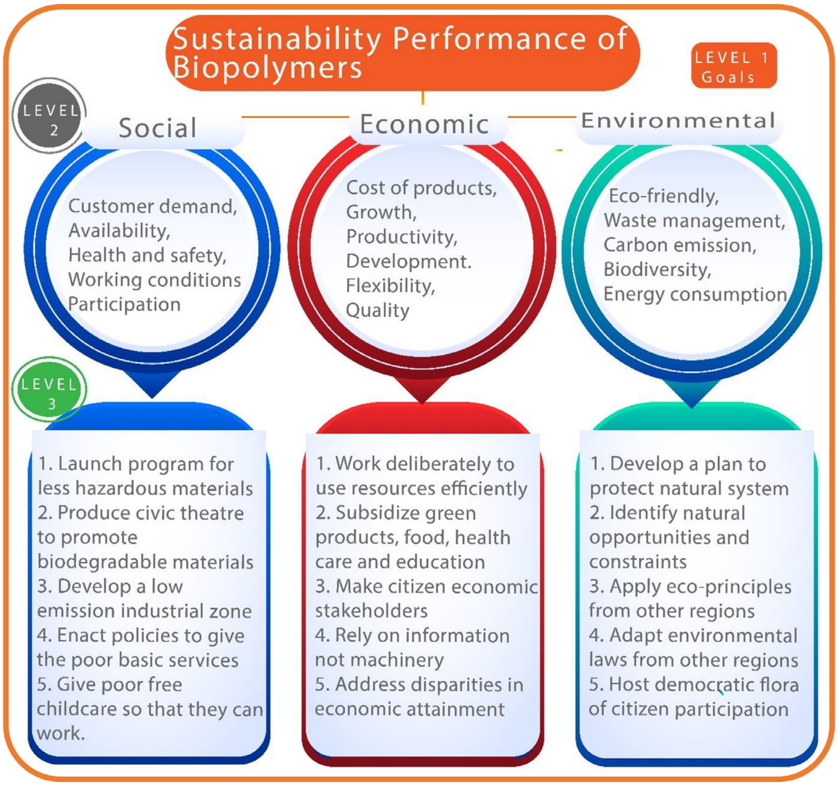


Fig. 5 – Sustainability performances of biopolymeric-based biomaterials (Figure modified from [56]).

2. Biopolymer-based sustainable materials

Biopolymers are derived from biological renewable resources such as animals, plants and microorganisms, which exhibit excellent biocompatibility, chemical versatility, non-toxicity, bioresorbability, bioactivity and tunable biodegradability. The use of these sustainable materials in the biomedical sector including bone, cardiac and liver regeneration, wound healing, and drug delivery systems, has been increasing day by day due to more refined and efficient treatments [59–62]. Some prominent natural- and synthetic-based biopolymeric materials and their biomedical applications are provided in Table 1. The biocompatibility of bioactive materials has influenced the functional properties of additively manufactured tissues or organs. Additionally, biomaterials require adherence of the native cells to maintain adhesion, viability and interaction [63]. At present, synthetic biopolymers induce inflammatory reactions. However, it is necessary to overcome issues related to the safety and efficacy of these materials. This can be done by synthesizing composite scaffolds through chemical modifications [64].

Natural bio-organisms including algae, fungi and bacteria decompose biopolymers into tiny molecules through anaerobic or aerobic techniques by forming organic H_2O and CO_2 products [108]. Additionally, these materials exhibit highly compatible behavior due to their resemblance with the extra-cellular matrix (ECM). ECM contains thick layers of tissues annexed together by adhesive polysaccharides or protein molecules. Moreover, it also promotes cell adhesion, interaction, proliferation and differentiation [109].

2.1. *Natural biopolymers*

Natural biodegradable polymers (polysaccharides and proteins) are highly versatile and used for tissue regeneration, gene delivery, controlled drug delivery, bio-actuators and other healthcare applications. These biomaterials are generally derived from plants, animals or microbes. Generally, natural biopolymers exhibit high molecular weight, which results in viscous polymer solutions that enable them to be used in the 3D printing. Consequently, processability and printability of these polymers remain a challenge [110]. Some of these polymers can be chemically modified, which improve non-toxicity, biocompatibility and biodegradability. Some natural biopolymers are chitosan, silk fibroin (SF), collagen, cellulose, gelatin, hemicellulose, alginate, hyaluronic acid (HA), lignin and starch. Despite excellent bioactivity, biocompatibility and biodegradability, natural biopolymers have some disadvantages such as poor mechanical properties, high water solubility, source instability, possible immunogenicity and denaturation during processing [111–113].

Chitosan, a polysaccharide material derived from the deacetylation of chitin, is found in crustacean skeleton and extensively applied in biomedical applications [114–116]. However, the low mechanical resistance of these materials limits their use in drug delivery applications [117–119]. Alginate, a heteropolysaccharide, which abundantly exists

Table 1 – Types of commonly employed biodegradable polymers for the fabrication of scaffolds, their characteristics, and recent biomedical applications.

Biopolymer type	Biopolymer	Sustainability credentials for biomedical applications	AM technique	Advantages	Disadvantages	Degradation time	Suggested polymers and bio-ceramics to develop composites	Formulations	Biomedical applications	Ref.
Natural	Chitosan	Biodegradable Low carbon footprint	Extrusion, SLA	Non-immunogenicity, easily metabolized, antibacterial activity, and biocompatibility	Low mechanical strength, brittle, stiff	>20 weeks	HAp, BG, alginate, or collagen	Sponge, hydrogels, composite scaffolds	Gene delivery, wound dressing, bone, nervous, skin, liver, cardiovascular, and cartilage TE	[65–67]
	Alginate	Lower carbon footprint Biodegradable	Extrusion	Non-immunogenicity, bioactivity, biocompatibility, and non-antigenicity	Limited toughness and mechanical strength	80 d	BG, HAp, chitosan, or PLA	Micro/nanosphere, hydrogels	Hollow vascular channels, bone, cartilage, neural, skin regeneration, and wound healing	[68–70]
	Cellulose	Excellent biodegradability Low carbon footprint	DIW, FDM, IJP	Bioactivity, excellent mechanical characteristics, and biocompatibility	Limited cell adhesion	Weeks to months	HAp, CNTs, chitosan, PLA, or PBS	Composite scaffolds	Neural, skin, tendons, muscle, cardiac, cartilage, and bone regeneration	[71–74]
	Collagen	Biodegradable Low embodied energy level and carbon footprint	Extrusion, IJP	High porosity, bioactivity, excellent mechanical characteristics, biocompatibility, and poor immunogenicity	Low antigenicity, low mechanical strength, and low stiffness	12 h	HA, PLGA, BG, or HAp	Scaffolds	Drug delivery, vascular, dental, cornea, bone, cartilage, and artificial skin regeneration	[75–77]
	SF	Excellent biodegradability Low carbon footprint	Micro-extrusion, SLA, IJP	Biocompatibility, excellent mechanical characteristics, high tensile strength, bioactivity, high flexibility, and low immunogenicity	Brittle, rapidly degrade	6 weeks	Collagen, HAp, PLA, or calcium phosphate	Scaffolds	Gene delivery, wound healing, hepatic, vascular, cornea, neural, tendon, bone, cartilage, and skin regeneration	[78–81]
	Gelatin	Biodegradable Low embodied energy level	Extrusion, SLA	Biocompatibility, bioactivity, ECM mimicked, poor immunogenicity, and better solubility	Rapid degradation, low mechanical strength, limited solubility in concentrated solutions	10 d	Chitosan, HAp, PLA, or PCL	Micro/nanosphere, hydrogels	Aortic valves, neovascularization, cartilage, neural, bone, and skin regeneration	[82–84]

(*continued on next page*)

Table 1 (*continued*)

Biopolymer type	Biopolymer	Sustainability credentials for biomedical applications	AM technique	Advantages	Disadvantages	Degradation time	Suggested polymers and bio-ceramics to develop composites	Formulations	Biomedical applications	Ref.
	Starch	Excellent biodegradability Low carbon footprint	Extrusion	Non-toxicity and biocompatibility	Brittle and less surface area	Several weeks	GO, BG, or PCL	Composite scaffolds	bone, skin regeneration, and drug delivery systems	[85–88]
	HA	Biodegradable Low embodied energy level	Extrusion	Non-toxicity, easily modified through chemical reaction, and biocompatibility	Fast degradation rate and low mechanical characteristics	4 months	PEG, PLA, PLGA, collagen, or chitosan	Scaffolds, hydrogels	Skin and neural regeneration	[89–91]
Synthetic	PLA	PLA degradation within the human body PLA copolymers, which can help in the adjustment of degradation	Extrusion, SLA, IJP	Highly flexible and biocompatible	Highly inflammable, low cellular adhesion, porosity and bioactivity, poor rate of degradation	20 months	HA, alginate, chitosan, PCL, HAp, or BG	Hydrogels, composite scaffolds	Suture, neural, bone, skin cartilage, cardiovascular, ligament regeneration, and drug delivery applications	[92–94]
	PCL	Slow degradation rate Water, solvent, oil, and chlorine resistant	Extrusion, SLA, IJP	Highly flexible, excellent mechanical characteristics, degradation and solubility, biocompatible, and minimal inflammability	Limited degradation and low cell adhesion	6–28 months	Chitosan, PLA, BG, or HAp	Composite scaffolds, hydrogels	Dentistry, vascular, bone, retina, skin regeneration, and pharmaceutical applications	[95–97]
	PGA	Insoluble in water Biodegradable	Extrusion, SLA, IJP	Excellent tensile strength, bioresorbable, and biocompatible	Limited solubility and rapid degradation	5 months	PLA, PEG, PLGA, collagen, or chitosan	Composite scaffolds, hydrogels	Surgical sutures, bone, ligament, and cartilage reconstruction	[98–101]
	PHB	Biodegradable	Extrusion, IJP	Excellent mechanical, barrier properties, piezoelectricity, and optical activity	Limited solubility, and low cell adhesion	6–10 months	Chitosan or alginate	Composite scaffolds, hydrogels	Surgical implants, biomedical devices, bone, skin, cartilage regeneration, or breast augmentation	[102–104]
	PVA	Biodegradable Low carbon footprint	Extrusion, IJP	Biocompatibility, non-toxicity, self-healing property, and hydrophilicity	Low cell adhesion	16–25 d	Gelatin, chitosan, PLA, or PGA	Hydrogels, composite scaffolds	Drug delivery, wound dressing, bone, cartilage, and skin regeneration	[105–107]

as an ingredient of cell walls of brown seaweed and in the capsule of bacteria pseudomonas sp. and Azotobacter sp, possesses the ability to form a gel upon the incorporation of divalent cations [120–122]. Additionally, it has also been used for preparing hydrogels through various crosslinking approaches for a wide range of applications in the biomedical area [123–125]. Collagen, a natural polymer, is a ubiquitous protein found in animals, especially in the human body. Collagen scaffolds contain the fibrous structure of principal receptors (integrins) with dimeric peptides [126]. For instance, Heo et al. [127] observed that the incorporation of umbilical vein endothelial cells (UVECs) and mesenchymal stem cells (MSCs) into collagen hydrogels significantly improved osteogenic differentiation, cell viability and vasculature ingrowth. Moreover, the blending of collagen with other natural biopolymers helps in forming fibrous polymeric scaffolds, which exhibit excellent strength and stability due to the crosslinked structure. Additionally, collagen sponges are also being used as a wound dressing material, due to porosity, structure and surface properties [128–130]. SF, a natural polymer of proteinic nature, extracted from Bombyx mori cocoons, spiders and silkworms, is highly elastic, strong and high strength-to-density ratio. The porosity of the structure can be improved by adding calcium phosphate (CaP) in silk without any noticeable changes in its compressive behavior [131–133]. Nowadays, silk-based hydrogels are employed to release potential anticancer drugs including doxorubicin. Additionally, they also help in delivering genes, growth factors, proteins and plasma molecules [134–137]. Starch is a renewable polymer obtained through plants. This material is primarily deposited in tubers, seeds or roots of plants. Its structure contains amylopectin and amylose, constituting about 98%−99% dry weight of this biopolymer. Modified starch employed in acetylated, phosphate ester and grafted forms for drug release applications [138–140]. Gelatin is one of the most versatile and promising natural biopolymers derived through partial hydrolysis and denaturation of collagens. It originates from different sources including pigskin, hides, fish and cattle bones, and contains proline, glycine and hydroxyproline constituents [141–143]. Excellent viscosity, gel strength and low melting point are some of its unique characteristics that appear due to the presence of amino acids [144–146]. Cellulose, a renewable and biodegradable polysaccharide, is abundantly available in natural biological sources ranging from plants (bamboo, wood, bast and cotton) to micro-organisms (algae, bacteria, and fungi) [147]. However, cellulose shows minimal solubility in the organic solvent and difficulty in melting due to strong hydrogen bonds, which makes its processability highly cumbersome [148]. Cellulosic fibers are mostly employed to reinforce the matrices of bioactive materials, which are manufactured through the AM technology. Similarly, bioinks for the AM technology can also be prepared by using nanocellulose materials such as cellulose nanofibrils (CNF) and cellulose nanocrystals (CNC) as a reinforcing media [149–151]. HA, an emerging and versatile linear polysaccharide, naturally occurs in the body consisting of glycosaminoglycan with non-sulfated bonds [152], and plays an important role in cellular adhesion and differentiation, which makes it highly suitable for modern therapeutic formulations [153].

2.2. *Synthetic biopolymers*

Diverse and versatile synthetic polymers such as polyanhydrides, polyamides, poly-α-hydroxyesters, polyurethanes and poly(ortho-esters) can be applied in tissue regeneration, medical devices, drug and gene delivery systems due to their modifications or tailorable designs [154–156]. These polymers have relatively low production cost compared to natural biodegradable polymers [156–158]. Aliphatic polyesters can be used as substitutes to petrochemical polymers due to their excellent mechanical properties and biodegradability. Synthetic biodegradable polymers including PLA, polyhydroxybutyrate (PHB), polyvinyl alcohol (PVA), polyethylene glycol (PEG), poly(lactide-co-glycolide) (PLGA), poly(glycerol sebacate) (PGS), polybutylene succinate (PBS), PCL, and polyglycolic acid (PGA) have gained considerable attention in healthcare systems.

Nowadays, synthetic biopolymers are considered attractive alternatives for the biomedical sector. These polymers provide better control over molecular weight and chemical composition compared to their natural counterparts. Most synthetic biodegradable polymers are aliphatic polyesters like PLA, PCL, PGA and their copolymers [159–163]. These polymers show high biocompatibility and controlled degradation rate. Furthermore, their degradated products *in vivo* have not produced any toxic effects on tissues [164]. Additionally, polymers with improved mechanical properties are developed by manually controlling synthetic parameters and designs. However, some synthetic biopolymers exhibit *in vivo* degradation and yield acidic degradated products that lower the local pH value, thus, resulting in the acceleration of the degradation rate of grafts and triggering inflammatory foreign body reactions at the transplantation location. Compared to natural biopolymers, synthetic biopolymers lack cellular adhesion; however, the chemical modifications of these biopolymers can help in improving cell adhesion [165]. These biopolymers are highly beneficial in the biomedical sector and their characteristics can be tuned for tissue regeneration applications [166].

PLA, an eco-friendly synthetic biopolymer, is one of the most promising sustainable biomaterials used in healthcare systems [167]. Lactic acid can be acquired through sugar fermentation, which is derived from renewable resources like corns and sugarcanes [168]. Some limitations like hydrophobicity, slow degradation rate, and low impact resistance associated with PLA polymer. The blending of PLA with other polymers helps in improving its mechanical properties [169]. PCL is an aliphatic semi-crystalline, biocompatible, easily accessible, hydrophobic nature, and biodegradable polyester, which is widely applied for tissue regeneration and wound healing applications [170–172]. PCL exhibits tailorable biological properties, mechanical strength, and physiochemical conditions. It also exhibits excellent permeability to deliver therapeutic molecules in TE, however, undesired burst release and low encapsulation limit its utilization in drug delivery applications. Additionally, the properties of PCL can be improved by developing copolymers through the combination of PCL with other poly(α–hydroxy esters) like poly(d, L-lactic acid-co-ε-caprolactone) (PDLLACL) and poly(l-lactic acid-co-ε-caprolactone) (PLCL) [173]. PGA,

Table 2 – Advantages and disadvantages of conventional manufacturing techniques applied for developing biomedical products.

Conventional techniques	Advantages	Disadvantages	Ref.
Freeze drying	**(i)** Suitable technique to develop interconnected pores **(ii)** Low temperature **(iii)** Distinct leaching is not necessary	**(i)** Irregular and small pores **(ii)** Time consuming process	[183]
Gas foaming	**(i)** Porous scaffolds **(ii)** Do not use organic solvents	**(i)** Pore geometry cannot be controlled **(ii)** Require excessive heat **(iii)** Non-interconnected pore structures	[184]
Electrospinning	**(i)** Controlled porosity, fiber diameter and pore size **(ii)** Micro- to nano-sized diameter scaffolds **(iii)** Highly porous scaffolds	**(i)** Use organic solvents **(ii)** Low mechanical strength **(iii)** Pore size is reduced with fiber thickness	[185–187]
Thermally induced phase separation	**(i)** Highly porous 3D scaffolds **(ii)** Excellent mechanical properties	**(i)** Small pores (<200 µm) **(ii)** Use of organic solvent, which are harmful to cells	[188]
Solvent casting	**(i)** Expensive equipment is not required **(ii)** Ease of fabrication	**(i)** Develop simple shape scaffolds only **(ii)** Use residual solvents	[189]
Solvent casting /particulate leaching	**(i)** Expensive equipment is not required **(ii)** Ease of fabrication	**(i)** Protein denaturation **(ii)** Lack of control on the interconnectivity of pores **(iii)** Only form simple shape scaffolds **(iv)** Residual solvent is harmful to cells	[190]
Powder forming	**(i)** Scaffolds with high porosity **(ii)** Tailorable pore size	**(i)** Use organic solvents	[191]
Sol-gel method	**(i)** Develop scaffolds by using different types of ceramics	**(i)** Low mechanical strength of scaffolds	[192]

semi-crystalline aliphatic polyester similar in biochemistry to PLA, is a well-known bioresorbable tissue-engineered polymer, which is extensively explored for the bioengineering field. Additionally, the fast-degrading nature of PGA makes it a good candidate for short-term tissue scaffolds [174–176].

3. Conventional manufacturing techniques

It is difficult to control pore parameters as well as incorporate intricate architectural details, while ensuring reproducibility through conventional manufacturing techniques like gas foaming, freeze drying, powder forming, solvent casting, solvent casting/particulate leaching, sol-gel method, electrospinning, and thermally induced phase separation [177–179]. These conventional techniques are unable to generate fully interconnected and uniform pores in tissue scaffolds [180]. Additionally, it is almost impossible to avoid deviation during the conventional fabricating processes, which may result in the failure of the developed tissue constructs [181]. Table 2 summaries the key advantages and disadvantages of different conventional manufacturing techniques. 3D printing technology has led to the implementation of AM technology, which precisely controls the porosity as well as can distribute them uniformly throughout the tissue scaffolds [182].

4. Additive manufacturing techniques

AM technology has been widely explored by biomedical engineers to manufacture a variety of customized products for healthcare systems. The technology is highly beneficial to develop patient-specific anatomic models and medical implants by using an appropriate 3D printing process [193–195]. The transformation of reasonable AM and biopolymer availability are significant elements for their selection in biomedical applications [196–198]. Biopolymers for the 3D printing should ideally possess good printability, processability, structural stability, and high-shape fidelity, as well as precise and accurate 3D plotting of polymers [199–201].

Fig. 6 depicts the general classification of 3D bioprinting processes as per the American Society for Testing and Materials (ASTM) International. Among these processes, extrusion-based printing (fused deposition modeling (FDM) and direct ink writing (DIW)), inkjet printing (IJP)/binder jetting (BJ), stereolithography (SLA) and digital light processing (DLP) are vastly applied for the 3D bioprinting of sustainable polymeric materials [202–205]. Each of the 3D printing techniques has its advantages and limitations. Table 3 describes the schematic diagram and key aspects of some AM processes, which are generally adopted in the 3D manufacturing of biopolymer-based scaffolds and TE applications.

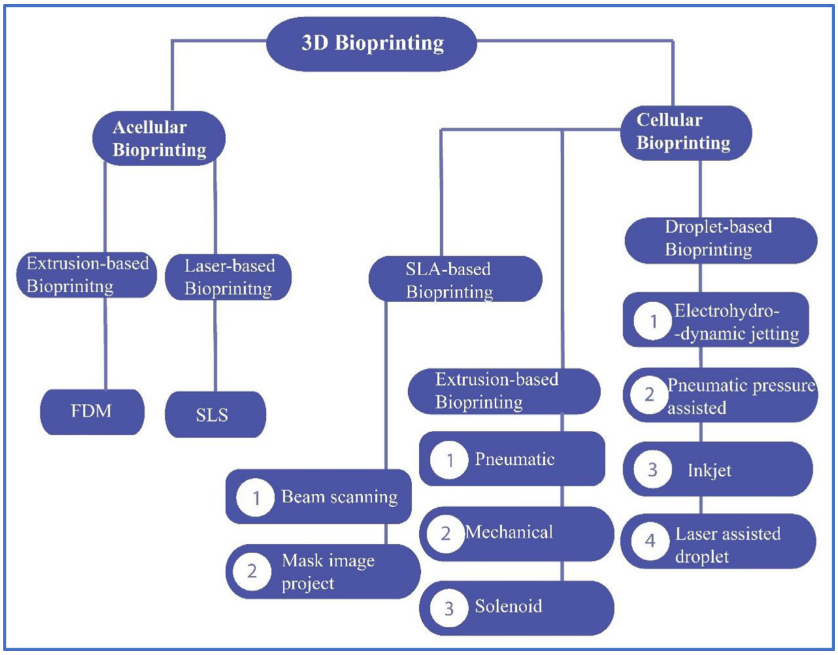


Fig. 6 – Classification of 3D bioprinting processes commonly applied in biomedical applications.

4.1. *Extrusion-based printing*

Extrusion-based printing was one of the earliest technologies that was previously applied to develop prototypes by using metal or plastic as a feedstock material [226]. Even today, the extrusion-based 3D printing technique is the most common, relatively straightforward, and cost-effective AM process applied for prototyping biopolymers [227]. Different feeding mechanisms including piston-, pneumatic- or screw-type used to extrude viscous materials with a viscosity between 30 mPa.s to 6 × 10^7 mPa.s [228]. Irrespective of the type of extrusion mechanism, the ink will be extruded continuously to perform a layer-by-layer deposition on the print bed, which solidifies to develop 3D objects, as illustrated in Fig. 7A. Biomedical applications usually employ micro-extrusion techniques to print highly dense cellular structures in a controlled fashion. The extrusion-based printing is further divided into FDM and DIW, based on the printing temperature [229–231]. FDM is considered a highly suitable strategy for the printing of biopolymers, in which thermoplastic filaments are heated into a molten state or semi-liquid state and extruded through an orifice onto a printing platform [232]. However, this strategy usually extrudes only viscous polymeric materials at room temperature and low resolution is achieved during the process [233]. In contrast, DIW is an extrusion-based printing technique exhibiting the ability to extrude biopolymeric-based viscoelastic ink in the liquid or heated form to generate fibers at ambient temperature. The deposition of these fibers into a specific pattern helps to produce scaffolds for tissue regeneration [234]. This technique can help in developing multipolymer-based tissue constructs. The manufactured bioinks must possess appropriate rheological characteristics, extraordinary shape retention ability, and high storage modulus [235]. Furthermore, bioinks should be able to hold their shape without depending upon the drying or solidification of raw materials. Bioink materials containing high-storage modulus make them highly suitable materials for developing bone regeneration scaffolds [236].

4.2. *Vat photopolymerization*

Vat photopolymerization is another effective technique used for the processing of biopolymeric composites. In this technique, 3D objects are formed by exposing photo-sensitive polymers to light or ultraviolet (UV) radiation [238]. Here, UV light is used to trigger a reactive species or catalyst for the radical photopolymerization of methacrylates. Such a technique is highly attractive due to its printing speed and high resolution. Based on the variation of curing source, this technology is further categorized into SLA and DLP [239].

SLA, a fascinating 3D printing process, uses selectively cross-linked materials including elastomers, thermosetting plastics, ceramic-based resins, and bioink materials in the presence of UV or visible light to develop patterned structures [240]. It is widely applied for producing biopolymer-based porous scaffolds and intricate constructs both for hard and soft tissue regeneration applications [241]. This technique facilitates the high printing resolution of values up to 20 µm and is considered one of the most accurate 3D printing techniques. Therein, the curing is triggered through the degradation of photo-initiators upon exposure to a light source [242], as illustrated in Fig. 7B. Thermoset resins in the SLA technique usually exhibit limited degradability under the action of the light source. Therefore, the combination of biodegradable polymers including diethyl fumarate (DEF), poly(propylene) fumarate (PPF), poly(trimethylene carbonate) (PTMC) and poly(d,l-lactic acid) (PDLLA) was applied for developing tissue biodegradable scaffolds [243]. However, SLA

Table 3 – Description about general additive manufacturing processes.

AM technologies	3D printing	Key Aspects	Resolution	Materials for 3D printing	Processing parameter	Biomedical applications	Cell viability	Ref.
Extrusion	FDM	**(i)** High mechanical strength **(ii)** Freedom in the selection of materials	100–700 µm	Nanocellulose, PLA, PCL, PLGA, PEG, and HA	Physical crosslinking, freeze-drying	Prostheses, orthoses, bone, cartilage, and vascular TE	80%–96%	[206–208]
	DIW	**(i)** High resolution **(ii)** Complex porous scaffolds	100–600 µm	Viscous biopolymer such as CNC, starch, gelatin, alginate, maize protein, k-carrageenan	Freeze drying	Bone TE, drug delivery systems, and personalized medicine	80%–96%	[209–211]
Vat Polymerization	DLP	**(i)** Higher accuracy and good surface finish **(ii)** High printing speed	15–100 µm	PEG, PEGDA, PDLLA, and PCL	UV or visible light	TE, drug delivery systems, and complex organ structures	> 90%	[212–214]
	SLA	**(i)** High precision and resolution **(ii)** Can be used for cell patterning and growth factors	5–100 µm	Photo-polymerizable resins of CNCs, silk, and alginate	UV or visible light	Prostheses, surgical instruments, bone and cartilage TE	> 90%	[215,216]
Laser-based printing	SLS	**(i)** High processing temperature **(ii)** Difficult to print biological materials or cell structures	10–120 µm	PVA, PLGA, PCL-based biopolymer composites	Laser action	Prostheses, orthoses, bone, and cartilage TE	N/A	[217–219]
	SLM	**(i)** Rough surface **(ii)** Material wastage	30–150 µm	PP, PU, metals, and alloys	Laser action	Prostheses, orthoses, and bone TE	N/A	[220–222]
Inkjet printing /binder jetting	IJP	**(i)** Multi-cell heterogenous constructs **(ii)** Cell aggregation **(iii)** Low resolution	20–200 µm	Less viscous materials including alginate, SF, nanocellulose, PEG, and PEGDMA	Liquid binding agent	Personalized medicine, liver, skin, bone regeneration, and drug delivery systems	85%–98%	[223–225]

is not a suitable technique for the simultaneous printing of living cells due to the insolubility of photo-initiators in water solution which makes cells highly toxic. Furthermore, cells are traumatized due to the action of the UV light upon curing. Due to this reason, cells are incorporated after the development of scaffolds [244].

DLP technique is a rapid 3D printing process, which has gained significant attraction in the TE field due to its customizability and high precision [245]. In this process, the curing laser beam is controlled through a digital mirror device (DMD). The DMD contains an array of micro-mirrors that regulates the laser beam [246]. It can cure a complete layer simultaneously, thus, reducing printing time significantly compared to the traditional SLA process [247]. This process is highly suitable to develop intricate ceramic products with high accuracy and resolution, along with desirable mechanical characteristics. The variation in photocurable resin formulations affects the end-use characteristics of the printed scaffolds [248]. Thus, this process helps in developing 3D-printed scaffolds with specific characteristics and functionalities through the regulation of resin formulations [249].

4.3. *Laser-based printing*

Laser-based printing approaches consist of two printing techniques i.e., SLM and SLS for the processing of biopolymeric powders, which use laser light to fuse the material [250]. In the SLM technique, polymeric granules are completely melted, whereas, SLS permits heating below melting temperature just to fuse materials [251]. This approach uses a heater to preheat the powdered feedstock into the build cavity and a heating source (laser radiation) to fuse (sintering or melting) different cross-sections, as

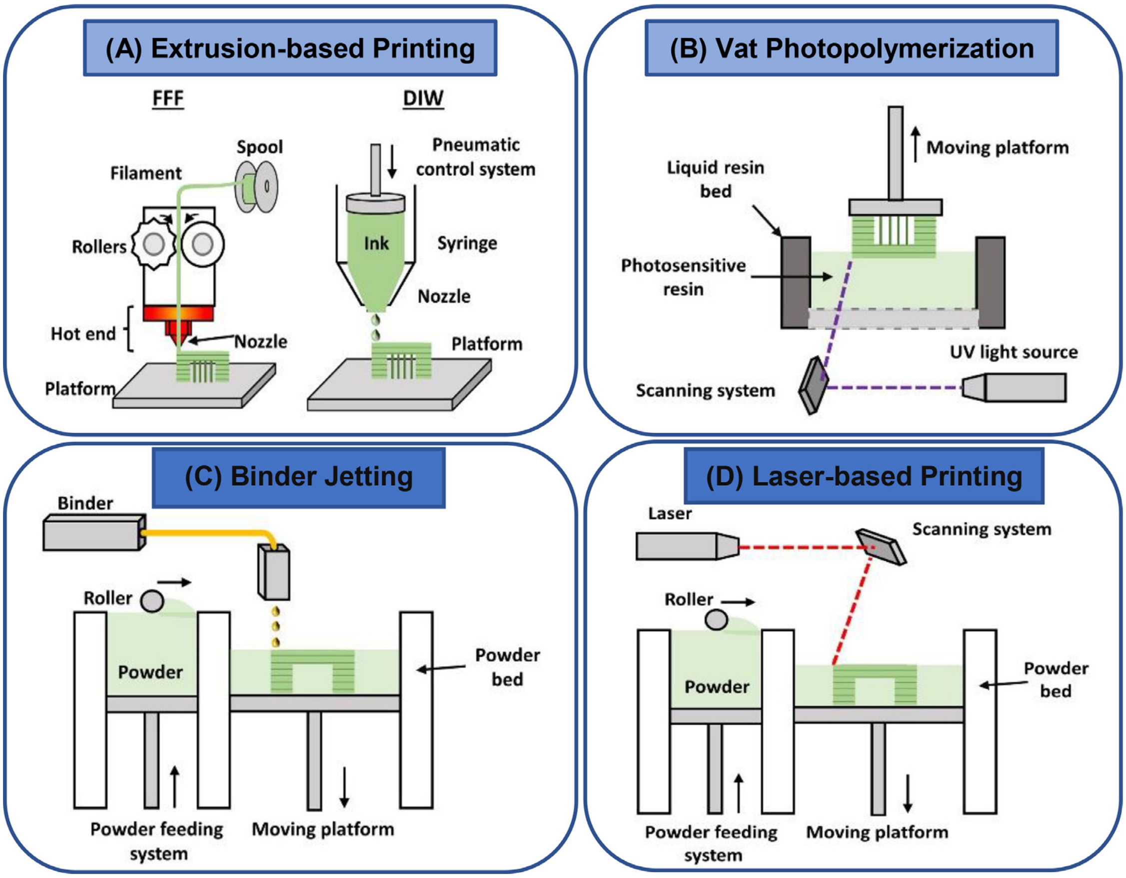


Fig. 7 – Schematic illustration of different AM processes; (A) FDM and DIW printing techniques; (B) Vat photopolymerization; (C) BJ/IJP; (D) SLM (adapted with permission from [237], copyright 2021, Elsevier Inc.).

illustrated in Fig. 7D. This layer-by-layer melting and followed by a solidification process develops 3D objects. SLS/SLM approach develops accurate 3D-printed products compared to other processes like FDM or SLA [252]. Biomaterials such as biopolymers and ceramics are mainly applied in the SLS technique. This approach uses a variety of biopolymeric sustainable composite materials like PCL, PLA, PDLLA, poly(hydroxybutyrate-co-hydroxyvalerate) (PHBV), PVA, PCL/HAp, PLA/PCL/HAp to print scaffolds for BTE, cardiac TE, and cartilage TE applications [253]. For instance, Patel et al. [254] developed PHBV-based biodegradable scaffolds for BTE by using the SLS method and observed degradation mechanism and comparable mechanical properties.

4.4. *Inkjet printing*

IJP technique provides rapid prototyping by depositing tiny photopolymerized ink suspension/solution onto the substrate to develop 3D models and scaffolds, as illustrated in Fig. 7C. It is a powerful tool to deposit biomolecules, polymers, and living cells with high resolution and efficiency [255]. In this technique, for most cases, the viscosity of the bioink should be lower than 10 mPa∎s for effective printing. Additionally, this technique offers low cell densities and high fabrication speed compared to other 3D printing processes [256].

IJP has mainly two working modes; drop-on-demand (DOD) IJP and continuous inkjet (CIJ) printing [257]. DOD, a non-contact 3D printing technique, uses tiny ink droplets of diameter (25–50 mm) that are developed on-demand, and direct the binder droplets with the help of pressure or voltage pulses. This technique is mostly applied to develop scaffolds for TE applications [258]. It possesses excellent control over droplet directionality, uniformity and size. Additionally, the quality of printing depends upon the positional accuracy of ink droplets. In CIJ printing, less viscous bioink materials are converted into a continuous droplet flow after passing through a nozzle (or a set of nozzles), to fabricate 3D objects. The spacing and size of binder droplets are regulated through a pressure wave pattern [259]. IJP is used to develop scaffolds by using both ceramics and biopolymer-based biomaterials like HAp, BG, PLA, PCL, PGA, etc. There is a variety of applications of IJP in other biomedical applications like personalized medicine, controlled drug delivery and protheses [260].

4.5. *Bioprinting*

Bioactive materials are natural or engineered materials that interact with the living tissues without producing any adverse effects and ensure treatment, augmentation or substitution

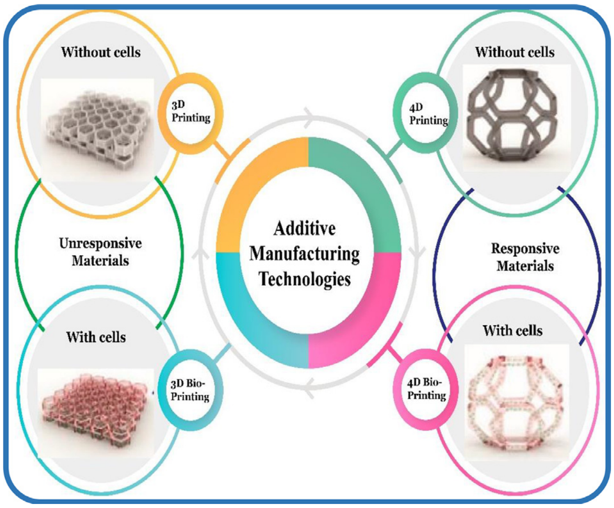


Fig. 8 – Schematic diagram illustrating the difference between 3D/4D bioprinting and 3D/4D printing (adapted with permission from [273], copyright 2022 Elsevier B.V.).

of organs [261]. In other words, the advancement in 3D printing technology has resulted in the development of 3D commercial bioprinters that include BioBots, Aether, Regenhu, and Cellink [262–265]. 3D bioprinting, an emerging and innovative technology, is derived from AM technology and incorporates the viable cells with bioactive materials iteratively to fabricate biomedical components (shown in Fig. 8) that have revolutionized the TE, bone regeneration and pharmaceutical sectors [266–269].

Bioinks, as feedstock materials for the 3D bioprinting help to develop intricate and heterogeneous architectures like vasculatures, enhance cell adhesion, growth and differentiation with native tissues [270]. In comparison to traditional 3D printing technologies, the development of artificial tissues is more challenging in 3D bioprinting due to the selection of cell growth, types, differentiation factors, construction and functionalities of tissues [271]. Nowadays, 3D bioprinting is fulfilling the demands of traumas, cancers, tooth extraction and accidents by modulating porosity and their uniform dispersion during human interaction. However, there is a need to address some challenges including cell incorporation problems, structural activities and feedstock requirements, in this approach [272].

4.6. *4D printing*

Four-dimensional (4D) printing, an innovative technology, involves the combination of stimuli-responsive materials and a 3D printing technology to develop dynamic patient-specific scaffolds [274]. This technology uses stimuli-responsive polymers as a feedstock material, which can change to a temporary state or return to their original state upon exposure to external stimuli, as illustrated in Fig. 8. It was initially introduced by Tibbits in 2013 and has gained tremendous attraction in the biomedical field, due to its ability to produce tissue scaffolds with a dynamic environment [275]. 4D bioprinting, mostly an extension-based 4D printing, is extensively applied in healthcare systems, which involves the maturation of living cells after 3D printing [273]. During the maturation process, cell-incorporated 3D-printed scaffolds self-transform themselves in the presence of stimuli like light, humidity, heat, magnetic field, electric field, ultrasound, pH, etc. [276].

Table 4 summarizes different stimuli-responsive biopolymers, which are well-suited for biomedical applications, especially TE applications. Beside stimuli-responsive polymers, lipids and hydrogels have been vastly applied as feedstock materials for the 4D bioprinting [277–279]. Additionally, different types of smart hydrogels including peptide, natural and synthetic hydrogels have found their applications in the biomedical sector. These hydrogels develop architectures with tailorable porosity and excellent cell interconnectivity [280].

5. Biopolymeric nanocomposites

Biopolymer-based tissue constructs exhibit poor barrier properties and low thermal stability along with low mechanical characteristics [293]. In contrast, biopolymeric nanocomposites incorporate nanosized materials, which improve the mechanical characteristics of biopolymers [294]. These nanocomposites exist in the form of nano-filament composites, nano-layer composites or nano-particulate composites [295]. Table 5 incorporates some of the recent biopolymeric-based nanocomposites used to develop scaffolds in tissue regeneration.

The characterization of the polymer nanocomposites is an analytical approach, which helps to evaluate their size, structure, physical and chemical properties. The incorporation of nanoparticles (NPs) into biopolymers provides better control on size, morphology and dimensions of nano-constructs. Nevertheless, proper dispersion and integration of NPs into biopolymeric matrices are necessary for cell proliferation, adhesion and infiltration within scaffolds. For instance, Liu et al. [300] incorporated tricalcium phosphate (TCP)-based nanomaterials into PCL/PEG-based 3D-printed composite bone scaffolds for improving the mechanical properties. Fig. 9A depicts the scanning electron microscope (SEM) analysis, which showed that composite scaffolds contain uniformly dispersed TCP. Such an uniform dispersion of TCP into biopolymer matrices improved the mechanical properties and cell viability.

Nanocelluloses in the form of CNCs and CNFs are vastly employed, as fillers to develop tissue scaffolds [319]. For instance, Baniasadi et al. [316] developed 3D-printed scaffolds for soft tissue regeneration by using xanthan gum (XG)/CNC, as illustrated in Fig. 10B. The authors reported excellent swelling ratio, porosity and mechanical properties of scaffolds, which can be applied for soft tissue regenerations. Additionally, these scaffolds showed better attachment, differentiation and proliferation of liver cancer cells.

Biopolymers are often used in a mixture with some other inorganic fillers such as ceramic or metal NPs, nano-fibers, graphene, carbon nanotubes (CNTs) as well as living

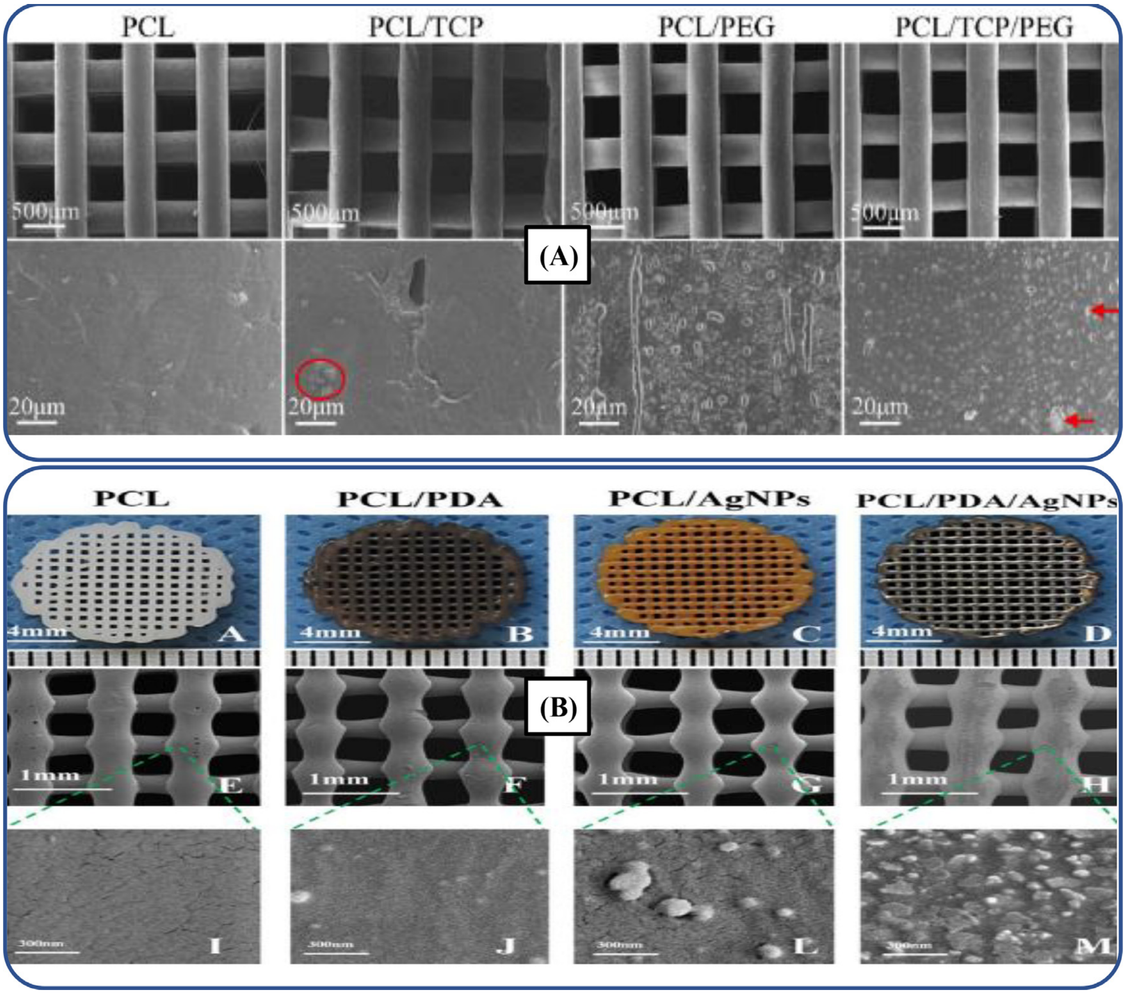


Fig. 9 – (A) Surface characterization of composite scaffolds, where PCL/PEG/TCP-based composite scaffold showed excellent dispersion of the NPs (adapted with permission from [300], copyright 2022, Elsevier Ltd.); (B) Surface morphology and microstructure of 3D-printed bone scaffolds (adapted with permission from [318], copyright 2019, Elsevier Ltd.).

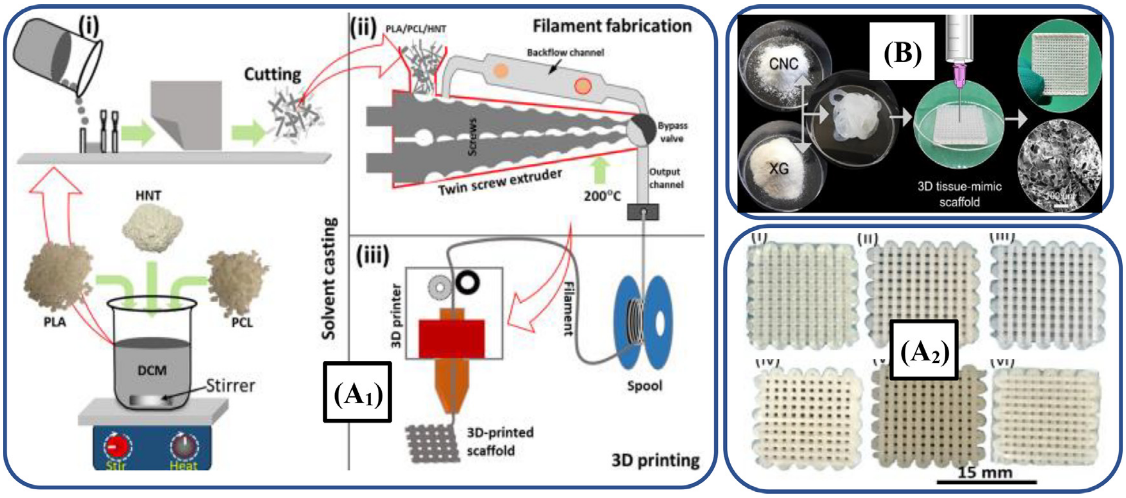


Fig. 10 – (A_1) Schematic illustration of 3D-printed PCL/PLA/halloysite scaffolds; (A_2) Optical photographs of 3D-printed scaffolds printed by varying halloysite (adapted from [306], under the Creative Commons Attribution License 4.0); (B) CNC, as a filler to develop XG/CNC-based scaffolds for repairing soft tissues (adapted with permission from [316], copyright 2022 Elsevier B.V.).

Table 4 – Stimuli-responsive biopolymers used to develop smart materials for healthcare system.

Stimuli-responsive biopolymeric composites	AM technology	Stimulus	Applications	Ref.
PLA/Fe_3O_4	FDM	Magnetic	Tracheal stents	[281]
PLA-PCL copolymer	FDM	Temperature	Elbow protection	[282]
PCL/Fe_3O_4/BG	FDM	Magnetic	Bone tissue scaffolds	[283]
Collagen/agarose/iron NPs	DIW	Magnetic	Cartilage tissue scaffolds	[284]
Gelatin/chitosan	Extrusion	Temperature	Tissue vascularization	[285]
PCL/Fe_3O_4	SLA	Magnetic	Tissue scaffolds	[286]
PEGDA	SLA	Light	Optogenetic muscle	[287]
Methacrylated alginate & Methacrylated HA	Extrusion	Humidity	Tissue vascularization	[288]
PLA	FDM	Temperature	Protective visors frame	[289]
Alginate/glycerin	Extrusion	pH	Skin dressing	[290]
PLA/Fe_3O_4/benzophenone	DIW	Magnetic	Cardiovascular implant	[291]
Collagen fibers	Extrusion	Temperature	Left atrial appendage occlusion devices	[292]

Table 5 – Summary of nanocomposites which are obtained by incorporating NPs into biopolymers developed through various AM techniques.

Biopolymers	NPs	AM process	Applications	Ref.
Alginate	HAp	Bioprinting	Bone TE	[296]
PVA/sodium alginate/CNF	HAp	Extrusion	Bone TE	[297]
PLA/GelMA	Gold NPs	FDM	Bone TE	[298]
PCL	Mesoporous BGs	Bioprinting	Bone TE	[299]
PCL/PEG	β-TCP	Extrusion	Bone TE	[300]
PCL	HAp	SLS	Bone TE	[301]
PLLA/PHBV	CaP	SLS	Bone tissue regeneration	[302]
PCL	Zn/HAp/GO	Micro-extrusion	Bone TE	[303]
PCL/PEG	HAp	Extrusion	Bone tissue regeneration	[304]
GelMA	HAp	DLP	Bone TE	[305]
PCL/PLA	Halloysite	FDM	Bone tissue regeneration	[306]
PCL	Strontium/HAp	Extrusion	Bone TE	[307]
Alginate	BGs	Extrusion	Bone tissue regeneration	[308]
PCL	GO	Extrusion	Bone TE	[309]
PEGDA	CNCs	SLA	Soft TE	[310]
Alginate	MWCNTs	Extrusion	Vascular tissue regeneration	[311]
PCL	MWCNTs	Extrusion	Cardiac TE	[312]
PCL	CNFs	FDM	Drug eluting cardiovascular scaffolds	[313]
Chitosan/alginate	HAp	Hybrid 3D printing	Cartilage tissue regeneration	[314]
Alginate/thymoquinone	Halloysite	Extrusion	Cartilage tissue repairing	[315]
Xanthan gum	CNC	DIW	Liver TE	[316]
PLA	Halloysite	Extrusion	Soft TE	[317]

cells which are obtained from some living materials [320–323]. Among these inorganic materials, CNTs are highly effective for developing 3D-printed biopolymeric-based nanocomposite scaffolds for bone, cardiac and neuronal tissue regeneration, due to their extraordinary electrical conductivity, mechanical properties and distinct dimensional features [324]. CNTs also help to improve strength, flexibility and biocompatibility, along with the reduction of thrombosis and induction of angiogenesis during tissue regeneration [325–327]. For instance, Lee et al. [328] developed porous PEGDA/multi-walled carbon nanotube (MWCNT)-based nerve scaffolds through the SLA technique. The results indicated that the incorporation of MWCNTs promoted the growth and proliferation of neuronal cells, thus, it is a highly effective strategy for developing scaffolds for nerve TE applications. However, these materials exhibit non-resorbable behavior upon *in vivo* experimentation [329]. In another study, Alam et al. [306] developed PCL/PLA/halloysite scaffolds by using FDM technique, as illustrated in Fig. 10A. The results revealed that halloysite-incorporated scaffolds exhibited cellular adhesion, cytocompatibility and biodegradation rate. Thus, these scaffolds have promising applications for bone regeneration.

Anti-microbial properties of biopolymer composites can be enhanced by using metal-based micro- and NPs like bronze, copper and silver. These anti-bacterial properties in the biopolymer composites are essential for tissue scaffolds [330–333]. For instance, Sang et al. [334] coated gold NPs on the surface of PCL-based scaffolds developed through 3D printing. Such NPs enhanced osteogenic differentiation and anti-microbial properties of 3D-printed bone scaffolds. Likewise, Li et al. [318] printed anti-microbial dual functional PCL-based scaffolds with self-assembly micro-nano surface, PDA and silver NPs manufactured through the FDM technique, as illustrated in Fig. 9B. The NP-incorporated scaffolds exhibited excellent cytocompatibility, anti-bacterial, and mechanical properties. These scaffolds demonstrated their excellent potential for bone tissue regeneration.

There is a great demand for bioactive materials like TCP, hydroxyapatite (HAp) and bioactive glass (BG) in TE and regenerative medicine, due to non-toxicity, biocompatibility and better interaction with the human body, which accelerates the healing mechanism [335–337]. HAp, an inorganic component, is highly suitable for developing biopolymer-based nanocomposites for bone tissue regeneration that provides excellent cell adhesion, proliferation, and differentiation [338]. BG is a commercially available micro-sized filler and pure BG cannot be employed for developing tissue scaffolds, due to lose of its amorphous characteristics at a high sintering temperature [339]. Similarly, BG/biopolymer composites are special type biomaterials, which are used in healthcare systems for various applications ranging from surgical implants to tissue regeneration scaffolds [340]. However, bioactive reinforced-biopolymer scaffolds possess excellent biocompatibility, bio-functionality, biodegradability, and mechanical properties [341]. Aráoz et al. [342] incorporated BG into PHBV to fabricate 3D-printed scaffolds for bone tissue regeneration with biological and mechanical properties similar to ECM of trabecular bone.

6. Scopes of biopolymeric composites in healthcare system

Biopolymeric composites are widely used in many clinical and biomedical applications [343]. These sustainable materials have also addressed the demands of environmental toxicological and public health studies, due to inherent properties including biodegradability, non-toxicity, biocompatibility, flexibility,and renewability [344]. A wide range of natural and synthetic biopolymers are now under extensive consideration for many applications such as 3D anatomical models, TE, surgical equipment, scaffold design and artificial implants [345]. Particularly, these composites have myriad of scopes in both hard and soft TE [346]. This section illustrates some of the key applications of 3D-printed biopolymeric composite materials.

6.1. *Tissue engineering*

Biodegradable polymer-based porous scaffolds developed through the 3D printing processes are vastly applied as artificial ECMs to support native tissues, which help in regenerating and reconstructing tissues [347]. Sometimes, biologically active molecules or cells are incorporated to promote tissue regeneration. Depending upon the type of application, these porous scaffolds should possess excellent biocompatibility, cytotoxicity, porosity, optimal pore size and interconnectivity. Furthermore, porous scaffolds have a significant role in the application of drug delivery systems, the development of biomedical devices and surgical instruments, and the encapsulation of human and animal cells [348–350].

Additionally, 3D-printed human organs, stents, medical devices and drug delivery systems have been developed using biodegradable polymers [351–353]. For instance, Misra et al. [353] developed a multi-drug eluting 3D-printed stent by incorporating graphene nano-platelets into the biodegradable PCL-based polymer through an extrusion-based process. This printed stent was deployed in a pig heart, as shown in Fig. 11A. The improved mechanical properties, as well as *in vitro* results, depicted that these novel biodegradable stents can be employed for treating heart patients suffering from blocked coronary arteries. Table 6 provides the summary of different 3D-printed biopolymeric composites employed in different soft and hard tissue regeneration applications.

6.1.1. *Hard tissue engineering*

Natural and synthetic 3D-printed biodegradable polymers have huge potential to be used for hard tissue (bone) regeneration due to their biocompatibility and cytotoxicity [371]. Furthermore, these 3D printing processes have the flexibility to provide any complex shape using biopolymers along with satisfactory biological, physical as well as mechanical properties [372–374].

Bone, a naturally regenerative tissue, may suffer significant trauma due to accidents, thus, hindering its normal regeneration, which causes bone defects [375]. Bone defects require artificial scaffold support during the healing process and bone growth. Since the inception of 3D printing techniques, myriad of biomedical researchers tried to develop scaffolds for bone tissue engineering (BTE) applications, as making scaffolds as this technology is simple and easy. For instance, Dienel et al. [354] employed the SLA technique to fabricate biodegradable implants for a bone generation. In this study, the 3D-printed scaffolds were manufactured by incorporating 51 wt% of β-tricalcium phosphate (β-TCP) into PTMC to get high resolution and best quality implant. Fig. 11B depicts 3D-printed porous scaffolds embedded into the human jaw. Similarly, Ben and Tan [355] employed PCL-based biodegradable material for the fabrication of scaffolds to heal the socket of human tooth, as depicted in Fig. 11C. For this purpose, a 3D printing technique was used to fabricate the PCL scaffold that could be used in the bone healing of the human tooth. The 3D-printed scaffold was inserted into the teeth socket of the human without using the filler and observed the results after 6 months. The results depicted that the insertion of a biodegradable PCL-based scaffold significantly healed the bone.

In another study, Choi et al. [376] developed PLA-based biodegradable polymers that could be used effectively in the formation of bone scaffolds. For this, a FDM-based technique was used to fabricate the specimens by incorporating a chain extender and a chemical foaming agent and observed the improvement in the morphology, porosity, and melting properties. Similarly, Shim et al. [377] studied the effect of PLGA/PCL/β-TCP-based scaffolds through FDM for bone regeneration and osteointegration of dog tooth. Fig. 12A_1 depicts the sequential procedure of this work adopted by the authors to manufacture 3D-printed scaffolds. For *in vitro* examination, the developed 3D-printed membrane was implanted into the dog's mouth, as shown in Fig. 12A_2. Both

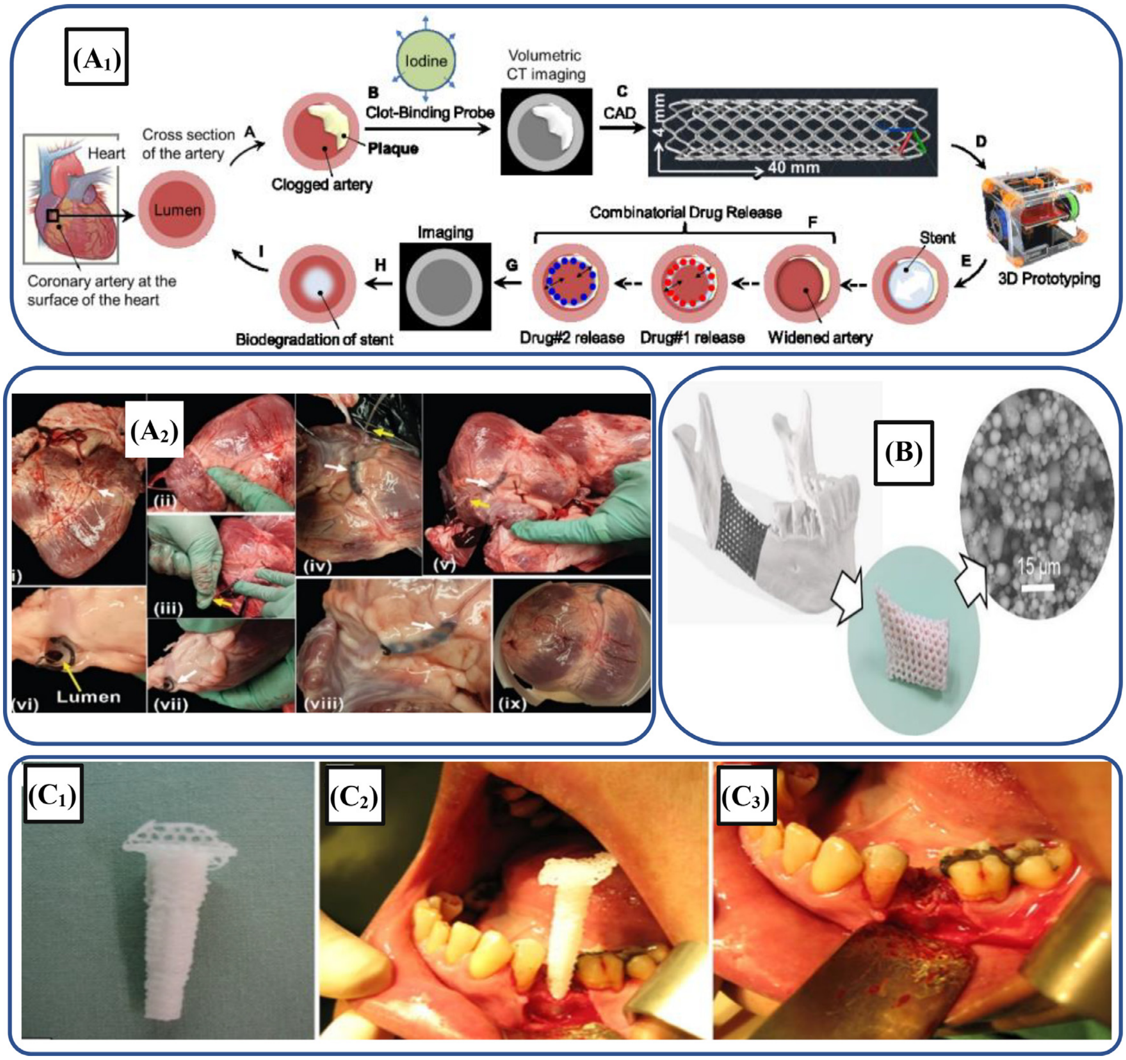


Fig. 11 – (A$_1$) Schematic illustration depicting different steps for fabricating micro-stents; (A$_2$) Sequential demonstration of 3D-printed stent PCL-based polymer composite implanted in the heart of the pork (adapted with permission from [353], copyright 2017 WILEY-VCH); (B) Implantation of 3D-printed PMTC-based scaffolds into the human jawbone manufactured through SLA strategy (adapted with permission from [354], copyright 2019 American Chemical Society); (C$_1$) 3D-printed PCL-based polymer scaffold; (C$_2$) Insertion of scaffold into the tooth socket of human mouth; (C$_3$) Trimming of the excess scaffold (adapted with permission from [355], copyright 2014 John Wiley & Sons Ltd)

in vivo and *in vitro* results further help to print scaffolds for applications.

Zhang et al. [378] explored a strategy to repair bone defects using the PLA/HAp-based biodegradable scaffold. The preparation of these scaffolds was performed by the vascularized BTE of the rabbit using an *in vivo* bioreactor. Fig. 12B$_1$ depicts the experimental procedure adopted by the authors to completely analyze the *in vitro* behavior of the fabricated scaffold. In this methodology, the tibial periosteum capsule was filled with PLA/HAp composite scaffolds and rabbit bone marrow cells, as depicted in Fig. 12B$_6$. After 8 weeks, the results depicted that these scaffolds are helpful in generating vascularized bone tissues. The mechanical properties of biopolymer-based scaffolds are matchable to the properties of the targeted hard tissues. Additionally, the degradation rate of the scaffolds is the same as that of the replacement rate of cells. It helps in the replacement and remodeling of natural ECM. Table 7 provides most remarkable, recently fabricated 3D-printed biopolymeric composite-based bone scaffolds, their properties, morphologies, and research highlights.

6.1.2. *Soft tissue engineering*

3D-printed biopolymeric composites are promising candidates for mimicking native soft tissues, as illustrated in Fig. 13. Several soft tissues including cartilage, urethra, nerve, skin, tendon, liver, ligament, intestine, and vascular are continuously performing their function in the human body. In comparison to hard tissues, soft tissues exhibit distinct properties including compliant modulus of elasticity, flexibility, and weak mechanical properties, therefore, semi-crystalline biopolymeric materials are not considered for

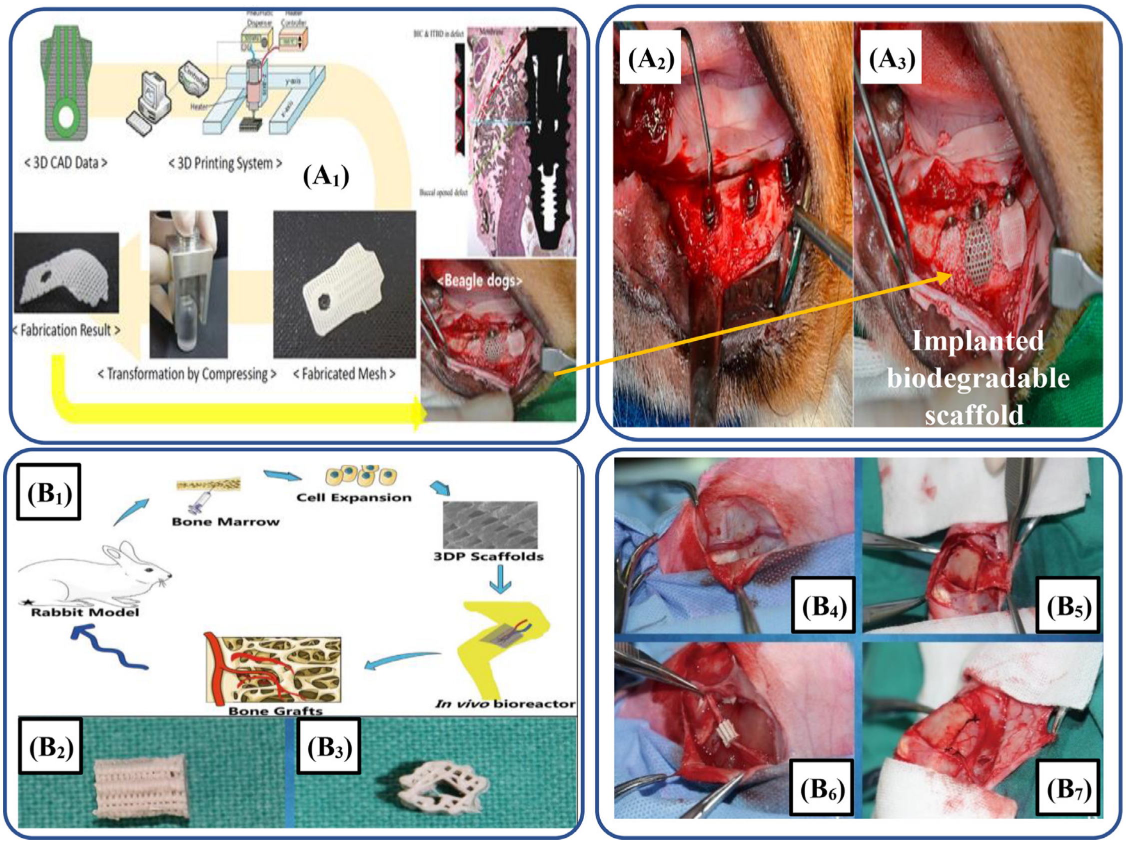


Fig. 12 – (A_1) Sequential procedure starting from CAD design of membrane to the implantation of membrane into the edentulous mandibular alveolar ridge; (A_2) Implantation of implants into the edentulous mandibular alveolar ridge; (A_3) Used the grafting material to compromise and fill the defects and then membrane was implanted (adapted from [377] under the Creative Commons Attribution License 4.0); (B_1) Schematic illustration showing the experimentational procedure of *in vitro* vascularized tissue generation of the bone; (B_2) 3D-printed PLA/HAp-based composite scaffold in lateral and (B_3) front view; (B_4) Figure showing the saphenous arteriovenous blood bundles; (B_5) Periosteum was displayed on the surface for surgery; (B_6) Implantation of PLA/HAp-based composite scaffold; (B_7) Scaffold was rolled in the form of capsule (adapted from [378] under the Creative Commons Attribution License 4.0).

these soft-tissue applications [391–394]. Additionally, the composition and structural characteristics of these scaffolds should be matchable to ECM tissues for helping in cell growth, proliferation, and differentiation. Similarly, biocompatibility, porosity, and nutrient transportation of these scaffolds are other essential attributes for soft tissue regeneration [395]. Table 7 also includes some of biopolymeric composite-based scaffolds fabricated through 3D printing techniques for soft tissue regeneration applications.

Different natural biopolymers (α-keratin, chitosan, HA, alginate and collagen) and synthetic biopolymers (PCL, PGS, PEG, PLA and their copolymers) can be employed to print scaffolds for soft TE applications [396]. For instance, Liu et al. [397] regulated the elastic modulus and stiffness of the PLLA by incorporating PCL-based biopolymer and noted that PLCL-copolymer scaffolds Fig. 14 Aexhibited good biocompatibility and mechanical properties. Thus, copolymerized PLCL-based scaffolds show promising potential for the regeneration and repairing of muscle, cardiac, tendon and skin tissues. Similarly, customized bioinks and PCL-based biopolymer were employed by Cho et al. [398] to develop biocompatible dome and spherical-shaped adipose tissue assemblies, as illustrated in Fig. 14C. Thus, the research has shown great promise for regenerating breast tissues.

Various fibrous materials including collagens through the 3D printing techniques produce scaffolds for wound dressing and skin regenerative therapies [399]. For instance, Ramasamy et al. [400] printed collagen/PCL-based biodegradable scaffolds through a extrusion-based process, as shown in Fig. 14B, and observed excellent cell differentiation, viability and reproducibility.

3D-printed artificial skin tissues contain different bioactive materials, growth factors and cells [27]. Several researchers have 3D-printed skin constructs by incorporating stem cells, antimicrobial particles and growth factors. For instance, Afghah et al. [401] developed poly(propylene) succinate (PPS)/PCL-based scaffolds by incorporating anti-microbial silver granules and human dermal fibroblast (HDF) cells. 3D-printed skin constructs exhibited excellent antimicrobial characteristics and degradation behavior, thus, considered as a potential candidate for skin TE applications. In another study, Zhang et al. [402] developed 3D hybrid cell-laden skin

Table 6 – Biopolymeric scaffolds manufactured through various 3D printing techniques.

Type of tissue	Target tissue	Biopolymeric material(s)	Printing technique	*In vitro* study	Structure	Ref.
Hard	Bone	PEG/Silk/PCL	Extrusion-based 3D printing	BMSCs	Crypt-like structures	[356]
	Bone	Gel/PVA	Extrusion-based 3D printing	MG63 cells	–	[357]
	Bone	PLA	FDM	hBMSCs	–	[358]
	Bone	PVA/BC	FDM	Human osteoblast cells	–	[359]
Soft	Cartilage	PCL/PLA/PEG	FDM	hBMSCs	Layer by layer-based honeycomb structure	[360]
	Cartilage	SF/PEG	Extrusion-based 3D printing	Chondrocytes	Disk/meniscus-shaped scaffold:	[361]
	Cartilage	SF/Gelatin	Extrusion-based 3D printing	hMSCs	Layer-based 3D structure	[362]
	Nasal cartilage	Collagen	Extrusion-based 3D printing	Human chondrocytes	Microporous structure	[363]
	Nerve	Alginate/CMC/ agarose	DIW	Human iPSC-derived glial cells	Layered porous structure	[364]
	Nerve	PCL	Electrohydrodynamic jet-based 3D printing	PC12	Tubular multi-layered complex	[365]
	Skin	Keratin/glycol chitosan methacrylate	Extrusion-based 3D printing	hASCs	"NTU"-based 3D model	[366]
	Skin	PEG/SF	DLP	NIH/3T3	3D lattice structure containing thin keratin layer	[367]
	Cornea	GelMA	Extrusion-based 3D printing	Human keratocytes	Complex porous	[368]
	Liver	SF/Gelatin	Extrusion-based 3D printing	Hepatocytes, Huh7	Six-layered-based scaffolds	[369]
	Lung	SF/CNF	Extrusion-based 3D printing	Lung epithelial stem cells	Two crossing layers	[370]

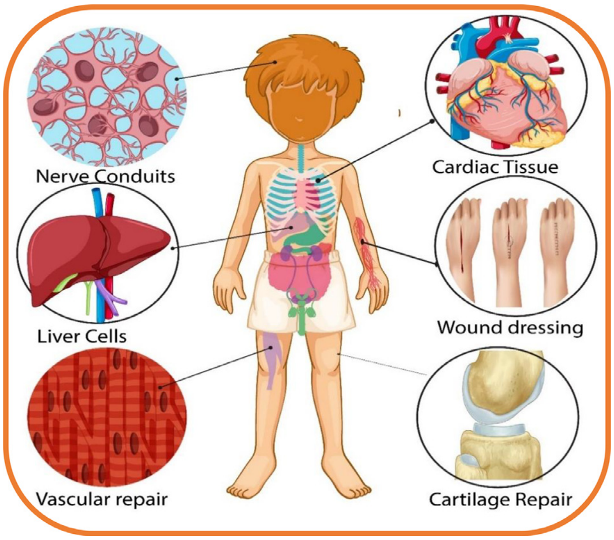
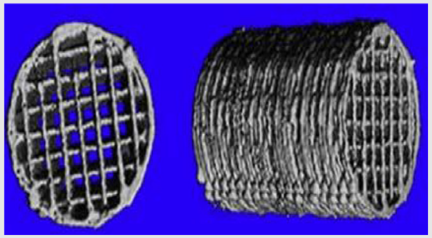
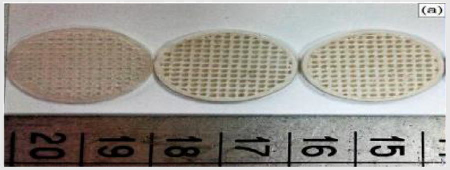
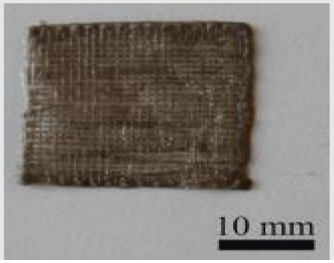


Fig. 13 – Various parts of the human body where 3D-printed biopolymeric composites can be used to regenerate soft tissues.

constructs by using PVC-based biodegradable polymers and poly(N-isopropyl acrylamide-co-acrylic acid) (PNIPAAm-AA)-based hydrogels, as illustrated in Fig. 14D. The *in vitro* experimentation revealed that cell-laden constructs exhibited excellent superficial cornification, splitting, and sprouting of the subcutaneous ECs. These artificial tissues have the potential to be applied for wound healing applications.

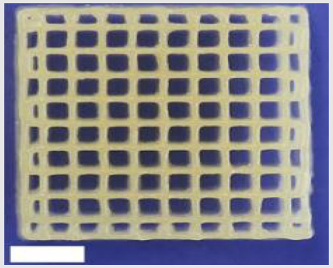
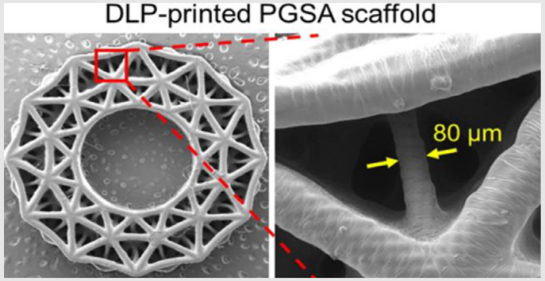
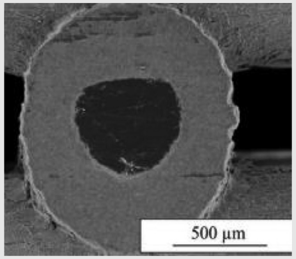
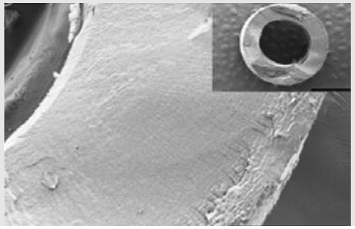
Peripheral nerve injury (PNI) cannot be self-healed and requires neural grafting or end-to-end suturing for its remedy. 3D printing is a highly suitable and versatile approach for developing patient-specific branched or unbranched conduits with high resolutions, better features and native scale dimensions [403]. Biopolymer-derived sustainable biomaterials exhibit incomparable biological properties, which are equivalent to ECM. Thus, they provide sites for biological cues and protein binding that regulate the cell behavior. Recently, different biopolymer scaffolds including CNFs, alginate, gelatin, starch and collagen have gained attraction for TE and are used to develop the next-generation conduits for neural tissue regeneration [404]. The rapid development in the nerve regeneration yields multiform biopolymer-based nerve scaffolds with different micro/nano-scaled structures, which possess excellent biological characteristics, cues, and appropriate mechanical

Table 7 – Recently adopted different 3D-printed biodegradable polymer composite-based scaffolds for tissue regeneration.

AM process	Biopolymeric composites	Mechanical characteristics	Morphology	Highlights	Ref.
FDM	PLGA/HA/HACC	Compressive strength: 31.3 MPa Tensile strength: 22.7 MPa Elastic modulus: 1.9 GPa		The results of the *in vivo* study showed that the biodegradation of the scaffolds was influenced by the bone infection and helped in the repairing of the bone.	[379]
Extrusion	Alginate/gelatin/CNC	Storage modulus: ~150,000 MPa at 100 rad/s		Rapid bone grafting has been noted in the rat CCD-1 defects model in the presence of the biopolymers-based scaffolds after 21 d of the transplantation.	[380]
FDM	PLA/HAp	Nozzle diameter: 0.2 mm Layer thickness: 50 μm		Young's modulus, similar to the modulus of the cancellous bone when 50 wt% of HAp were used.	[381]
Extrusion	MWCNTs/PCL	Melting temperature: 90 °C Air pressure: 6 bar Deposition velocity: 20 mm/s		The *in vitro* study depicted that implanted scaffold containing 3 wt.% of MWCNTs significantly repaired the bone tissues.	[382]
Micro-extrusion	Alginate/gelatin/GO/chondroitin sulfate	Compressive modulus: 100 kPa		The incorporation of GO in biopolymer-based scaffolds exhibited excellent cell proliferation, adhesion, and proliferation. *In vitro* analysis showed excellent bioactivity, cytotoxicity, and biocompatibility. These scaffolds are excellent candidates for TE.	[383]

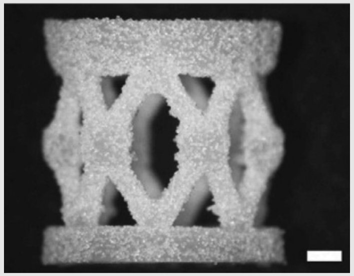
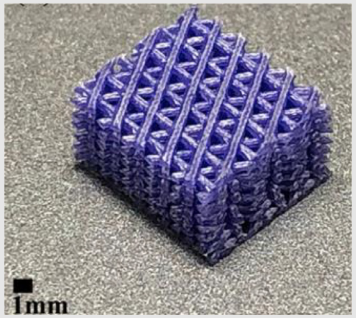
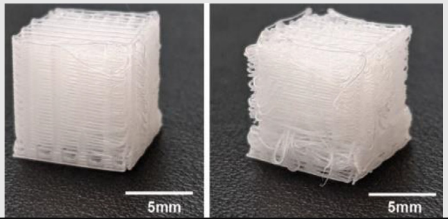
(*continued on next page*)

Table 7 (*continued*)

AM process	Biopolymeric composites	Mechanical characteristics	Morphology	Highlights	Ref.
Extrusion	Silica NPs/oxidized alginate	Yield stress: 79 Pa with 2 wt.% of NPs		The results exhibited that incorporation of silica NPs enhanced mechanical stability, shear-thinning properties, and high fidelity.	[384]
DLP	PGSA	Feature thickness: 80 μm Elastic modulus: 3668.7 kPa Ultimate tensile strength: 919.1 kPa		The results revealed that PGSA-based biodegradable tubular scaffold exhibited excellent mechanical properties and degradation kinetics. Thus, it has the potentiality to be applied for tissue regeneration applications including vascular grafting.	[385]
DLP	β-TCP/PCL	Compressive strength: 11 ± 4 MPa		The experimental results indicated that 3D-printed hybrid scaffolds exhibited excellent compressive strength. Thus, these rigid bioactive scaffolds have the potential to be applied for BTE applications.	[386]
DLP	PCL/PEG/GelMA	Diameter: 1.5 mm, 2 mm, and 2.5 mm Wall thickness: 0.75 mm, 1 mm, and 1.5 mm		3D-printed scaffolds exhibited excellent biocompatibility and mechanical properties. Hence, these composite scaffolds will be highly suitable for nerve repair.	[387]

(*continued on next page*)

Table 7 (continued)

AM process	Biopolymeric composites	Mechanical characteristics	Morphology	Highlights	Ref.
SLS	PCL	Laser power: 0.3 – 0.7 W Laser beam diameter: 260 μm, 390 μm Elastic modulus: 11.3 ± 0.5 MPa		PCL-based porous scaffolds have depicted excellent biocompatibility and comparable elastic modulus. Therefore, these scaffolds can be applied for bone regeneration.	[252]
FDM	PCL/PGA/yarn fiber	Tensile strength: 79.7 MPa Elastic modulus: 3.5 GPa		Stiffness and tensile strength of 3D-printed biodegradable scaffolds were enhanced, significantly with the incorporation of yarn fibers. Additionally, these scaffolds exhibited excellent biocompatibility and cytotoxicity. These scaffolds have the potential to be applied for bone regeneration.	[388]
FDM	PLA	Yield strength: 60 MPa Young's modulus: 4 GPa		3D-printed vascular stent exhibited excellent self-expandable and thermal properties. The synergetic combination of these properties makes this 3D-printed product a promising candidate for solving complications of cardiovascular disease.	[389]
FDM	PCL	Compressive strength: 0.65 MPa Compressive modulus: 10.60 MPa		Build envelope temperature, nozzle temperature, material volume and deposition speed are important parameter for determining the fidelity of PCL lattice scaffold structures.	[390]

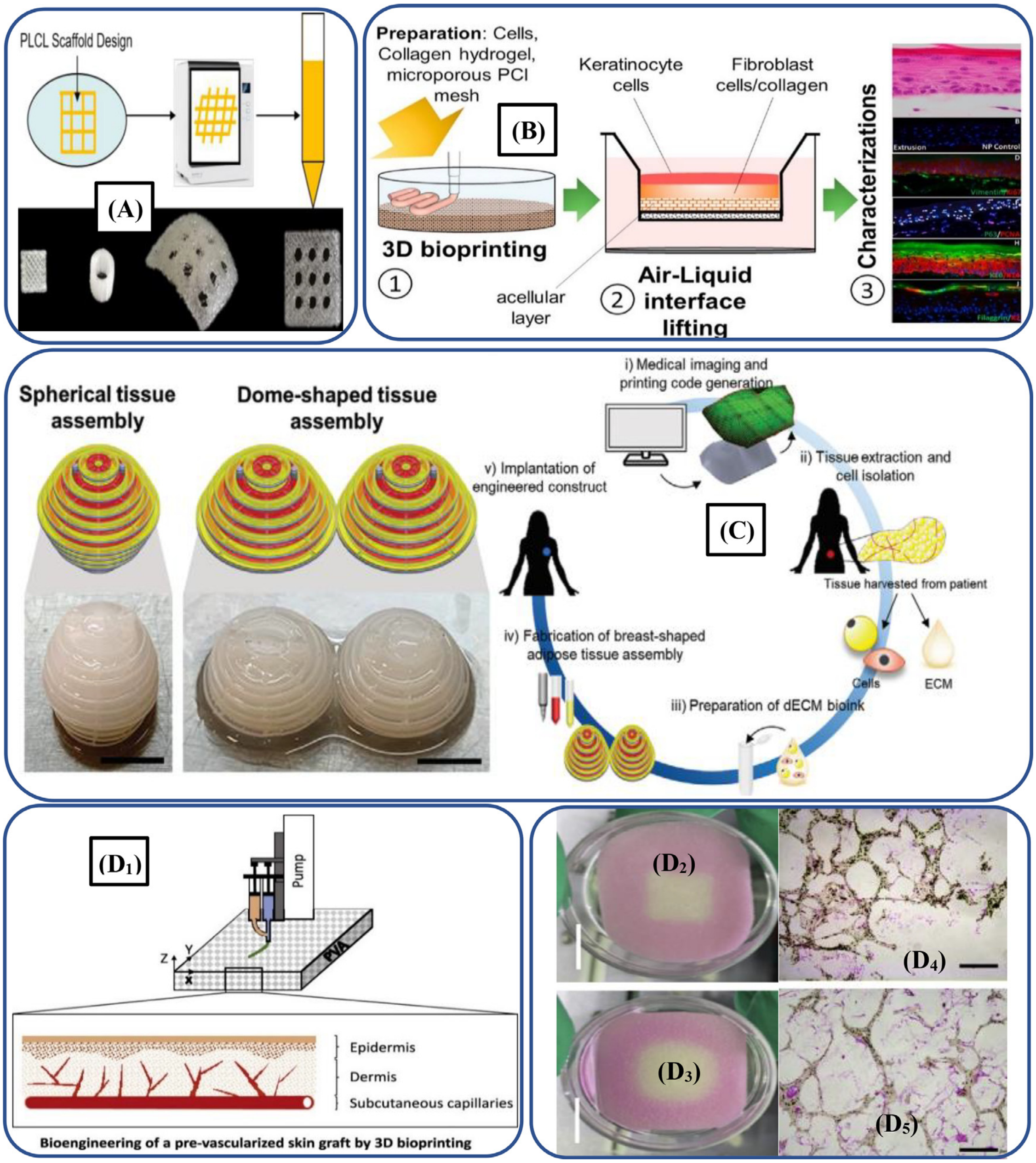


Fig. 14 – (A) PLCL-based 3D-printed scaffolds which exhibited tailorable elasticity, stiffness as well as excellent biocompatibility (adapted with permission from [397], copyright 2020 Royal Society of Chemistry); (B) Schematic process illustration depicting the collagen/PCL-based scaffolds and their characterizations (adapted with permission from [400], copyright 2020 Elsevier B.V.); (C) PCL-based biodegradable polymer used to develop dome and spherical-shaped adipose tissue assemblies, which depicts its potential utilization for developing breast-replicating soft tissue repairing (adapted from with permission [398], copyright 2020 Wiley-VCH GmbH);(D_1) Biopolymer-based 3D-printed hybrid skin constructs; (D_2-D_3) Multi-layered PVA-based porous cell-laden scaffolds; (D_4-D_5) Hematoxylin and Eosin stain images depicting the distribution of cells in multi-layered 3D-printed scaffolds (adapted with permission from [402], copyright 2020 Elsevier B.V.).

strength to fulfill the nerve regeneration requirements. The mechanical properties and internal microstructures of nerve guidance conduits (NGCs) may be determinants in promoting axonal regeneration and remyelination. Yoo et al. [405] combined electrospun PLCL and 3D-printed collagen hydrogel to develop a single-lumen nerve conduit to repair PNI. The results indicated that developed NGCs significantly promoted myelin regeneration, axonal growth, and nerve function recovery.

In another study, Ye et al. [406] employed the DLP process to fabricate NGCs by using GelMA-based hydrogels, as illustrated in Fig. 15A. These 3D-printed NGCs depicted excellent support for the differentiation, migration, proliferation and survival of neural cells along the longitudinal channel. Likewise, Zhang

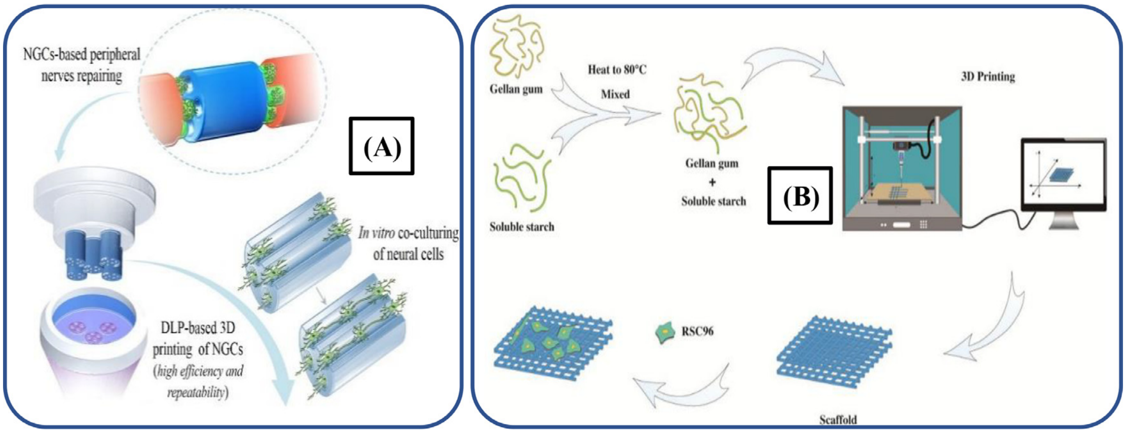


Fig. 15 – (A) Schematic illustration of GelMA-based hydrogels NGCs fabricated through DLP (adapted from [406], Creative Commons Attribution 4.0 International License); (B) Schematic diagram depicting the cell-laden starch/gellan gum-based composite scaffold for PNI treatment (adapted from [407] Creative Commons Attribution 4.0 International License).

et al. [407] developed starch/gellan gum-based composite scaffolds via an extrusion-based 3D printing, as depicted in Fig. 15B. These porous structured scaffolds exhibited excellent biodegradability, biocompatibility, printability and cytotoxicity, which can permit their use for treating PNI.

6.2. *Pharmaceutical and other biomedical applications*

The applications of 3D-printed biopolymer composites vary from nose reconstruction to dental manufacturing, human ear construction to bone regeneration, and surgical instruments manufacturing to developing human hand models. Fig. 16 depicts some of the applications of biopolymeric composites in the healthcare system. Controlled drug delivery systems are important to improve the therapeutic efficiency of drugs. Delivery rates of drugs must meet the physiological conditions [408–415].

3D printing is an emerging technology that uses biopolymers to fabricate drug dosage forms in different intricate shapes. These polymers modulate the drug release rate and provide physical stability to active drug ingredients [418]. However, the usage of 3D-printed biopolymer dosage must fulfill regulatory requirements, in terms of safety and quality standards for human use. FDM and IJP are the most preferred 3D printing techniques used in pharmaceutics and drug delivery applications. These techniques provide high accuracy, patient-customized drugs, quick drug release, and high dosage loading of drugs [419]. However, they suffer from low productivity, compared to conventional fabrication techniques of biomedicine. Different biopolymers have been developed as delivery mediums by using 3D printing technologies. For example, Tappa et al. [420] fabricated 3D-printed biomedical implants and medical devices using PCL-based biodegradable polymer and incorporating estrogen or progesterone. The printed samples were surgical meshes, subdermal rods, medical devices, and pessaries. This study also gives a feasible concept for the application of drug delivery systems. Moreover, 4D printing has also gained significant attraction in the pharmaceutical industry [421]. For instance, Melocchi et al. [422] used water-responsive PVA-based polymer for intravesical drug delivery systems manufactured through FDM.

7. Future perspectives of 3D-printed biopolymeric composites

3D printing technology has shown significant advancement through biopolymers for constructing 3D-hybrid tissues with tunable mechanical properties and controllable biological characteristics. Despite extraordinary advancements in the 3D printing of biopolymeric composites for a wide range of applications, further research is needed to address the remaining challenges. The new generation of printing technologies construct tissue scaffolds through the combination of hydrogels, synthetic and natural-based biopolymers [423]. For instance, Morris et al. [424] developed PEGDA/chitosan-based hybrid scaffolds through the SLA technology. To use its full potentials, it is essential to develop nanometer-to-millimeter hierarchical biopolymer-based architectures. Advanced hybrid manufacturing (i.e., traditional manufacturing processes with 3D/4D printing) technologies can be employed to fabricate intricate constructs. For instance, an artificial collagen/fibrin hydrogel with electrospun PCL and animal chondrocytes was employed for the construction of cartilaginous tissues through an electrospinning/hybrid IJP system [425].

Indeed, 3D-printed biodegradable-based biopolymers have transformed the design and manufacturing landscapes of scaffolds. These biopolymers are successfully employed in the fabrication of synthetic bone models through the FDM technology [426]. However, over the technology possesses low printing resolution which is especially true for the 3D bioprinting of trabecular bone architecture. Hence, there is a further need to investigate 3D printing and hybrid technologies other than the FDM technology for the fabrication of 3D-printed biopolymer-based bone scaffolds.

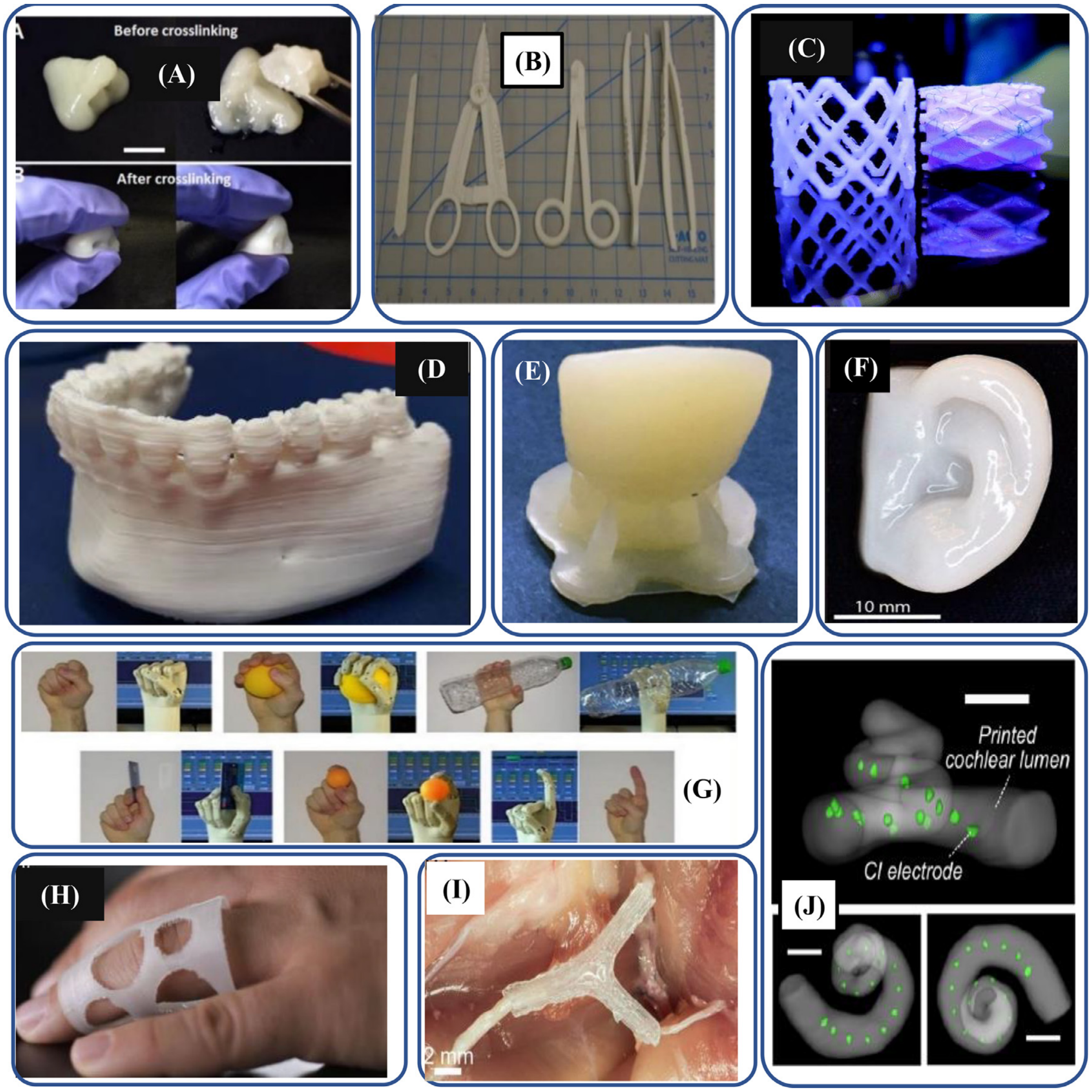


Fig. 16 – 3D-printed biopolymer-based manufactured parts for healthcare systems; (A) CNF/GelMA-based composite used to develop 3D-printed nose structure (adapted with permission from [408]); (B) 3D-printed surgical instruments including scalpel handle, hemostats, needle drivers, forceps nylon surgical set (adapted with permission from [409], copyright 2016 Société Internationale de Chirurgie, part of Springer Nature); (C) 3D-printed biopolymer stent (adapted with permission from [410], copyright 2017, Mary Ann Liebert, Inc.); (D) 3D-printed anatomical models PDLLA-based mandibular model (adapted with permission from [411], copyright 2020 Elsevier Ltd.); (E) 3D-printed denture containing HA-loaded PEGDA resins (adapted with permission from [412], copyright 2021, Biomedical Engineering Society part of Springer Nature); (F) 3D-printed alginate/CNF-based human ear model (adapted with permission from [413], copyright 2015 American Chemical Society); (G) Exo-prostheses: multifunctional prosthetic 3D-printed hand prototype fabricated through fiber-reinforced nylon (adapted with permission from [414], copyright 2014, Springer Science Business Media Dordrecht); (H) Personalized medical 3D-printed PHBH/CNC-based device for finger dislocation (adapted with permission from [416], copyright 2020 American Chemical Society); (I) 3D-printed implanted nerve scaffold NGF gradient for sensory path signals and GDNF gradient for motor path signals in the scaffold (adapted with permission from [415], copyright 2015 WILEY-VCH Verlag GmbH); (J) 3D-printed biomimetic cochleae (adapted from [417], under the Creative Commons Attribution License 4.0).

Biodegradable polymers should fulfill the safety standards, which require long-term and rigorous efforts. Furthermore, there is a need to modulate the degradation rate of the developed scaffolds for providing appropriate mechanical support to the regenerated tissues. The use of biopolymers for soft and hard tissues requires collaborative efforts of material scientists and researchers of relevant fields. There is a need to further explore a few perspectives for 3D-printed biodegradable polymers including mechanical properties and smart mechanisms for their degradability in the complex natural micro-environment. For instance, a largely material extrusion-based technique has been

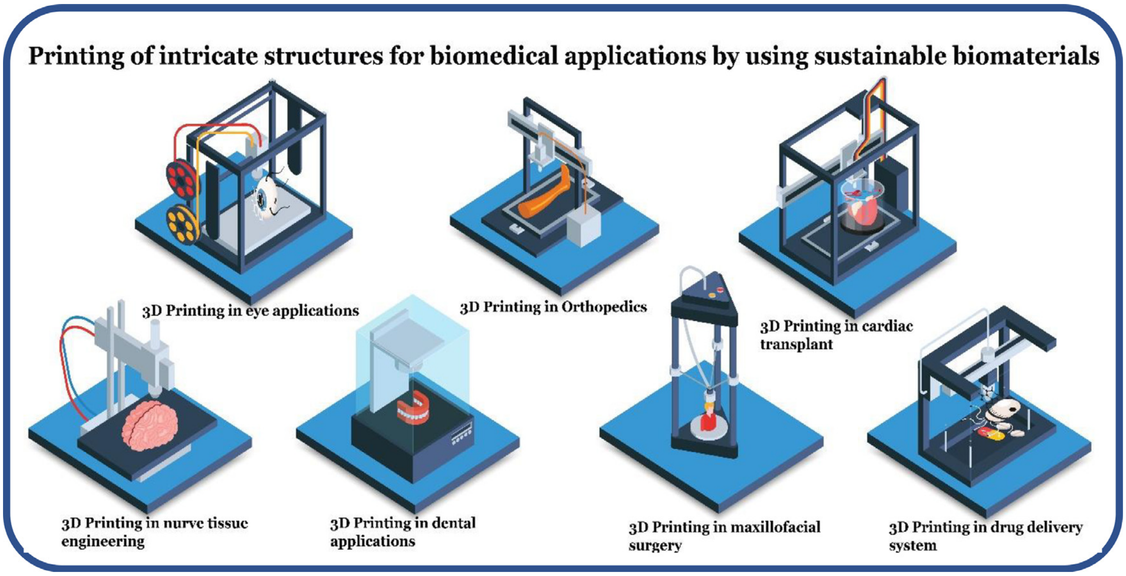


Fig. 17 – Glimpse of future of 3D-printed biopolymer composite in different applications.

widely employed for scaffold manufacturing [427]. However, this technique is not flexible enough to load fillers. Hence, it cannot achieve the required mechanical characteristics and biocompatibility. These novel avenues require insightful exploration for developing efficient tissue scaffolds.

Biopolymer composites can contribute to healthcare systems, due to their improved biodegradability, biocompatibility, renewability, sustainability and bioresorbability [428]. Furthermore, insightful comprehension of the composition of biopolymers along with *in vitro* and *in vivo* analyses will be helpful in producing novel hierarchical scaffolds. Fig. 17 shows the future of 3D printing biopolymers in different biomedical applications. Currently, many 3D printing technologies are employed to develop biodegradable-based polymer scaffolds [429], however, their actual utilization on the commercial scale depends on the fulfillment of different scaffolds criteria including mechanical integrity, thermal stability, chemical composition and biological characteristics. Additionally, the biological cell growth or adhesions with scaffolds is imperative to boost their clinical applications. Therefore, it is essential to further investigate and characterize additively manufactured biopolymer-based scaffolds with a focus on establishing their clinical role in BTE and other biomedical applications.

There is a need to develop biopolymer-based composite tissue grafts for addressing the issues of tissue interfaces including tendon-to-bone, ligament-to-bone, and cartilage-to-bone. Sustainable gradient biomaterials with anisotropic structural properties will help to reestablish tissue connectivity, and function as well as improve long-term clinical outcomes. Machine learning and artificial intelligence may also help to adjust the chemical structure of biopolymer composites for developing gradient tissue constructs.

The availability of appropriate biopolymers for the 3D printing is still limited compared to the materials available for traditional fabrication techniques. There is a need to evaluate further biomaterials for achieving more feasible combinations. By overcoming this challenge, the utilization of 3D printing technology will be increased in the pharmaceutical industry. Additionally, shape-recovery polymers and hydrogels also exhibited tremendous potentials for the pharmaceutical sector. 3D bioprinting technologies are extensively applied to develop intricate tissue structures through a controlled and automated approach [430]. However, the dynamic behavior of tissues cannot be precisely imitated by the presently manufactured structures. Additionally, tissue structures may undergo conformational changes during tissue repair and regeneration [431]. Consequently, time-dependent stimuli response can be employed in the 3D-printed tissues to ensure their structural transformations.

In addition to this, a novel 4D bioprinting technology has been devised by researchers via cell traction forces and stimuli-responsive bioactive materials especially smart biopolymers that help to construct tissues of dynamic nature [432]. This technology is highly suitable to develop intricate dynamic structures, smart medical devices or complex human organs. However, the concept of 4D bioprinting is still in the nascent stage and its realization in clinical applications is limited. Moreover, it is extremely difficult to predict the deformation of 4D printing due to the lack of computational modeling. Similarly, there is a need to develop bioink materials for 4D printing by considering their biocompatibility and stiffness. Furthermore, 4D bioprinting requires further research on multiple-responsive stimuli, as *in vivo* environments might possess more than one stimulus. Additionally, valiant efforts are worth devoting to developing biopolymer-based products for the biomedical sector through 4D printing in certain conditions where unresponsiveness of the 4D-printed parts is required for certain stimuli including temperature and pH.

To conclude, both natural and synthetic biopolymers have exceptional utilizations in the 3D printing, due to their biodegradability, renewability and biocompatibility. These polymers can be used to repair/develop ears, bones, heart

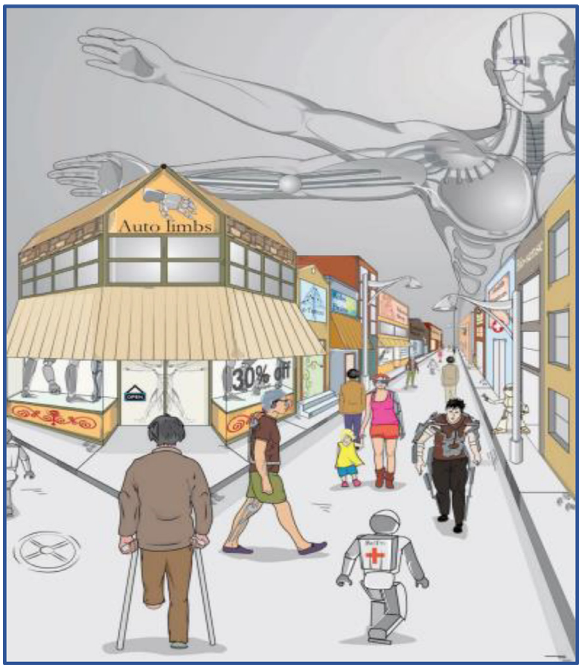


Fig. 18 – Recent developments in sustainable biomaterials are leading towards a cybernetic future (adapted with permission from [433], copyright 2018 Wiley-VCH GmbH).

valves, stents and organs, as well as can help to produce medical equipment. Furthermore, the implants exhibit the necessary deformable and soft characteristics to perfectly align with the native tissues. The integration of bioelectronics with the human body will take this world towards a cybernetic future, as illustrated in Fig. 18. Biopolymer-based scaffolds will help to treat patients with organ or tissue malfunction, due to different factors and road accidents, cancers, injuries, trauma, burn diseases, metabolic disorders and war injuries. Artificial parts have the same biological and mechanical properties as organs, which are employed as life saviors in the case of a shortage of donors at a crucial time.

Conficts of interest

The authors declare no conflict of interest.

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