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Additive Manufacturing of Hydrogels in Tissue Engineering

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ABSTRACT

Systematically review the development of 3D printing, describe the area of 3D printing hydrogel research, and describe the development of 3D printing hydrogel. Different hydrogels have applications in engineering, and other additive manufacturing procedures can be used to create biomedical products. However, due to its lack of structural strength, several additives are added to improve the hydrogel matrix's mechanical properties. This review article thoroughly discusses using different hydrogels, such as organic, synthetic, and composite, as potential bio-ink materials for tissue engineering. We extensively discussed various hydrogel sources, how they are made, and their unique features for tissue engineering. The fundamental and technological difficulties of producing hydrogel bio-ink materials for tissue engineering using additive manufacturing are also discussed. The current development of 3D printing on hydrogels has made incredible progress.

1. Introduction

Additive manufacturing, sometimes called "3D printing," is a method for making three-dimensional objects by adding layers of materials. The method has been used in many fields, such as engineering, architecture, and, more recently, hydrogel-making. Hydrogels are soft, flexible polymers that absorb water [1]. They are used in many biomedical applications, such as drug delivery, wound healing, tissue engineering, and regenerative medicine. In modern engineering processes, designers, engineers, and technicians often use computer-aided technologies to test their products at each stage of the product development cycle [2-3]. These computer-aided technologies include the following: Computer-aided design (CAD), computer-aided manufacturing (CAM), and computer-aided engineering (CAE) [4]. Peiyan Shen et al. [5] used CAD to create a 3D model of the hydrogel-based sensor, CAM to produce the tool paths required to print the sensor, and CAE to simulate the printing process and improve the design. CAD, CAM, and CAE were used to make the finished sensor, an innovative medical tool that could accurately track glucose levels in real time.

Several methods can be used to make polymer-based hydrogels, including solution casting, gelation, and electrospinning. To make complicated hydrogel structures with great precision and reproducibility, 3D printing technology has come to light as a successful and promising method [6]. Using 3D printing to make hydrogels has led to the developing of ideas and methods for tissue engineering and regenerative medicine. Manufacturing hydrogels can make use of a variety of 3D printing techniques. According to the International Standards

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Organization and American Society for Testing and Materials standards, there are seven major categories of additive manufacturing/three-dimensional printing (AM/3DP) processes (ISO/ASTM 52900:2015). For a brief explanation of each AM process, see fused filament fabrication (FFF) and modeling (FDM) [7-8]. Material jetting (MJ), binder jetting (BJ), sheet lamination (SL), vat photopolymerization (VP), powder bed fusion (PBF), directed energy deposition (DED), and material extrusion are the first seven methods (ME) [9-10]. It can be changed quickly and is easy to use, and extrusion-based printing is the most common way to make hydrogels. In extrusion-based printing, hydrogel ink is pushed through a nozzle and laid down layer by layer to create a 3D structure [11-12]. Usually, ink is made from a hydrogel precursor solution, which can be crosslinked to develop a stable hydrogel structure [13]. Hydrogels are manufactured additively using the stereographic method, a 3D printing process. This method uses a stereolithography printer (SLA), direct ink writing (DIW), and photosensitive resin to build up hydrogel structures layer by layer. UV radiation is then used to crosslink the hydrogel, creating a solid, biocompatible structure. This method is promising for making biomedical devices and scaffolds for tissue engineering because it makes it possible to make complicated shapes with high resolution and accuracy [14].

Fused deposition modeling (FDM), a popular type of additive manufacturing, is used to make three-dimensional objects. This method deposits molten material one layer at a time to build a finished good. In the case of hydrogels, FDM has been used to make a wide range of biomedical devices, such as scaffolds for tissue engineering, drug delivery systems, and biosensors. The method is a good choice for working with hydrogels because it is flexible, cheap, and accurate [15].

This paper presents an overview of many kinds of hydrogel precursor solutions that can be used for 3D printing. These include natural and synthetic polymers as well as hybrid materials. Gelatin, collagen, chitosan, and alginate are natural polymers frequently utilized to make hydrogels because of their biocompatibility, biodegradability, and capacity to replicate the extracellular matrix (ECM) in nature. Due to their adaptable mechanical qualities, chemical stability, and simplicity of modification, synthetic polymers, including polyethylene glycol (PEG), polyvinyl alcohol (PVA), and polycaprolactone (PCL), are also utilized to make hydrogels [16]. Hybrid materials, like natural and synthetic polymer blends, are increasingly used in making hydrogels because they have a more comprehensive range of mechanical, tribological, and biological properties. [17].

2. 3D Printing Technologies for Hydrogels

A rapidly developing technology called 3D printing makes producing complex objects from digital models possible. There are numerous 3D printing technologies available, each with specific benefits and drawbacks. Stereolithography (SLA), Digital Light Processing (DLP), Inkjet and Direct Ink Writing (DIW) are four standard 3D printing methods in hydrogels. In the late 1980s, 3D Systems invented stereolithography (SLA), one of the earliest 3D printing technologies. SLA [18] uses a pot filled with liquid photopolymer resin, which hardens when exposed to UV light. The pattern of the object to be printed is traced onto the surface of the liquid resin using a UV laser, which causes it to solidify and adhere to the prior layer. Layer by layer, this process is continued until the thing is finished. SLA is perfect for producing prototypes and models for sectors like automotive, aerospace, and medicine since it can produce items with flawless surface quality and high levels of precision. SLA has significant drawbacks, though, like the requirement for support structures to keep the item from collapsing when printing [19]. The support structures, which can take time to remove, might affect the surface finish of the object. SLA can only print using photopolymer resins, which can be pricey and have limited material qualities. SLA and DLP use photopolymer resin to produce objects. But DLP does not use a laser to expose the resin to light [20]. Instead, it uses a digital light projector. The projected light pattern causes the resin to solidify and take on the appropriate shape. DLP is another type of vat polymerization printing process, and it can print faster and make more oversized items without sacrificing accuracy [21]. DLP is a fantastic option for manufacturing huge volumes of things since it is less likely to have faults and defects. Removing support structures from DLP, like SLA, can take some time. DIW [22] is a type of 3D printing that builds things layer by layer from a liquid feedstock. Droplets of the feedstock are deposited onto a substrate with the help of a nozzle, and the substrate is then heated or lit up to cure it.

Again, and over again, until the thing is finished, this process is performed [23].

DIW has many advantages over SLA and DLP, such as the ability to print on ceramics, metals, and polymers, among other things. The technology also enables the production of objects with intricate interior structures and geometries. Developing medical implants, devices, and electrical components is a specialty of DIW [24]. 3D printing innovations like SLA, DLP, and DIW have changed the industrial sector by making it possible to create complicated products with extreme precision and accuracy. Each method has pros and cons, and the best one depends on the project's specifics. DLP is great for quickly generating vast volumes of items, while SLA is great for producing highly detailed products with a flawless surface finish. DIW is ideally suited for fabricating intricate things from a variety of materials. In the years to come, we may anticipate even more exciting advancements in 3D printing as technology progresses (**Fig. 1**) [25].

A non-contact printing method called inkjet printing uses tiny ink droplets to reproduce digital data from a computer on a surface [26]. Drop-on-demand and continuous inkjet systems are two categories of inkjet printers. A constant stream of ink leaves the print head (nozzle) under pressure in a continuous jet system to form a jet. Electrical impulses that control the direction of travel can then fragment the jet into droplets. When an actuator is pulsed, a single droplet of predetermined ink volume can be ejected through a piezoelectric or thermal head [27] in a drop-on-demand system. In customized polymer deposition, inkjet printing is a crucial technology. The method allows for printing numerous materials into structures with high precision and a resolution of 50–500µm, making it perfect for manufacturing complicated scaffolds [28].

A highly hydrophilic, three-dimensionally networked gel called hydrogel may quickly swell in water and hold onto a significant amount of water without dissolving while in this state.

Hydrogels can absorb a lot of water because of their crosslinked networks, and the amount of water absorbed is directly related to the level of crosslinking. Water absorption decreases as the degree of crosslinking increases. This characteristic is similar to soft tissue.

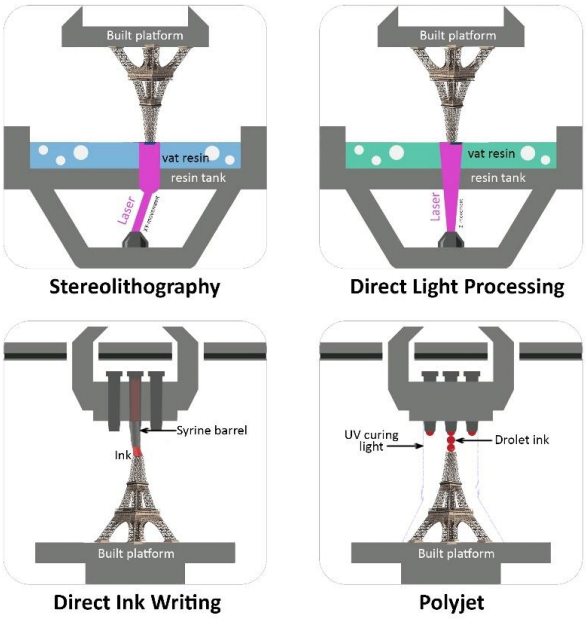

Fig. 1. Schematic summary of Additive manufacturing techniques in hydrogels: stereolithography (SLA), direct light processing (DLP), direct ink writing (DIW) and Inkjet (polyjet).

There are several ways to group hydrogels into different groups. Based on the differences in how the networks of hydrogels are connected, they can be split into two groups: physical gels and chemical gels (Figure 2). Electrostatic interactions, hydrogen bonds, and chain entanglements are just a few examples of the physical forces that cause physical gels to form. This gel is non-permanent and can be converted into a solution by heating; it is also known as a pseudo- or thermos reversible gel. Synthetic hydrogels [29] can have a wide range of properties by changing the type of polymer and the number of cross-links. Cross-linking synthetic polymers like poly (ethylene glycol) or poly (acrylic acid) results in natural hydrogels [30] made from natural polymers like collagen, chitosan, and alginate; these hydrogels often have excellent biocompatibility and biodegradability. pH-responsive hydrogels [31] changing the pH of the environment is one way to control how quickly a drug is released, and these hydrogels can help with that. They modify their swelling behavior in response to pH variations. Temperature-responsive hydrogels [32] have swelling changes in response to changes in temperature, making these hydrogels great for things like intelligent wound dressings that can respond to

changes in body temperature. Double-network hydrogels [33] are made of two networks of polymers with different properties, like stiffness and toughness, so these hydrogels have better mechanical properties. Self-healing hydrogels [34] can fix themselves when they get hurt. This makes them helpful in making artificial cartilage and treating wounds. Conductive hydrogels [35] can be used in applications like biosensors and neural interfaces since they can conduct electricity. Injectable hydrogels [36] may be injected into the body with minimal trauma and are valid for tissue engineering and drug delivery, among other things.

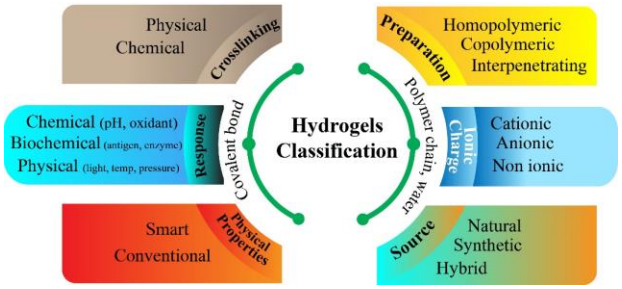

Fig. 2. A schematic illustration of the classification of hydrogels.

3. Properties of hydrogels in 3D printing

3.1 Degradability and biocompatibility

Due to its capacity to create complex structures with high resolution and controlled porosity, hydrogel 3D printing has become more prevalent in tissue engineering and regenerative medicine. However, the biocompatibility and degradability of the hydrogel 3D printing materials are essential for their use in living things. Biocompatibility is the ability of a material to get along with living cells and tissues without causing damage or inflammation. The biocompatibility of 3D printing materials made of hydrogel has been proven in numerous studies. For instance, Shen et al. [36] demonstrated that human mesenchymal stem cells could adhere to, proliferate, and differentiate on a hydrogel scaffold made of polyethylene glycol diacrylate and gelatin methacrylate. The biocompatibility of a 3D-printed hydrogel scaffold made of chitosan and gelatin was also shown in work by Jialin Chen et al. [37] using mouse fibroblasts and human umbilical vein endothelial cells.

Another crucial characteristic of hydrogel 3D printing materials is degradability. Since natural tissue can replace them over time, hydrogels that break down are perfect for tissue engineering and regenerative medicine. Hydrogel 3D printing materials break down by adding degradable parts to the polymer chains or changing how much they are cross-linked (Figure 3). For instance, Jian Guan et al. [38] showed that a hydrogel made of 3D-printed polyethylene glycol diacrylate and gelatin methacrylate could degrade in vitro, with over 50% of the scaffold disintegrating after 21 days. Similarly, Lin Huang et al. [39] demonstrated that a 3D-printed hydrogel scaffold made of poly (ethylene glycol)-diacrylate and hyaluronic acid could degrade in vitro, with over 70% of the scaffold dissolving after 28 days. For tissue engineering and regenerative medicine to work, 3D-printed hydrogel materials must be biocompatible and break down over time (**Figure 3**). Several studies have shown that hydrogel 3D printing materials are biocompatible and biodegradable, giving them a good chance for future medical use.

3.2 Mechanical Strength

A hydrogel is a three-dimensional network of chains made of hydrophilic polymers that can contain water.

Hydrogels have received much attention in the biomedical industries, including drug delivery, tissue engineering, wound healing, and biosensors, because of their distinctive physical and chemical features. One of the most significant elements affecting the application of hydrogels is their mechanical strength. Hydrogels' chemical makeup, degree of crosslinking, and preparation with solvent all affect how mechanically robust they are. Crosslinking density is one of the essential things that significantly affects the mechanical strength of hydrogels. Hydrogels with high crosslinking densities have greater mechanical strength [40]. Researchers have used many different methods to study the mechanical properties of hydrogels, such as tensile testing, compression testing, and indentation testing. Compression testing is often used to measure the compressive modulus of

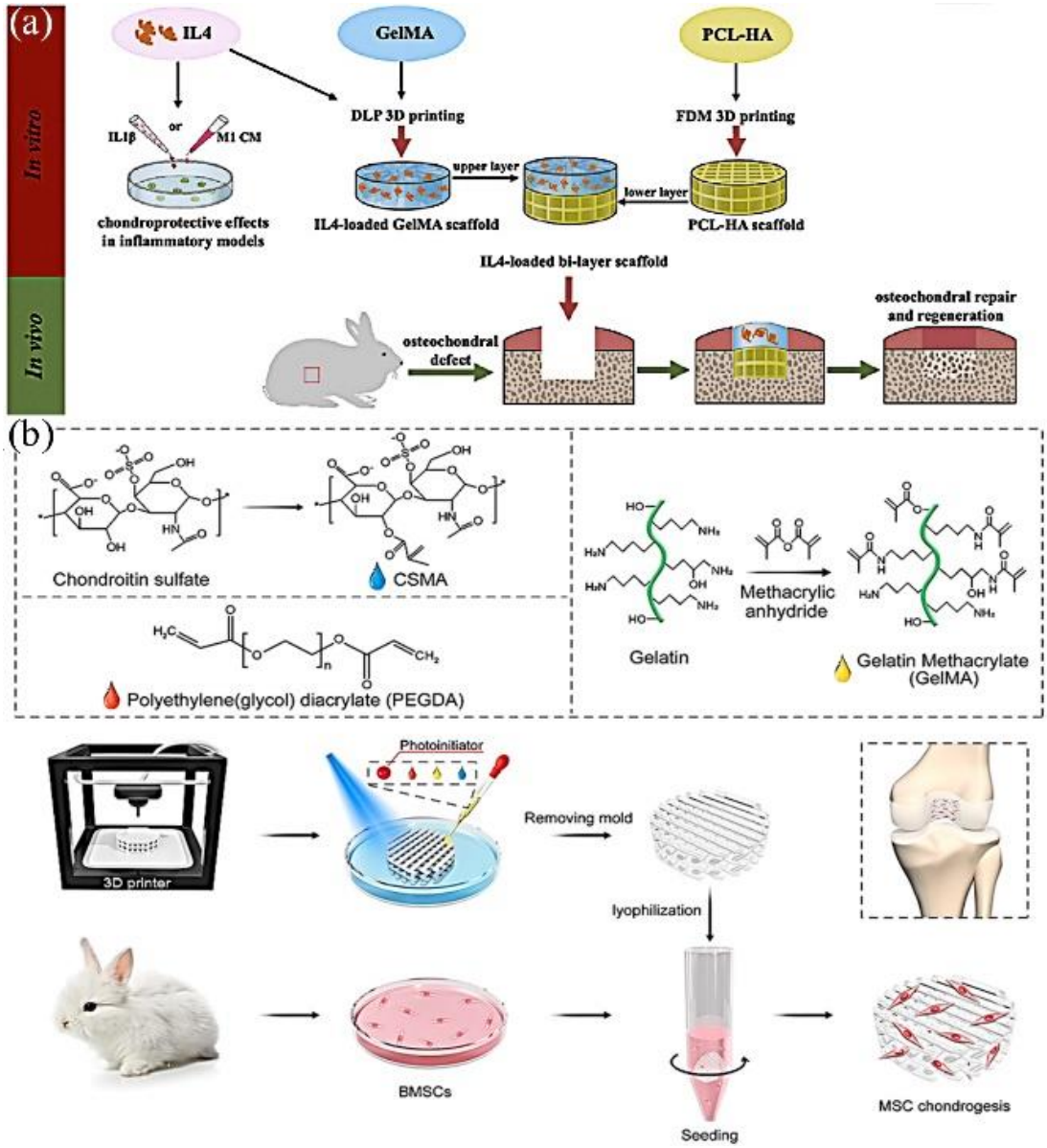

Fig. 3. (a) The creation of 3D-printed hydrogel scaffolds is shown schematically in [38] (b) the fabrication of hybrid scaffolds: A schematic representation of the synthetic approach for CSMA and GelMA, as well as a 3D-printed scaffold that has cells isolated and implanted on it [39].

hydrogels, which measures how well they don't change shape when compressed [41]. Breakthroughs have been made to make more robust, flexible, and tougher hydrogels. These hydrogels were created by strengthening the hydrogel network with nanoparticles, nanofibers, or carbon nanotubes. These strengthening chemicals add more structural support, improving hydrogels' mechanical properties (Fig. 4) [42].

3.3 Viscosity

The chemical makeup of hydrogels, the level of crosslinking, and the way the solvent is prepared all affect their viscosity, which is an important physical property. Viscosity, frequently determined using techniques like rheometry, is a fluid's resistance to flowing. For hydrogels to be used in biomedical settings, their viscosity is essential. For example, the ability of hydrogels to flow and release drugs at a controlled rate is critical to how well they work as drug delivery systems. The viscosity of hydrogels can also affect their mechanical characteristics, such as their elasticity and stiffness [43]. The molecular weight of the polymer chains, the level of crosslinking, and the concentration of the polymer in the solvent can all impact how viscous hydrogels are. For instance,

raising the solvent's polymer concentration can enhance the hydrogel's viscosity [44]. Much progress has been made in creating hydrogels with variable viscosity properties, including smart hydrogels that can react to environmental cues like pH or temperature. Molecular groups that respond to stimuli, such as ionic or hydrophobic groups, were added to the network of hydrogels to make these hydrogels [45].

3.4 Printability

The ability of hydrogels to be manufactured into intricate geometries with great precision and accuracy using 3D printing technology is known as "printability." Their suitability for 3D printing-based biomedical applications like tissue engineering and medication delivery depends heavily on this. Hydrogels can be printed differently depending on their chemical makeup, degree of crosslinking, mechanical properties, and the 3D printing process used. For example, surface modification techniques and chemicals that make things stronger have created hydrogels that are easier to print on [46].

3.5.1 Swelling: The high water content of hydrogels makes swelling one of their distinctive physical characteristics. Hydrogels can grow or shrink when their surroundings' pH, temperature, or ionic strength change. The degree of crosslinking, chemical makeup, and water content of the hydrogel all affect how much it swells. The ability of hydrogels to swell can be used for several biological purposes, such as drug delivery, tissue engineering, and biosensors. Knowing how hydrogels swell is essential to building and operating them well [49]. The following equation can be used to determine the swelling ratio (SR) at each time point: [50]

$$SR = (W_s - W_d) / W_d \text{ ---------- (i)}$$

Where W_d is the weight of the original freeze-dried hydrogel, and Ws is the weight of the expanded hydrogel at time t. The equilibrium-swelling ratio (ESR), the SR when the weight of the swollen hydrogel stays constant, can also be quantified using this method.

3.5.2 Porosity: Porosity is the fact that there are connected holes, or pores, in the hydrogel matrix. This is an essential physical property of hydrogels. Modifying the degree of crosslinking, chemical composition, and processing conditions can control hydrogel porosity. Because hydrogels have holes that can help move nutrients, oxygen, and waste products, these materials are appealing for tissue engineering and medication delivery. The porosity of hydrogels can also affect their mechanical properties, how they swell, and how fast they break down. Because of this, it is essential to understand how porous hydrogels are to design and optimize them for specific uses (**Figure 5**) [51-52].

3.5.3 Crystallinity: Most hydrogels are amorphous and don't have a crystalline structure because the polymer chains that make them up are arranged randomly. Still, some hydrogels can be crystalline if certain polymer chains or crosslinking happen in certain situations. In hydrogels, the degree of crystallinity can impact how they behave as they swell, how quickly they degrade, and other aspects. For example, compared to amorphous hydrogels, highly crystalline hydrogels may be stiffer and swell less than amorphous hydrogels. Techniques like X-ray diffraction and differential scanning calorimetry can be used to examine the presence of crystalline domains inside hydrogels [53].

3.5 Physical Properties

Hydrogels are unique materials with three-dimensional networks of hydrophilic polymer chains and unusual physical traits like high water content, biocompatibility, and tunable mechanical properties. Also, they can respond to stimuli by growing or shrinking in response to pH, temperature, or ionic strength changes. Hydrogels' mechanical properties, like their elasticity, strength, and stiffness, can be changed by changing their chemical makeup, level of crosslinking, and amount of water. The surface of hydrogels can also be altered to have specific properties, such as sticking, breaking down, or being compatible with living things [48].

PSS were evaluated rheologically and for printability. Optical microscope photos of 3.75% / 7.5% w/v 3D-printed objects Gelatin that have been temperature-pretreated and modified with 0.1 and 0.2mPy is used to create ADA-GEL (AG). As a standard, Pluronic F127 (40% wt) was used. Scale bars: 1 mm at the top, 500 µm at the bottom [47].

3.6 Chemical Properties: Different types of analysis can be used to find out about the chemical properties of hydrogels. These include gel permeation chromatography (GPC), nuclear magnetic resonance

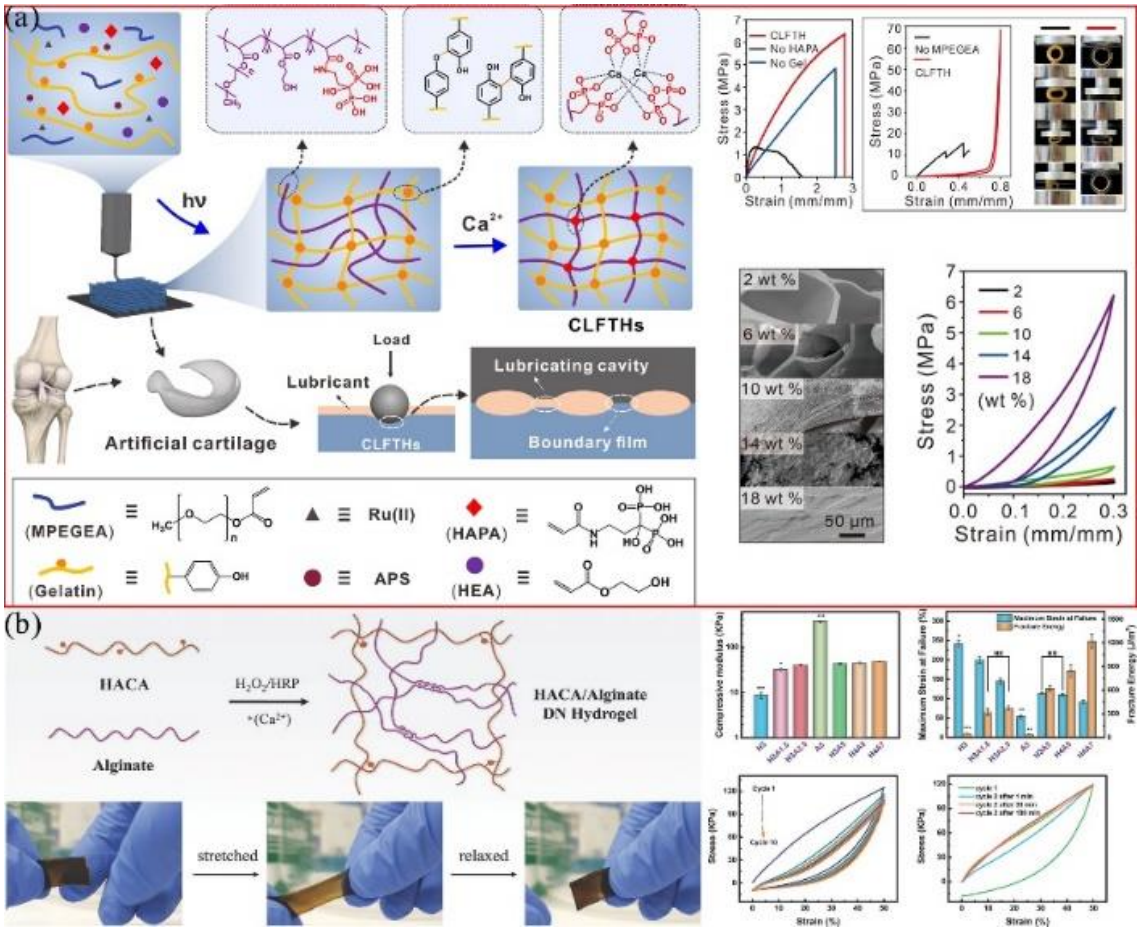

Fig. 4. (a) Adaptable CLFTH fabrication and use in biomimetic cartilage tissue engineering are shown schematically. Highly effective ROP3P is suitable for the flexible design of customizable CLFTHs for biomimetic cartilage applications and is compatible with standard 3D printing procedures and typical tensile stress–strain curves for the hydrogel samples of the CLFTH and the controls, which excluded HAPA and Gel, respectively [41], and (b) HACA/alginate DN hydrogel preparation and The compressive modulus of the single and DN hydrogels made of HACA/alginate, Maximum strain and fracture energy of hydrogels and single HACA/alginate, Ten continuous cyclic tensile tests on hydrogels containing [44].

(NMR), and Fourier transform infrared spectroscopy (FTIR). By looking at the infrared radiation that functional groups in the hydrogel matrix absorb, FTIR spectroscopy is a common way to find out what chemicals are in a hydrogel. Another powerful method that can reveal details about the molecular makeup and chemical structure of hydrogels is NMR spectroscopy. A size exclusion chromatography method called GPC can examine hydrogels' molecular weight distribution and crosslinking density.

The chitosan hydrogels' chemical makeup was looked at with FTIR to see if they had certain functional groups, like amino and hydroxyl. GPC was used to look at the crosslinking density of the hydrogels, and it was found that as the crosslinking density went up, the molecular weight distribution went down. NMR spectroscopy was also used to examine the hydrogels' chemical makeup and determine if any acetic acid was left over from making chitosan.

It is essential to know what hydrogels are made of chemically so that they can be designed and optimized for specific biomedical uses. Researchers can use different methods to analyze hydrogels to learn more about their chemical makeup, work, and how they are put together. This can improve hydrogels' biocompatibility, stability, and drug delivery properties [54-55].

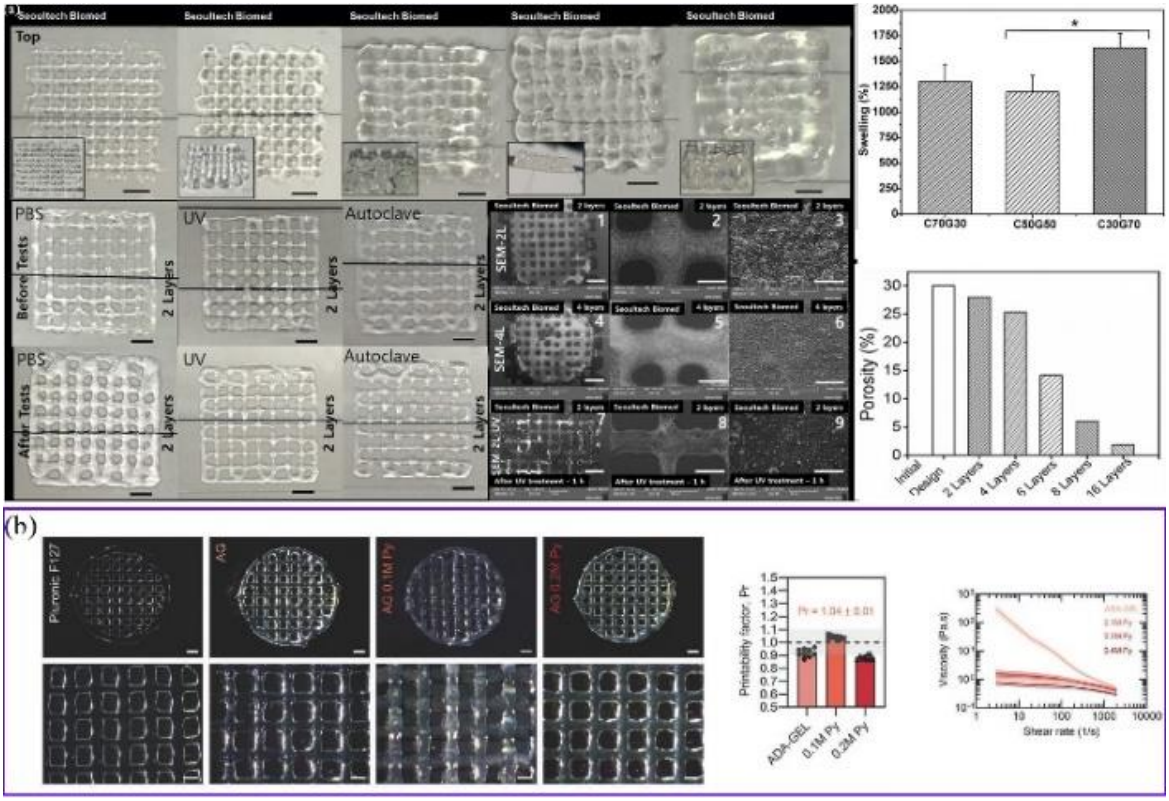

Fig. 5. (a) The C50G50 hydrogels are made of carboxymethyl cellulose (CMC) and glycol chitosan (GC). Images of 3D-printed samples with lattice structures before and after stability tests with PBS, UV irradiation, and autoclaving, digital pictures of the two-layer structures were taken. SEM pictures of samples with two-layer structures after UV treatment for one hour were also taken. The graphs on the right show the printed layers' strut diameters with the printed structures' length (mm) and porosity [46], and (b) Precursors of the conductive hydrogel ADA-GEL-Py: PSS were evaluated rheologically and for printability. Optical microscope photos of 3.75% / 7.5% w/v 3D-printed objects Gelatin that have been temperature-pretreated and modified with 0.1 and 0.2mPy are used to create ADA-GEL (AG). As a standard, Pluronic F127 (40% wt) was used. Scale bars: 1 mm at the top, 500 µm at the bottom [47].

3.7 Rheological properties: Hydrogels are three-dimensional polymer networks that can hold and absorb water without losing shape. Due to their distinctive qualities like high water content, biocompatibility, and mechanical strength, these materials have been extensively used in various sectors, including biomedical engineering, drug delivery, tissue engineering, and environmental science. Rheological characteristics, which explain how hydrogels deform and flow under stress, are a crucial component of hydrogels. Rheological measurements can tell a lot about the mechanical properties of hydrogels, such as their elasticity, viscosity, and shear modulus. A rheometer is a commonly used tool for evaluating the rheological characteristics of hydrogels. A rheometer uses controlled stress or strain to deform or flow the sample and then measures the change. Depending on the type of hydrogel and how it will be used, the rheometer can also apply shear, compression, or extensional stress.

Yunong Ao et al. [56] looked at the rheological properties of a hydrogel made of hyaluronic acid and chondroitin sulfate to help build cartilage. At different strain rates and amplitudes, a shear rheometer was used to find the hydrogel's loss modulus (G") and storage modulus (G'). The results showed that the hydrogel behaves differently depending on the frequency, with a higher G' value at lower frequencies. This indicates that the material is more resilient mechanically at low deformation rates. Rheological measurements are needed to describe how hydrogels behave mechanically and can also give important information about desiging and improving these materials.

4.1 Hydrogels' 3D printing polymer composition

Three-dimensional polymeric networks with a high water content are called hydrogels. They are widely used in biomedical and tissue engineering applications because they have unique properties like good water retention, biocompatibility, and elastic mechanical properties. The 3D printing of hydrogels has become a possible way to make complex structures and materials that can be used for many different things. This paper aims to provide an overview of the polymer composition used for 3D printing hydrogels.

4.1 Polymer Composition for 3D Printing of Hydrogels

Natural hydrogels are made up of biopolymers that are extracted from natural sources. These polymers can be changed to have a wide range of mechanical and biological properties. They are also safe for living things and break down naturally. Alginate, chitosan, collagen, gelatin, hyaluronic acid, and fibrin are some examples of natural hydrogels. Alginate is one of the most popular natural hydrogels for 3D printing because it is easy to crosslink with calcium ions and other divalent cations. Lee et al. [57] said 3D printing has been used to make vascularized tissues, wound dressings, and drug delivery systems. Synthetic hydrogels are made of manufactured polymers with specific properties, such as being biocompatible and biodegradable, and have mechanical properties that can be changed. Synthetic hydrogels are created with chemicals like poly(ethylene glycol) (PEG), poly(N-isopropyl acrylamide) (PNIPAAm), poly(vinyl alcohol) (PVA), and poly(ethylene oxide) (PEO). PEG is one of the most common synthetic hydrogels used for 3D printing because it can be crosslinked in different ways, such as through light-activated crosslinking or Michael addition reactions. Combining polymers made in a lab with those from nature creates hybrid hydrogels. Two types of hybrid hydrogels are gelatin-methacryloyl (GelMA), made up of gelatin and methacrylate groups, and alginate-PEG made up of alginate and PEG. GelMA is one of the most commonly used hybrid hydrogels for 3D printing. It is biocompatible, has elastic mechanical properties, and can help cells grow and multiply [58]. Bioprinting is a type of 3D printing that uses living cells and biomaterials to make complex tissue structures. For bioprinting, the mix of polymers can differ depending on the use and the mechanical and biological properties needed. Extracellular matrix (ECM) proteins like collagen and fibrin and synthetic polymers like PEG and PVA are examples of bioprinting polymers. Bioprinting has been used to make cartilage, bone, skin, and blood vessels, among other things (**Fig. 6**) [59].

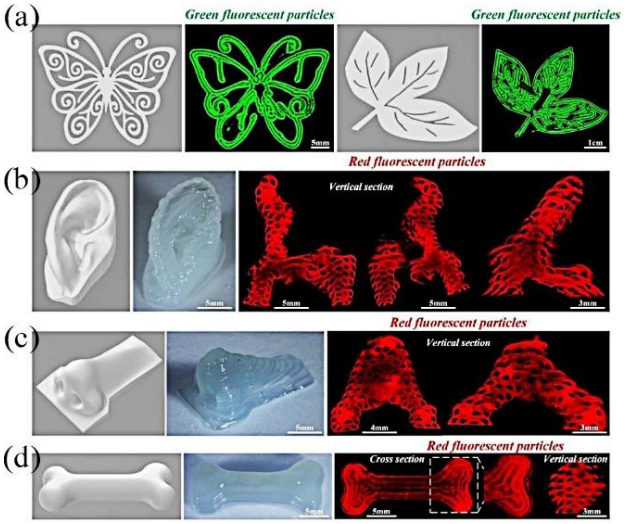

Fig. 6. (a) 2D vascular-channeled bioprinted butterfly and creates patterns, (b) solidifying ear bioprinted with vascular channels, (c) Solid nose with vascular channels that was bioprinted, and (d) Solid bone with vascular portions that was bioprinted [59].

Bioprinting can accurately stack cells and materials (bioinks) into three-dimensional complex structures. 3D bioprinting has been used extensively in biomedical fields like tissue regeneration and building pathological models. A variety of bioprinting technologies have been developed. Among them, the most common printing method is extrusion bioprinting, which controls the extrusion and assembly of bio-ink through digital design and then quickly shapes it to maintain the stability and fidelity of the printed structure. Bio-inks for extrusion bioprinting need to satisfy both printability and functionality, which are often in conflict with each other. For example, a hydrogel ink with a higher concentration (or viscosity) is more conducive to microfilament extrusion and structural stability, thereby achieving higher shape fidelity. Fang et al. [60] reported a cell-laden microgel with superelasticity and a heterogeneous tissue microenvironment glue biphasic bioink. The microgel biphasic bioink consists of two parts: the cell-laden microgel acts as a dispersed phase under close packing to form a first-level network; the hydrogel precursor acts as a continuous phase and penetrates the pores between the microgels **(Figure 7)**. A secondary network is formed between microgels. The ink has excellent rheological properties, shear

thinning, and self-healing properties during the printing process, and the printed structure also has excellent structural stability after cross-linking. Compared with pure hydrogel and pure microsphere bioink, this microgel biphasic bioink exhibits superelasticity and better cyclic tension-compression performance. More importantly, the design strategy of microgel biphasic bio-ink is suitable for various hydrogel materials and cross-linking strategies, including low-viscosity hydrogel inks that are difficult to use with conventional printing technology, which significantly expands the potential of bio-inks.

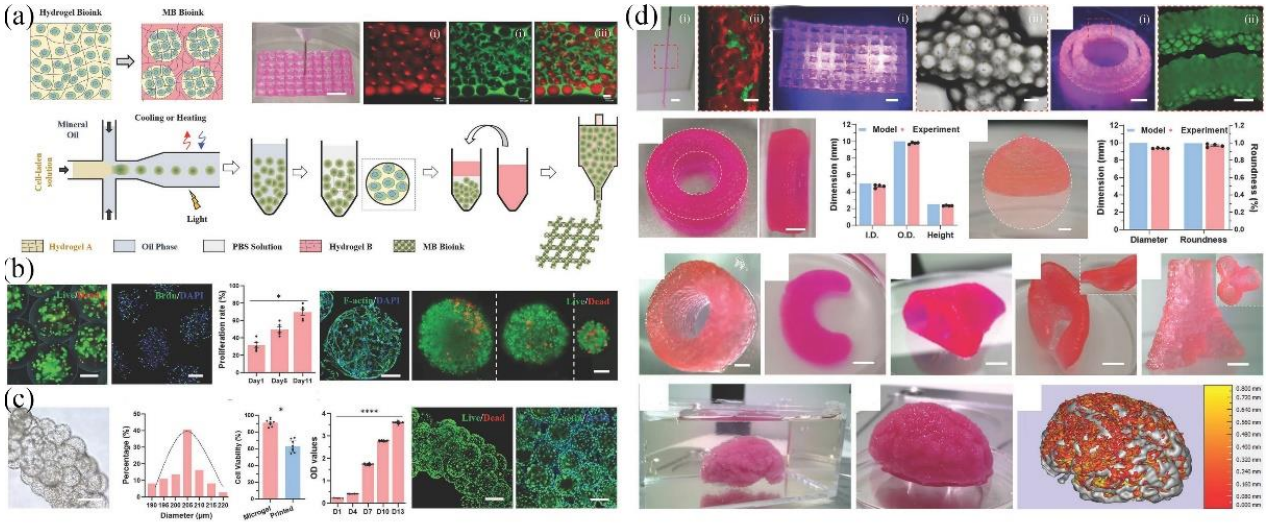

Fig. 7. (a) Cell-laden MB bio-ink fabrication and 3D printing Hydrogel bioink and MB bioink are shown schematically. MB bioink is used to 3D print meshlike structures. The MB bioink has separate microgels (5 wt% GelMA, shown in red) and a continuous polymer network (5wt% GelMA, shown in green), (b) Microgels are used to mark proliferating cells using Brdu staining, (c) The cell proliferation rate within microgels increases with culture time. The vitality of cells before and after printing Cell proliferation rates within MB bio-ink-printed fibers, and (d) MB bioink has 3D printing capacity and realism 3D printed mesh-like structures, double rings, tubular structures (left, top view; right, side view), hemisphere employing MB bioink, big vessel, meniscus, nose, ear, and bronchus, and enlarged view under confocal microscopy. A snapshot of a printed brain model after removing it from the suspension bath. A heat map displaying the geometric difference between the template (gray) and the print (red and orange). [60]

Gowsihan et al. [61] designed the critical role of hydrogels and 3D bioprinting in achieving the biological and structural complexity of bone tissue mimics and their role in guiding stem cell reconstruction (**Figure 8a**). Responsibility for the current stem cell niche. Current obstacles to bone tissue engineering include difficulty in replicating the structure and organization of bone and its dynamic remodeling process (functional and mature vascularization) in providing appropriate organ-level stimulation (mechanical loading and fluid flow). It is critical to overcome the spatial resolution limitations of 3D biomanufacturing technologies and innovate to construct complex hierarchical structures using cell hosts and material formulations. Pan et al. [62] successfully developed polyvinyl alcohol (PVA) + κ-carrageenan by preparing physically cross-linked hydrogels using biocompatible synthetic polymers and natural active macromolecule compound hydrogel ink. With the help of direct ink writing printing technology, precise printing preparation of complex hydrogel structures is achieved, including hydrogel tubes, three-dimensional scaffolds, ears, etc. (**Figure 8b-c**). Through freeze-thaw cycle post-processing technology, a physically cross-linked network is formed in the hydrogel structure, thereby preparing high-strength, swelling-resistant hydrogels. More importantly, the hydrogel is prepared through a purely physical process, with no reaction by-products or residual toxic substances, and κ-carrageenan has good biological activity. The prepared three-dimensional hydrogel scaffold can be directly used for 3D cell culture. , which has significant application value in bone tissue regeneration and skin repair.

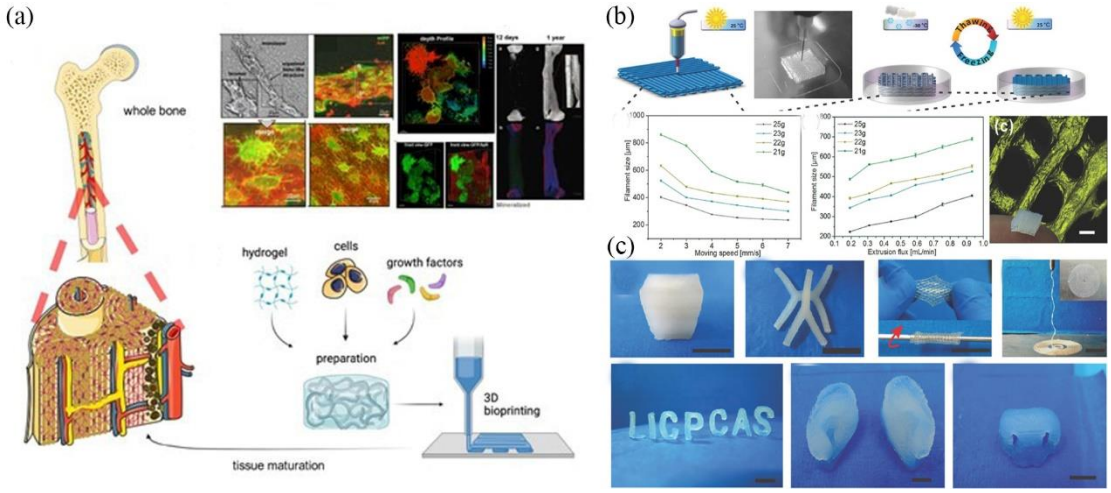

Fig. 8. (a) Bone structure, from entire bone to cortical and trabecular bone, with vascularisation that existing models cannot replicate. In vitro models of highly organized bone-like structures are currently available. Approaches using hydrogels in BTE are depicted schematically, integrating hydrogels (natural or synthetic), cells (mesenchymal stem cells), and growth factors (bone morphogenetic protein 2) with 3D bioprinting to lead to tissue development, [61] (b) Diagrams illustrating the production and postprocessing of 3D printed hydrogel structures, and (c) The printability of hydrogel inks, as well as 3D printed structures and objects. A woodpile-structured hydrogel scaffold and its fluorescence picture. An inverted quadrangular frustum pyramid, dendritic tubes, two-dimensional meshes, a plane spiral, the hydrogel letters "LICP CAS", a pair of ears, and a nose with cavities. [62]

Wang et al. [63] introduced that efficient bone regeneration requires regulation from the nervous system. After discovering that exosomes derived from Schwann cells, the glial cells in the peripheral nervous system, have excellent bone repair effects and great tissue engineering application potential, Schwann cell exosomes were used as the research object, conducted an in-depth discussion on how Schwann cells regulate bone repair through exosomes and related mechanisms and explored the effect of exosomes combined with 3D bioprinting technology in bone tissue engineering (**Figure 9a-b**). The authors highlight the critical role of Schwann cell exosomes in regulating the bone regeneration microenvironment by Schwann cells. It provides a new strategy for tissue engineering construction to promote neurovascularized bone regeneration by enhancing the regulatory effect of the nervous system. The method proposed in this study may be an effective way to improve the repair effect of bone defects inherently accompanied by neurological dysfunction. Nasim Annabi et al. [64] used recombinant human trophin as a bioink that was very flexible and compatible with living things to print complex soft tissues in 3D. A vascularized heart structure was bioprinted, and its function was evaluated in vitro and in vivo (**Figure 9c-f**). The results showed the potential of elastic bioinks to print functional cardiac tissue in 3D printing.

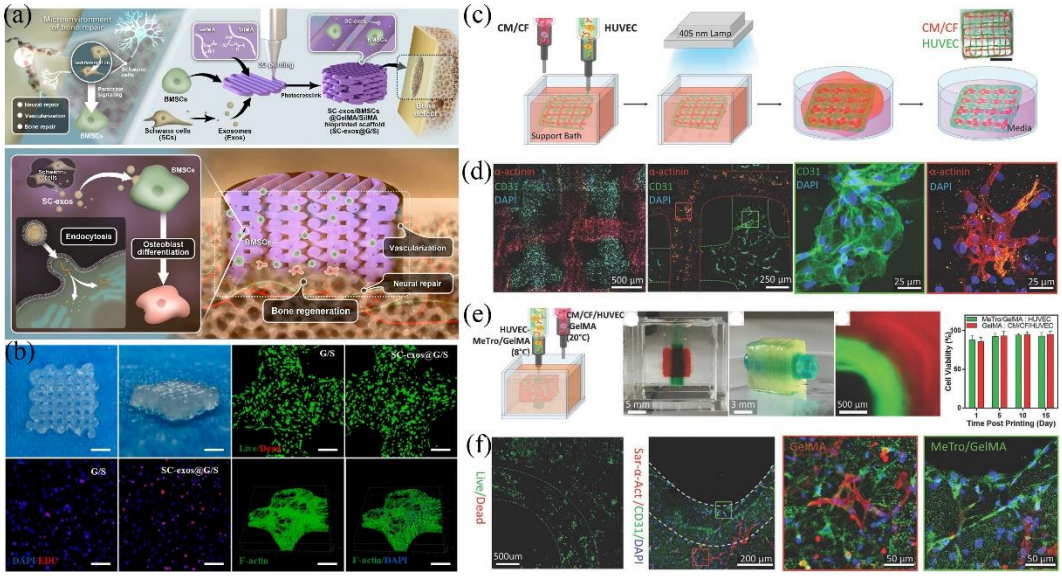

Fig. 9. (a) Diagram illustrating how SCs from the peripheral nervous system regulate the bone regeneration milieu and bone healing via paracrine activities, (b) Bioprinting was employed to build the structures, and the bio-inks used were GelMA, SilMA, SC-exos, and BMSCs cytoskeleton staining in bioprinted constructions with a bioink containing 8% GelMA and 2% SilMA, [63] and (c) Diagram of 3D bioprinting of cell-laden elastic constructions, (d) Red and green boxes indicate bioprinted CMs/CFs and HUVECs, respectively, (e) Fluorescein and rhodamine dyes were applied after 3D bioprinting vascularized heart constructions, photo-cross-linking, and washing processes. The viability of HUVECs, (f) the vascularized heart construct was stained live/dead on day 10 after bioprinting. [64]

Liu et al. [65] explored five themes while discussing 3D printing technology for vascular regeneration: what tissue engineering scaffolds are and how to use them for vascular regeneration, how to model vascular scaffolds in three dimensions, and what blood vessels signify. Commonly used 3D printing materials in stents include standard 3D printing technologies in the manufacturing and clinical transformation of vascular stents. In addition, given the advantages of traditional manufacturing techniques, the paper also discusses other techniques commonly involved in vascular stent preparation, including casting, electrospinning, and Lego-style construction. Jennifer et al. [66] have developed a technology called Sacrificial Writing Into Functional Tissue (SWIFT). One hundred thousand OBBs were made in this study using microwell arrays. OBBs are "organ building blocks" made up of induced pluripotent stem cells that are specific to each patient and are dense cell organoids. At 0–4 °C, the OBBs are mixed with an ECM solution that is made up of type-I collagen and matrix gel to make a living matrix with a lot of cells. Finally, perf-usable vascular channels are introduced via embedded sacrificial 3D bioprinting. Experimental results show that SWIFT bioprinting can quickly assemble perf-usable patient organ-specific tissues. He et al. [67] combined some work on coaxial bio-3D printing in recent years, sorted out and summarized the latest research progress on this technology, and wrote a related review. This study details the basic principles and technical characteristics of coaxial bioprinting and the latest attempts to use this technology to construct large-scale structures containing nutrient networks, especially vascularization. This technology makes rapid manufacturing of vascularized tissue and organ prototypes possible.

4.2 High-performance Polymers for 3D Printing of Hydrogels

Many people are interested in the 3D printing of hydrogels because it can make complex and one-of-a-kind structures for many uses, such as biomedical and tissue engineering. However, hydrogels often have limited mechanical properties, making their use in some situations difficult. So, high-performance polymers need to improve the mechanical properties of hydrogels for 3D printing. To better understand the high-performance polymers utilized for 3D printing hydrogels, this presentation will focus on their mechanical and tribological characteristics.

Polyurethane is a versatile polymer that is used in many different ways. It has good mechanical properties, such as strength, toughness, and wear resistance. To meet

different mechanical and tribological needs, PU can be made with different architectures, like linear and crosslinked networks. As a reinforcing agent, PU has been used to improve the mechanical properties of hydrogels, such as their tensile strength and elasticity. PU-based hydrogels have also been used as tissue engineering scaffolds, drug delivery systems, and wound dressings. They are biocompatible and have elastic mechanical properties [68]. Polyethylene glycol is often used in biomedical applications because it is biocompatible, has low toxicity, and has mechanical properties that can be changed. PEG hydrogels can be made with different functional groups and crosslinking densities, which change the material's stiffness, toughness, and strength. Alginate and gelatin are two natural hydrogels. By adding PEG as a strengthening agent, their mechanical properties, such as their compressive strength and modulus, have been improved. Almeida et al. [69] said that PEG-based hydrogels have also been used as tissue engineering scaffolds for treating wounds and drug delivery systems. Due to its biocompatibility and low toxicity, biodegradable polyester (polycaprolactone) is frequently employed in biomedical applications. PCL can be made with different molecular weights and structures, which may change the material's mechanical properties, such as its tensile strength, modulus, and elongation at break. As a reinforcing agent, PCL has been added to hydrogels to improve their mechanical properties, such as compressive strength and modulus. PCL-based hydrogels have also been used as drug delivery systems, wound dressings, and scaffolds for tissue engineering because they are biocompatible and have mechanical properties that can be changed [70]. Polyvinyl alcohol is a synthetic polymer used in many different ways because it dissolves in water, is biocompatible, and is not toxic. PVA hydrogels can be made with different functional groups and cross-linking densities, changing the material's stiffness, toughness, and other mechanical properties. PVA has been used as a strengthening agent in natural hydrogels like alginate and chitosan to improve their mechanical properties, such as compressive strength and modulus. Because they are biocompatible and have elastic mechanical properties, PVA-based hydrogels have also been used as tissue engineering scaffolds, drug delivery systems, and wound dressings [71]. Polyethylene terephthalate glycol is a thermoplastic polymer with good mechanical properties, such as high strength, toughness, and dimensional stability. It is often used in a wide range of applications. PETG has been used as a reinforcing agent to improve the mechanical properties of hydrogels, like their compressive strength and modulus. PETG-based hydrogels have also been used as drug delivery systems, scaffolds for tissue engineering, and wound dressings because they are biocompatible and can stretch [72]. *Polymethyl methacrylate* is a transparent thermoplastic polymer used in many different ways. It has excellent mechanical properties, such as high strength, stiffness, and resistance to impact. When PMMA is used as a reinforcing agent, it improves the mechanical properties of hydrogels, like their compressive strength and modulus. Because they are biocompatible and can stretch, PMMA-based hydrogels have also been used as scaffolds for tissue engineering, drug delivery systems, and wound dressings [73]. *Polyamide* is a thermoplastic polymer used in many different ways because it has good mechanical properties, such as being strong, stiff, and resistant to wear. PA has been used as a reinforcing agent in hydrogels to improve their mechanical properties, such as their tensile strength and toughness. PA-based hydrogels have also been used as scaffolds for tissue engineering, drug delivery systems, and wound dressings because they are biocompatible and flexible [74]. *Polystyrene* is a thermoplastic polymer that is used in many different ways. It has excellent mechanical properties, such as high stiffness, stable dimensions, and chemical resistance. PS has been used as a reinforcing agent to improve the mechanical properties of hydrogels, like their compressive strength and modulus. PS-based hydrogels have also been used as scaffolds for tissue engineering, drug delivery systems, and wound dressings [75]. This is because they are biocompatible and have elastic mechanical properties. Polypropylene is a thermoplastic polymer with good mechanical properties like high strength, stiffness, and chemical resistance. It is widely used in a wide range of applications. PP has been used as a reinforcing agent to improve the mechanical properties of hydrogels, such as their tensile strength and elasticity. Jiang et al. [76] say that PP-based hydrogels have been used as scaffolds for tissue engineering, drug delivery systems, and wound dressings because they are biocompatible and can change their mechanical properties. *Polyethylene* is a thermoplastic polymer used in many different ways because it has excellent mechanical properties, such as high strength, toughness, and chemical resistance. PE has reinforced hydrogels, enhancing their mechanical characteristics like compressive strength and modulus. PE-based hydrogels have also been used as scaffolds for tissue engineering, drug delivery systems, and wound dressings [77]. This

is because they are biocompatible and have elastic mechanical properties.

1. 3D printing of hydrogels with bioinspired structures

3D printing of bioinspired hydrogels is an overgrowing area that offers many ways to make new materials with unique structural and functional properties. Hydrogels are made of water-soluble polymer chains that are arranged in three dimensions. They can absorb a lot of water while keeping their shape. Hydrogels are different from other materials because they contain much water, are biocompatible, and are soft. These qualities make them useful in many fields, such as biomedicine, tissue engineering, and soft robotics.

Hydrogels that mirror the structural and functional characteristics of natural materials found in living organisms are called "bioinspired hydrogels." By copying the structures and properties of raw materials, bioinspired hydrogels can be more compatible with biological systems and have better mechanical and chemical properties. This method has been used to make hydrogels with different properties, such as being biodegradable, remembering their shape, and healing themselves. 3D printing is a powerful way to make complicated structures with complete control over their shape and layout. It is possible to 3D print hydrogels into intricate shapes that are challenging to produce using conventional manufacturing techniques. Inkjet, extrusion, and stereolithography are hydrogels' most frequently used 3D printing processes [78]. Here, we demonstrate a technique called "digital light 4D printing" (DL4DP) that generates dynamic 3D objects with preprogrammed morphologies and motions (**Figure 10(d)**).

Piezoelectric print heads are used in the non-contact inkjet printing process to drop tiny amounts of hydrogel precursor solution onto a substrate. Inkjet printing has been used to make hydrogels for various purposes, such as drug delivery and tissue engineering. This is possible because hydrogels with complicated geometries can be printed with high-resolution patterns. Extrusion printing is contact printing in which a syringe or nozzle puts hydrogel precursor solutions on a substrate. Extrusion printing has been used to make hydrogels with a high level of structural integrity for several uses, such as soft robotics and wearable technology. A laser is used in the layer-by-layer printing method known as stereolithography to polymerize hydrogel precursor solutions. Stereolithography can be used to make hydrogels with high-resolution details. These have been used for various things, like delivering medicine and repairing tissue. A variety of materials, including natural polymers like collagen, gelatin, and chitosan, as well as synthetic polymers like polyethylene glycol (PEG) and poly(N-isopropyl acrylamide), can be used to create bioinspired hydrogels (PNIPAM). Changing the chemicals in the hydrogel precursor solutions makes it possible to change the physical and chemical properties of the made hydrogels [79]. (**Figure 10(b)**) illustrates shape-morphing 3D structures with axisymmetric metrics.

Tissue engineering is one of the most exciting uses for 3D-printed bioinspired hydrogels. By copying the structure and function of natural tissues, 3D-printed bioinspired hydrogels can create the best environment for cells to grow and change. Hydrogels made with 3D printing have been used to make skin, cartilage, and bone, among other tissues.

Soft robotics is a promising area for 3D-printed bioinspired hydrogels. By copying the mechanical and structural properties of natural materials found in living things, 3D-printed bioinspired hydrogels can be used to make soft and flexible actuators for soft robotics. These soft actuators could be used in many fields, such as robotics, wearable technology, and medical equipment.

6. The hydrogels performance and behavior

Hydrogels are a type of material with unique mechanical properties that make them useful in a wide range of situations. These substances, which are made up of a three-dimensional network of crosslinked polymer chains, can hold a lot of water without breaking down. The nature of the polymer, the degree of crosslinking, and the amount of water in the hydrogel all affect its mechanical properties.

6.1 Hydrogels are made of polymers

Many synthetic and natural polymers can be used to create hydrogels. Typically, crosslinked polymeric networks are used to create synthetic hydrogels. Changing the polymer's chemicals and the crosslinking amount makes making synthetic hydrogels with specific properties possible. The synthetic hydrogels PEGDA (poly(ethylene glycol diacrylate)), PNIPAM (poly(N-isopropyl acrylamide), and poly(acrylic acid) are examples of PAA [83].

On the other hand, the biopolymers collagen, chitosan, and hyaluronic acid are frequently used to produce natural hydrogels. These materials can be crosslinked physically or chemically to create a three-dimensional network that can absorb water. Natural hydrogels have

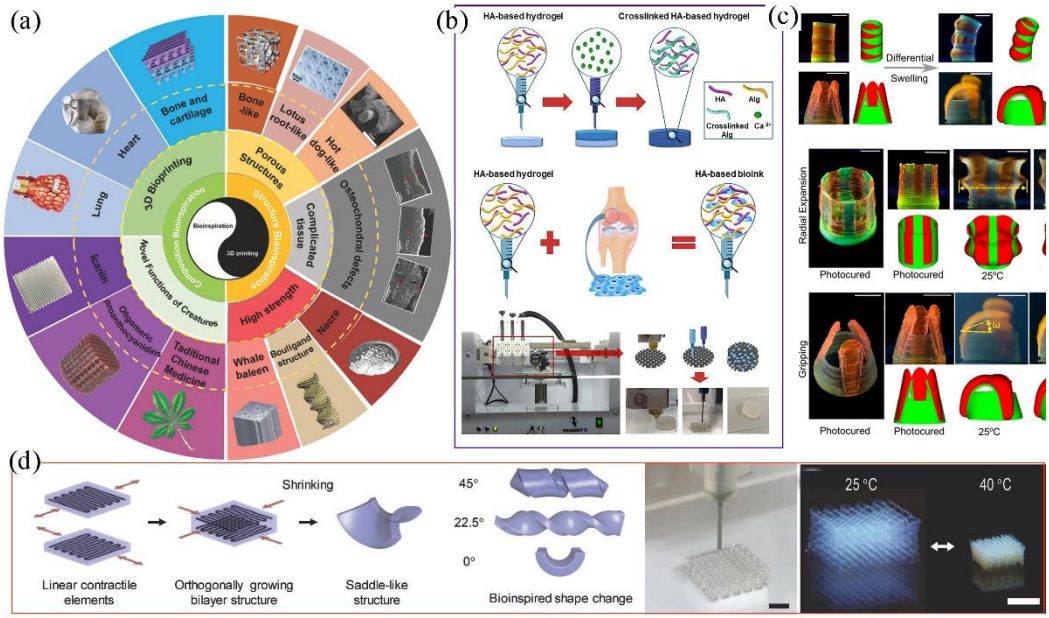

Fig. 10. (a) Fabricating the biomaterial for tissue regeneration via 3D printing and bioinspiration is an effective technique. The biomaterials created through 3D printing were inspired by biological composition. Through 3D printing, biomaterials are created for multifunctional repair that are inspired by the complex makeup of fascinating creatures and repair tissues [82], (b) Hydrogel formulation is influenced by nature, creating a bioink (hydrogel) based on hyaluronic acid (HA), Diagram of the 3D bioprinting procedure for manufacturing articular cartilage [79], (c) Bio-inspired tubes printed using dual-gel 4D technology. Tubes with vertical, regularly spaced segments that are radially symmetric. Thermoresponsive radial expansion of tubes with alternating vertical segments of active pNIPAM (red) and passive pAAM (green) segments is demonstrated in the results [81], and (d) Orthogonally developing hydrogel bilayer structures are printed in three dimensions using preprogrammed motions. Schematic showing how a bilayer structure of orthogonally oriented linear contractile parts can be used to produce 3D structures with programmed motions. Using a 200 µm nozzle to 3D print a layered lattice construction. Reversible volume change of a PNIPAM structure in response to temperature. [78]

drawn much attention in tissue engineering because they are biocompatible and can mimic tissues' extracellular matrix (ECM) [84].

6.2 Hydrogel Mechanical Characteristics

The polymer composition, crosslinking density, and water content are only a few variables that affect how hydrogels behave mechanically. The following are a few of the mechanical characteristics that are frequently used to describe hydrogels:

Modulus: The modulus of a hydrogel determines its stiffness or resistance to deformation. It is known as the stress-to-strain ratio and is often represented in units of Pascal (Pa). High-modulus hydrogels are stiffer and more deformation-resistant. Alginate hydrogels are used in tissue engineering, drug delivery, and other biomedical fields. Young's modulus is a way to measure how stiff or elastic a material is. It can involve compressing the material and measuring how it changes. The compression method is used to assess the Young's modulus of alginate hydrogels. The hydrogel is crushed between two plates on a mechanical testing machine. After measuring the compressive force and the resulting change in shape, the ratio of stress to strain is used to figure out Young's modulus. Without incurring damage to the hydrogel, it should be broken evenly and with an innovative application of force. The sample's size, shape, and compression rate may affect the measurement. Compressing alginate hydrogels is an excellent way to discover their mechanical properties [85-86]. Polyacrylamide (PAAM) hydrogels are often used in biomedical applications because they have good mechanical and swelling properties. *Rheometers* are devices that measure the rheological properties of materials in different situations. They can be used to study how PAAM hydrogels behave regarding their rheological properties. A sample is put between two parallel plates to find out how elastic PAAM hydrogels

are, and a rheometer is used to give it a small oscillatory deformation. After that, it is possible to determine the sample's elastic modulus by observing how the stress and strain readings alter over time or frequency [87-88]. Atomic force microscopy (AFM) can be used to measure the elasticity of hydrogels through indentation. The mechanical properties of the hydrogel are determined using this method by poking holes in it with a pointed probe and monitoring how it changes shape. Guanyu Chen et al. [89] used AFM indentation to measure the elasticity of alginate hydrogels. AFM indentation could be used to measure the sub-micron mechanical properties of the hydrogels accurately. The authors found that increasing the crosslinking density made the hydrogels more flexible. AFM indentation was used to find the elastic modulus of several hydrogels, including chitosan and polyacrylamide. The high spatial resolution of this method makes it possible to characterize heterogeneous materials and measure their local mechanical properties [90].

In order to measure the elastic modulus of soft materials, including hydrogels, atomic force microscopy (AFM) indentation investigations frequently use the Sneddon model [91] for spherical indenters. The sample must be made of a linearly elastic, homogeneous, and isotropic material for this model to work. It connects the force that is applied to the indentation depth and the sample's elastic modulus. A pointed probe with a spherical indenter is brought into contact with the hydrogel's surface, and a controlled force is used to indent the material. The ensuing deformation is measured, and the Sneddon model determines the hydrogel's elastic modulus. The Sneddon model has been used in many research studies to describe the mechanical properties of hydrogels. It can be used to quickly and accurately find the elastic modulus of these materials. The Sneddon model for spherical indenters is presented here.

$$F = \frac{E}{2(1-\nu^2)}\left[(a^2+r^2)\ln\left(\frac{r+a}{r-a}\right) - 2ar\right]$$
$$\delta = \frac{1}{2}a\ln\left(\frac{r+a}{r-a}\right),$$

Strength: A hydrogel's ability to withstand deformation or failure under load measures its strength. It is referred to as the highest stress that a hydrogel can withstand without cracking and is often given in units of Pascal (Pa). A hydrogel's ability to absorb energy without rupturing is a measure of its toughness. Its definition is the region beneath the stress-strain curve, typically given in units of joules per cubic meter (J/m^3). The swelling ratio of a hydrogel serves to measure its water absorption capacity. It is the proportion between the hydrogel's dry volume and the amount of water it absorbs [92]. Hydrogel synthesis and its characteristics are shown in Figure 11.

7. Tribological Properties of Hydrogels Polymer Compositions

Polymer networks called hydrogels have a lot of water incorporated into their structure. Because of their distinctive physical and chemical characteristics, they are appealing for various applications, including tribological ones. The polymer composition of hydrogels has a significant impact on their tribological characteristics. The tribological characteristics of hydrogels are significantly influenced by their polymer makeup. The polymer of choice can influence the friction and wear behavior of hydrogels, the crosslinking density, and the degree of swelling. Including nanoparticles or other additives can significantly impact hydrogels' tribological characteristics. For instance, silica or alumina nanoparticles can be added to hydrogels to increase their hardness and wear resistance, improving their tribological performance. Hydrogels' crosslinking density, swelling level, and polymer composition all affect their tribological characteristics. By choosing the suitable polymer and adding the suitable additives, hydrogels can change how they react to wear and friction, which makes them useful in many tribological situations [93].

Below are some hydrogels, their polymer makes, and sources that go over their tribological characteristics:

PVA hydrogels: PVA hydrogels have been shown to reduce friction and wear when used as coatings or lubricants. Polyvinyl alcohol (PVA) is a better lubricant than other materials. The tribological behavior of PVA hydrogel as a lubricant in artificial joints was examined in a study by Qin Chen et al. [94] (**Figure 12**). **Hydrogel made of poly(acrylic acid) (PAA)**: PAA-based hydrogels have been found to have good tribological properties, such as reduced friction and wear, due to their high water content, which acts as a lubricant. Zhang and Shi et al. [95] researched the tribological characteristics of poly (acrylic acid) hydrogels. **Polyethylene glycol (PEG) hydrogel**: PEG hydrogels are employed as coatings for biomedical equipment because it has been discovered that they have good lubricating characteristics. Hou et al. [96]

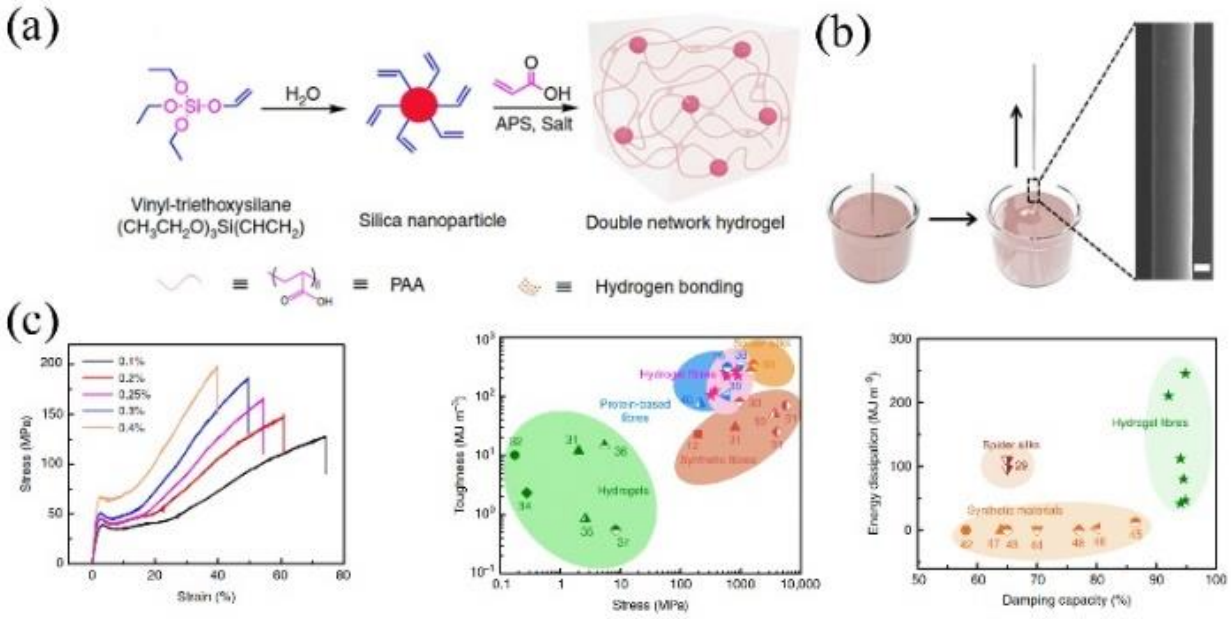

Fig. 11. (a) Hydrogel fiber preparation, shape, and mechanical strength a two-step hydrogel synthesis process that involves the creation of VSNPs and free radical polymerization, (b) A steel rod was dropped into a hydrogel reservoir to pull a single fiber, (c) Tensile stress-strain curves of hydrogel fibers were drawn with various VSNP contents following the setting. Researchers have compared the ability of hydrogel fibers (pink stars) to release energy and slow down vibrations with that of other common materials that do the same thing, such as spider silk (yellow symbols), protein-based fibers (blue symbols), and synthetic fibers (red symbols). The graphs' numbers match those in the sources. Comparison of the hydrogel fibers' (green stars) energy dissipation and damping capacity with that of other common energy-dissipating materials, including synthetic materials (yellow symbols) and spider silks (red symbols), as reported in the literature. The graphs' numbers match those in the sources [92].

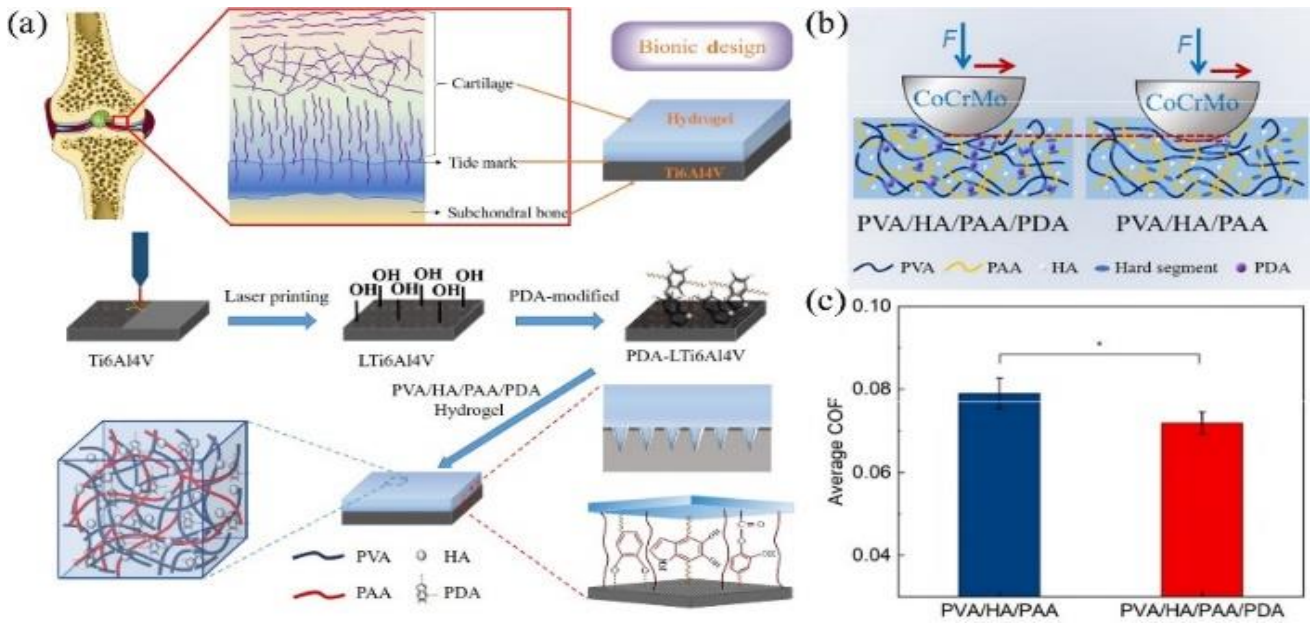

Fig. 12. (a) Ti_6Al_4V-hydrogel integrated material's bionic design is shown schematically in the image, (b) Schematic diagram of sliding friction of Ti_6Al_4V-PVA/HA/PAA hydrogel and Ti_6Al_4V-PVA/HA/PAA/PDA hydrogel. Average friction coefficient of Ti_6Al_4V-PVA/HA/PAA/PDA Hydrogel under, and (c) The Ti_6Al_4V-PVA/HA/PAA/PDA hydrogel and its average sliding friction coefficient. [94]

examined the tribological characteristics of PEG hydrogels used as orthopedic implant coatings. **Chitosan hydrogel**: Chitosan hydrogels are employed as coatings for biomedical equipment because it has been discovered that they have good lubricating characteristics. The tribological characteristics of chitosan hydrogels used as coatings for orthopedic implants were examined in a study by Vahid Adibnia et al. [97]. **Poly(N-isopropyl acrylamide) (PNIPAAm) hydrogel:** Scientists have found that PNIPAAm hydrogels can lubricate surfaces that change temperature, which means they can be used in biomedical devices for tribological purposes**.** The tribological characteristics of PNIPAAm hydrogels as lubricants in artificial joints were examined in a study by Wenhui Cao et al. [98]. **Poly(2-hydroxyethyl methacrylate) (PHEMA) hydrogel**: PHEMA hydrogels are employed as coatings for biomedical equipment because it has been discovered that they have good lubricating qualities. In a 2008 study, Bavaresco, V. P. et al. [99] examined the tribological characteristics of PHEMA hydrogels used as hip implant coverings

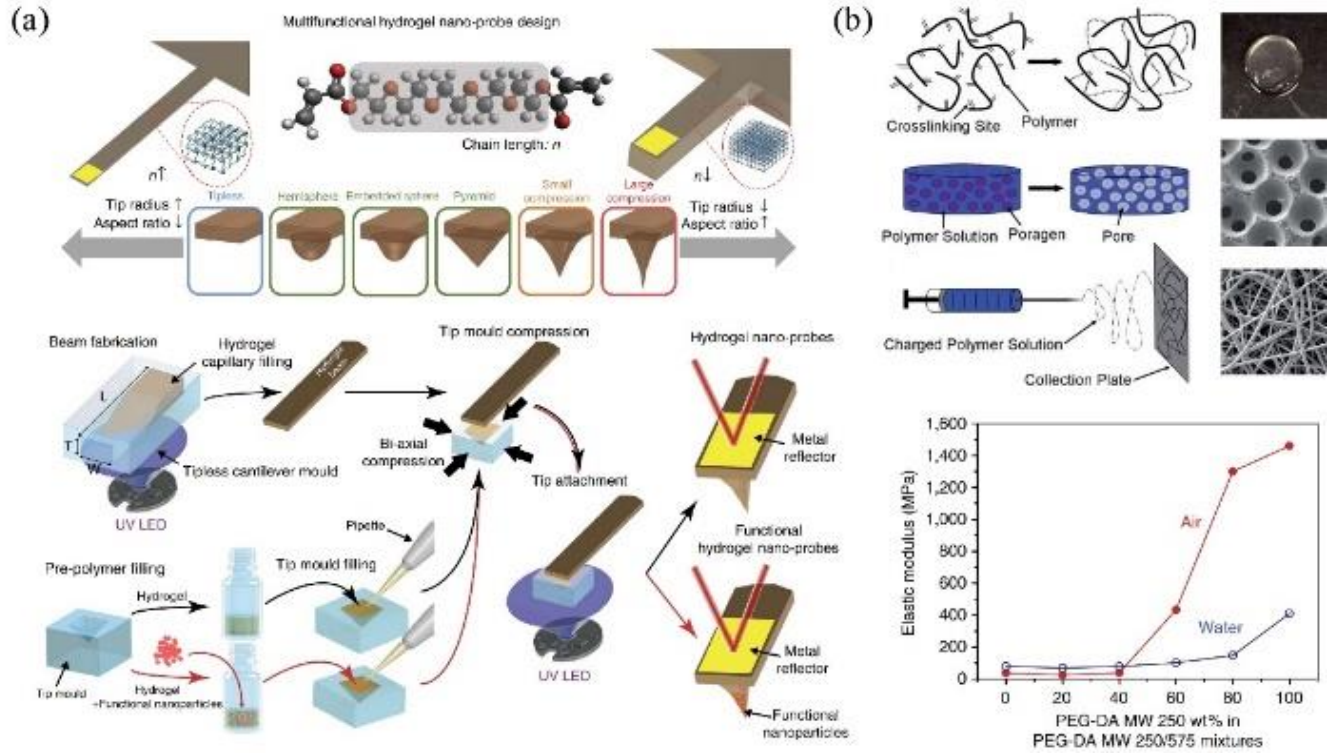

Fig. 13. (a) Conceptual diagram for the geometry of the beam and tip to adjust probe properties for various AFM applications. Tips-less hydrogel cantilevers can be made with spring constants that can change by many orders of magnitude. This is possible by filling capillaries with ultraviolet-curable hydrogels. When you make hydrogel AFM probes, you cure them with UV light before adding the pre-polymer solution to the cantilever beam mold. This makes a hydrogel cantilever that does not have any tips. The tipless hydrogel cantilever and tip firmly adhere to one another after the hydrogel in the tip mold undergoes a second round of curing with ultraviolet light [101], and (b) creation and morphology of scaffolds, reactive polymers are crosslinked to create a highly elastic hydrogel network, poragen leaching-induced development of porous networks, polymer electrospinning, in which a charged polymer solution is moved from a syringe to a connected surface by an electric field, leaving unique nano- or micrometer-sized fibers, and PEG-DA MW250/575 mixture elastic moduli in air [100] and water as a function of PEG-DA MW250 percentage of weight.

7.1 Hydrogels Mechanism and Design

Hydrogels are three-dimensional networks of hydrophilic polymers that can absorb and hold much water or biological fluid. Because of their distinctive physical and chemical characteristics, they have found wide-ranging uses in various industries, including tissue engineering, medication delivery, wound healing, and biosensors.

7.1.1 Mechanism of Hydrogels: Since they are hydrophilic, hydrogels have a unique mechanism for swelling and de swelling. The mechanism says that water molecules move through the chains of

hydrophilic polymers, making the hydrogel swell. Many variables impact the swelling behavior, including the crosslinking density, ionic strength, pH, temperature, and chemical makeup of the polymer chains. Osmosis and deformation of the polymer network are the two processes that primarily control how hydrogels swell. The osmotic process causes the water molecules in the hydrogel to move from the low-concentration zone to the high-concentration zone, which makes the hydrogel swell. The hydrogel gets more significant because the polymer chains in it take in water molecules and change shape during the deformation process of the polymer network [83].

7.1.2 Design of Hydrogels: Hydrogels must be well-designed to be used in a variety of applications. Natural, manufactured, or a combination of both polymers can be used to create hydrogels. Alginate, chitosan, collagen, hyaluronic acid, and gelatin are natural polymers used in hydrogel design. In contrast, polyethylene glycol (PEG), polyvinyl alcohol (PVA), poly (acrylic acid) (PAA), and poly (N-isopropyl acrylamide) are examples of synthetic polymers (PNIPAAm).

Crosslinking polymer chains to create a three-dimensional network is another step in constructing hydrogels. Either physical or chemical techniques can be used to create the crosslinks. Three different kinds of non-covalent interactions hold the molecules in the hydrogel network together these are hydrogen bonding, electrostatic interactions, and hydrophobic interactions. When you crosslink chemicals, you use things like glutaraldehyde, genipin, and carbodiimides to make covalent bonds between the polymer chains. Adding functional groups or bioactive compounds to hydrogels to give them specific properties or activities is another essential part of hydrogel design. **Figure 13** shows that cell-adhesive peptides, growth factors, and medicines can be added to hydrogels to make them more bioactive for tissue engineering and drug delivery. [100]

7.1.3 Ionic composite hydrogels

Ionic composite hydrogels comprise two or more different kinds of ionic chemicals or polymers that work together to generate a network structure. These hydrogels have numerous potential uses in fields like drug delivery, tissue engineering, and sensing.

Chitosan-polyacrylic acid (CS-PAA) hydrogel is designed as an ionic composite hydrogel. It results from the electrostatic interaction between negatively charged poly (acrylic acid) and positively charged chitosan. Due to the hydrogel's ability to swell and contract in response to variations in pH and temperature, this form of hydrogel has been investigated for its potential as a drug delivery method [102]. The hydrogel of poly(ethylene glycol) and poly(l-lysine), or PEG-PLL, is another example. It is made when positively and negatively charged PEGs interact with each other electrically.

Given that it can act as a scaffold for cells to grow and differentiate, this hydrogel has been researched for its potential in tissue engineering [103]. Ionic composite hydrogels can also be used as sensors because they can respond to changes in their environment, like when the temperature, pH, or amount of specific ions are present. A CS-PAA hydrogel, for instance, has been investigated as a pH sensor because it may alter its swelling behavior in response to pH variations [104]. To sum up, ionic composite hydrogels have several potential uses in various industries. Due to their distinctive features, they are strong contenders for applications in medication delivery, tissue engineering, and sensing. To completely comprehend their characteristics and possible applications, more investigation is required.

8. Application of Hydrogel

The three-dimensional networks of hydrophilic polymers known as hydrogels have a high water absorption and retention capacity. They are used in various industries, including medical, agriculture, and consumer goods. Hydrogels can be employed as drug delivery mechanisms, tissue engineering scaffolds, and dressings in biomedicine. Hydrogels can be utilized in agriculture as plant growth stimulants and soil moisture retention agents. Hydrogels are in consumer goods, including contact lenses, diapers, and food products like edible coatings, fat substitutes, and sensor platforms. Hydrogels are being used increasingly as a result of ongoing research into new uses for them.

8.1 Biomedical and pharmaceuticals application

Crosslinked polymer networks called hydrogels have a high water absorption and retention capacity. They have unique features like being biocompatible, having a high water content, mechanical and chemical properties that can be changed, and the ability to deliver drugs and biomolecules in a controlled way. These features make them promising materials for many biomedical and pharmaceutical uses (**Figure 14**). Hydrogels can be employed as scaffolds for regenerating diseased or damaged tissues in tissue engineering, one of their most

important uses. The extracellular matrix (ECM) of natural tissues can be copied in hydrogels, which creates a three-dimensional space for cells to grow and differentiate. They can also be functionalized with growth factors, peptides that bind to cells, and other biomolecules to promote cell division and proliferation. As an illustration, Qingxi Hu et al. [105] created a hydrogel scaffold based on chitosan and gelatin to treat spinal cord injuries. The scaffold demonstrated encouraging results in fostering nerve regeneration. Because they have the potential to encapsulate and release pharmaceuticals in a regulated manner, hydrogels can also be employed as drug delivery systems. They can release drugs at a particular spot in response to various stimuli, including temperature, pH, and enzyme activity. This can lessen the adverse effects of conventional drug delivery techniques and boost therapeutic effectiveness. Zheng et al. [106] created a pH-responsive hydrogel-based drug delivery system that demonstrated better anticancer activity and decreased toxicity compared to free medication for the treatment of gastric cancer. Hydrogels have other pharmaceutical uses outside of tissue engineering and drug delivery, like wound healing and diagnostics. Hydrogel dressings can hasten the healing process and lower the risk of infection by creating a moist environment for wound healing.

Moreover, hydrogels can be functionalized with biomolecules to find particular analytes in body fluids, including blood glucose levels. For instance, Bordbar-Khiabani et al. [107] created a hydrogel-based glucose-responsive sensor for the non-invasive monitoring of blood glucose levels. Early animal testing of the sensor was encouraging.

Fig. 14. Diagram demonstrating the use of hydrogels in Tissue Engineering.

8.2 Personal Care

Because of their distinctive physical and chemical characteristics, hydrogels are used in various personal care products. These are a few instances: Hydrogels can be used as wound dressings because they absorb and hold much water. They facilitate a moist environment for wound healing and may even control infection. Hydrogels make many contact lenses because they are supple, flexible, and allow oxygen to reach the eye. Because of this, they are more pleasant to wear than other kinds of lenses. Hydrogels can be found in various skin care products, including masks and moisturizers. They hydrate the skin while also assisting in enhancing its texture and appearance. Hydrogels can provide grip and control without leaving a sticky residue in hair styling products like gels and mousses. Hydrogels can be used in mouthwashes and toothpaste to help eliminate plaque and give breath a fresher taste. They can also be utilized in dental implants to encourage healing and stop infection.[108].

8.3 Environmental Remediation

The hydrophilic polymer chains that make up hydrogels are arranged in three dimensions and can absorb and hold vast volumes of water or aqueous solutions. Hydrogels have been thoroughly studied and used in numerous industries because of their unique characteristics, including environmental remediation. Eliminating heavy metals from contaminated water is one of the principal uses of hydrogels in environmental remediation. Hydrogels can function as adsorbents by joining with heavy metals to create complexes that are easy to remove from water. Hydrogels can also be used during soil cleanup to encapsulate contaminants in the soil and prevent their movement.

Hydrogels have also been employed to purge water from organic contaminants. They can function as sorbents, binding to particular organic contaminants to remove them from the water. Additionally, hydrogels are capable of transporting bacteria that can break down organic contaminants in water. Hydrogels have been used in the cleanup of oil spills. Oil and other hydrocarbons can be effectively removed from water using hydrogels, which can absorb them. The hydrogel can then be used to collect and recycle the absorbed hydrocarbons. [109]

9. Conclusion and Outlook

There are a lot of different ways to study how artificial soft tissue living cell vascularized scaffolds are made in tissue engineering research. This article looks at and summarizes the different ways that soft tissue scaffolds are made. It focuses on the pros and cons of additive manufacturing methods for making multi-material,

multi-cell, and vascular living cell scaffolds. It is believed that the composite construction of hydrogels and cells is the critical point and difficulty of soft tissue scaffolds. The leading technologies that can help get past this problem are high-precision additive manufacturing technology, its manufacturing process, and the way that hydrogel, cells, and growth factors are put together. This technology is complex to use because there is a lot of basic research on how additive manufacturing can be used in transplantation and regenerative medicine and how soft materials like hydrogels and cells can be made to fit into high-precision additive manufacturing equipment. Tissue engineering's use of hydrogel additive manufacturing (AM) brings unique challenges. Although hydrogels show promise in simulating biological tissues, they have trouble retaining their structural integrity when printed. Their low viscosity and high water content can cause collapse and shape distortion. The delicate balance needed to sustain cellular viability while printing hydrogel structures makes it difficult to achieve ideal mechanical characteristics and functionality. Ongoing research is needed to generate printable hydrogel bio-inks that meet biological and rheological parameters. For successful implementation in tissue engineering applications, issues with post-printing procedures and attaining accurate control over microarchitecture and macrostructure must also be resolved.

With the help of a crosslinking agent, for example, covalent bonds are made between the polymer chains during chemical crosslinking. Enzymes are used in the process of enzymatic crosslinking to catalyze the formation of links between polymer chains. In conclusion, 3D printing technology has completely changed how hydrogels are made, allowing for the precise, repeatable creation of complicated structures. Using different hydrogel precursors and crosslinking techniques has opened up new ways to create cutting-edge products and treatments based on hydrogels. More research needs to be done to find the best ways to print and crosslink the hydrogel so that it has suitable mechanical and biological properties.

Declaration of Competing Interest

The authors confirm that they have no known financial or interpersonal conflicts that would have appeared to impact the research presented in this study.

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