Review Article

Recent Advances on Electroconductive Hydrogels Used in Heart Repair and Regeneration

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Myocardial infarction (MI) permanently damages cardiac tissue. Tissue engineering exhibits tremendous potential as a strategy for developing engineered tissue to repair congenital abnormalities in the heart and/or cardiovascular tissue. Electroconductive hydrogels (EHs) are prepared from synthetic or natural biodegradable polymers and conductive components that could partially restore the myocardial/ventricular electromechanical coupling and synchronized heartbeats. Also, EHs are ideal materials for the preparation of cell culture and induction carriers, engineered scaffolds, and patches, as well as cell and gene delivery carriers, all of which aid in tissue formation. Except for a brief introduction to the classification and synthesis of EHs, this review discussed the recent progress and challenges of EHs applied in cardiac repair and regeneration to provide a reference for the further application of EHs in treating cardiovascular diseases. Figure abstract: the EHs category and the potential application of heart repair and regeneration in this review.

1. Introduction

Ischemic heart disease, typified by MI, is a leading cause of fatality in China and even the globe, with mortality exceeding that of various cancers, imposing a significant burden on the global society and the economy [1, 2]. Ischemia and hypoxia of coronary arteries cause necrosis and fibrosis in the myocardium, along with the myocardium cells’ very restricted regeneration capacity, ultimately resulting in scar tissue, aberrant ventricular remodeling, and arrhythmias [3]. The only therapeutic alternative for patients with end-stage heart failure is heart transplantation, but postoperative complications and a scarcity of organ donors significantly restrict the number of transplantation cases [4]. Therefore, heart failure necessitates novel therapeutic strategies. Bioengineering to generate functional cardiac tissue via the integration of materials science and stem cell biology has been proved a highly promising strategy for treating MI in recent decades [5]. The emergence of hydrogels offers promise for many challenging areas of cardiac tissue engineering. Hydrogels are highly aqueous porous materials that are one of the few biomaterials capable of resembling the extracellular matrix to prepare an engineered scaffold. Besides excellent biocompatibility and biomanufacturing stability, hydrogels incorporate accessible adjustment and delivery of physical and chemical properties. Hydrogels derived from natural materials, in particular, can circumvent immunoreaction to a particular degree, and their biodegradability and low toxicity also fulfill the requirements of tissue engineering [6]. Along with its ability to cover diverse geometries of damage and resemble the natural extracellular matrix and cell-proliferating nutrients, hydrogels are very biocompatible [7]. Hydrogels, particularly injectable ones, have many benefits including avoiding complicated surgery on large-sized wounds, filling irregular wounds, and delivering medications and growth factors, which have drawn an increasing amount of attention [8–10]. Hydrogels are thus an appealing material for heart repair and regeneration.

Hydrogels are prepared from various natural and synthetic materials, primarily including hyaluronic acid, collagen, gelatin, chitosan, matrix glue, alginate, fibrin, poly (2-hydroxyethyl methacrylate) (PHEMA), poly (N-isopropyl acrylamide) (PNIPAAm), poly (ethylene glycol) (PEG), and
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2. Synthesis and Classification of EHs

2.1. Conducting Polymer-Based Hydrogels. Conductive polymers (CPs) are a class of organic material with optical and electrical properties comparable to nonpolar semiconductors and metals, and the merits of conventional polymer materials [22]. The primary CP types include polyaniline, polypyrrole, polyphenylene, and polyacetylene. Electronic conductivity is achieved by the conjugated \( \pi \) bonds on conductive polymers with simple, ubiquitous, cost-effective, and efficient synthesis, as well as an accessible functional modification at the molecular level [23, 24]. A strong recommendation is to examine the following review to understand more about the underlying structure, the conductive mechanism, and the differences between different conducting polymers [24–27]. Nerve tissue engineering, heart tissue engineering, muscle tissue engineering, bone tissue engineering, and other domains have demonstrated that the inclusion of conductive polymers in biomaterials may increase the conductivity of the whole system [28–33]. The improvement of synthesis techniques, such as dispersion polymer, side-chain functionalization, and graft modification [34] (Figure 1), allowed for the appropriate avoidance of conductive polymers' drawbacks, like insolubility, low processability, and poor biocompatibility. However, biomedicine requires stricter biocompatibility and nonimmunogenenicity of conducting polymer-based hydrogels to avoid aberrant fibrosis encapsulation induced by nonspecific protein adsorption on implant surfaces. Table 1 outlines some current uses of conducting polymer-based hydrogels in heart repair and regeneration.

2.2. Carbon-Based EHs

2.2.1. Graphene. Graphene is a two-dimensional hexagonal carbon lattice with three \( \sigma \) bonds and an out-of-plane \( \pi \) bond connecting to adjacent atoms [40]. Graphene is inherent in electrical conductivity, strong tensile properties, high thermal conductivity, magnetic properties, optical properties, and chemical stability [41]. Chemical vapor deposition, electrochemical stripping, and mechanical cracking of graphite could synthesize pure graphene [42]. Also, the physical and chemical modification could generate graphene derivatives including graphene oxide (GO) and reduced graphene oxide (rGO). Over the past two decades, graphene-based EHs have been applied to tissue engineering, medication and gene delivery, bioimaging, biosensors, 3D printing, and other fields of regenerative medicine [42, 43] (Figure 2). It was revealed that each form of graphene shows diverse and unique adjustable characteristics, making graphene one of the most significant options for developing electrochemical sensors based on nanocomposites [41]. While graphene and its derivatives have been incorporated into some synthetic strategies to develop EHs with strong electrical and mechanical properties, they occasionally exhibit low water solubility in hydrogels and tend to aggregate in solution. The current solutions include wet spinning technology and in situ redox to avoid abnormal conductivity in hydrogels [44, 45]. Notably, graphene’s cytotoxicity is highly dependent on its size, shape, surface area, charge, and functional groups, necessitating a thorough assessment of its biocompatibility in biomedical application research to enable future clinical transformation [46, 47].

2.2.2. Carbon Nanotube. Carbon nanotubes (CNTs) are single or multiwall nanostructures with a high aspect ratio formed of a carbon atom lattice. CNTs are often synthesized via laser cutting, arc discharge, and chemical vapor deposition. CNTs incorporate superior physical characteristics such as a high aspect ratio, a low density, a high electrical...
conductivity, and a high compressive and tensile strength [48]. CNT has been demonstrated to be an appealing material for biomedical applications when integrated with EHs, where CNT substantially improves electrical conductivity and decreases brittleness [18, 49–51]. However, the high van der Waals force, strong hydrophobicity, and low entropy of CNTs result in heterogeneous polymers in solution [52]. Surface coating, functionalization of other groups, and

![Figure 1](https://example.com/figure1.png)

**Figure 1**: Schematic diagram of preparing functional CP. (a) CP compound, (b) Side chain modification CP, and (c) Electroconductive graft polymer [34]. Copyright 2021, with permission from Elsevier.

| Biomaterial | Conductivity | Mechanical properties | Model | Application |
|-------------|--------------|-----------------------|-------|-------------|
| PPy + chitosan + collagen + PEO [30] | $\approx 150 \times 10^{-3}$ S/m | Young’s modulus = 1.09 MPa; tensile strength = 4.6 MPa; elongation = 4.2 | In vitro: Fibroblast cell | Improved cell adhesion, growth, and proliferation |
| PEDOT: PSS + collagen + alginate [35] | $27 \pm 8 \times 10^{-2}$ S/m | N/A | In vitro: Cardiomyocyte | Enhanced electrical coupling and myocardial cell maturation |
| PPy + chitosan [36] | Improved the conduction velocity of cardiac scar tissue | N/A | In vitro: Cardiomyocyte; ex vivo: isolated cardiac scar tissue | Improved electrical transmission and resynchronize cardiac contraction, reduced susceptibility to arrhythmias |
| PANI + chitosan + phytic acid [37] | $16.2 \pm 0.43$ S/m | Young’s modulus = 6.73 ± 1.14 MPa; tensile strength = 5.26 ± 2.25 MPa | Ex vivo: Cardiac slices and whole hearts | Enhanced electronic stability |
| HPAE–Py + gelatin [38] | $6.51 \pm 0.12 \times 10^{-2}$ S/m | Young’s modulus = 35 Kpa | In vivo: Myocardial infarction in rats | Enhanced the conduction of electrophysiological signal and revascularization |
| PANI + collagen + hyaluronic acid [39] | $0.2 \pm 0.06$ S/m | Young’s modulus = 2 ± 1 MPa; tensile stress = 9.3 ± 0.5 MPa | In vitro: Cardiomyocyte | Improved contractile amplitude and contraction time of cardiomyocyte; improved electrical coupling |

Abbreviations: PPy: polypyrrole; PEO: poly (ethylene oxide); PEDOT: PSS: poly (3,4-ethylenedioxythiophene): polystyrene sulfonate; PANI: polyaniline; and HAPE-Py: hyperbranched poly (amino ester)-pyrrole.
dispersants such as microgel particles to alter the solution environment are recognized methods for partly addressing the issues mentioned above [52–55]. Also, it is essential to assess the toxicity and inflammatory response of CNTs in vivo.

2.2.3. MXene. MXene is a two-dimensional transition metal carbide, nitride, and carbonitride with many advantages including cellular compatibility, a very high specific surface area, adjustable conductivity, and water-dispersible workability. MXene has generated considerable research interest since its first introduction in 2011, and its superior performance makes it an attractive option for various biomedical and tissue engineering applications [56–58]. The following focuses on the synthesis strategy of MXene and the techniques for doping and compounding MXene with other materials to prepare EHs [59, 60]. Modifications or self-assembled hydrogel platforms could address the low dispersibility of MXene nano pieces in water [59]. The research on MXene’s toxicity to humans and the environment is ongoing [61–63]. Table 2 highlights some current applications of carbon-based EHs in cardiac repair and regeneration.

2.3. Metal Nanoparticles EHs. Ranging in diameter from 1 to 100 nm, metal nanoparticles are colloids with a high surface-to-volume ratio. The unique electrical activity, optical properties, magnetic properties, antibacterial properties, biocompatibility, mechanical properties, and catalytic properties of metal and oxide nanoparticles such as gold, silver, platinum, ferric oxide, zinc oxide, and zirconia make them an attractive choice for the synthesis of composite EHs in the field of biological materials [18, 72] (Table 3, Figure 1). However, the disadvantages of high cost, cytotoxicity, and others are also noticeable. Metal nanoparticles are synthesized through electrochemistry, photochemistry, various physical reduction techniques, and biosynthesis, among others [73, 74]. The synthesis techniques impact metal nanoparticles’ type, size, shape, and functionalization route, further influencing their physicochemical characteristics and stability. EHs have been designed and synthesized using a range of various metal nanoparticles for a variety of biological applications including biosensing, bioimaging, and tissue engineering. Many metal nanoparticles have been utilized to design and synthesize EHs for many biological applications including biosensing, bioimaging, and tissue engineering [75–79].

3. EHs for Heart Repair and Regeneration

3.1. Cell Culture and Induction. EHs represent a significant stride in correctly resolving the cell fate of cardiomyocytes and their derived stem cell phenotypes. EHs manufacturing is a complex undertaking with the ultimate goal of replicating the ECM microenvironment in vitro to promote the appropriate cell-cell and cell-matrix interactions that drive the maturation of cardiomyocytes [80]. In order for EHs to induce cell differentiation, promote cell maturation, and regulate electrical signals, they must possess minimal bio toxicity, conductivity, and cross-linking with cardiac myocytes. Melero et al. [81] cross-linked cellulose acetate hydrogel (HAC) with EDTAD (ethylenediaminetetraacetic acid dihydrate). The results exhibited obvious chelation with calcium and magnesium ions in vitro and influenced

Figure 2: Overall application of graphene-based materials in regenerative medicine and tissue engineering [42]. Copyright 2016, with permission from Elsevier.
### Table 2: Applications of carbon-based EHs in cardiac repair and regeneration.

| Biomaterial                               | Conductivity (S/m) | Mechanical properties | Model                        | Application                                                                 |
|-------------------------------------------|--------------------|-----------------------|------------------------------|----------------------------------------------------------------------------|
| RGO + dECM [64]                           | 3.3                | Compressive modulus 17.5 KPa | Ex vivo: Heart tissue        | Enhanced myocardial contractility and upregulated genes regulating systolic function improved the maturation and beating properties |
| Graphene                                  |                    |                       | In virto: Mesenchymal stem cell | Good biocompatibility and potential to promote cardiomyogenic differentiation |
| Graphene [65]                             | N/A                | N/A                   | In virto: Cardiomyocyte       | Induced cellular orientation, maturation, and anisotropy                     |
| Heart-derived ECM + SWCNTs [66]           | N/A                | N/A                   | In virto: Cardiomyocyte       | Provided mechanical support and electrical connectivity to cardiomyocytes enhanced remodeling and regeneration |
| Polycapro lactone + silk fibrin + carbon nanotubes + GelMA [67] | ≈6.5 × 10⁻⁵ S/m | ≈27 MPa              | In virto: Cardiomyocyte       | Reduced fibrosis and increased formation of a blood vessel network and immature cardiomyocytes |
| Carbon nanotube                            | ≈1 × 10⁻⁴ S/m      | Shear modulus ≈ 0.6 KPa | In virto: Cardiomyocyte       | Promoted myocardial cell alignment and improved the synchronization of heart cells |
| Carbon nanofiber + collagen [69]          | N/A                | Newton force ≈ 3.1 N  | In virto: Cardiomyocyte       |                                                                              |
| SACNTs + GelMA [70]                       | N/A                | N/A                   | In virto: Cardiomyocyte       |                                                                              |
| MXene                                     | PEG + Ti3C2Tx Mxene [71] | 0.1 S/m        | Young’s modulus = 144.5 ± 8.8 KPa | In virto: Cardiomyocyte                                                                 |

Abbreviations: rGO: reduced graphene oxide; dECM: decellularized extracellular matrix; ECM: extracellular matrix; SWCNTs: single-wall carbon nanotubes; GelMA: gelatin methacrylate; SWNT: single-walled carbon nanotube; SACNTs: super aligned carbon nanotubes sheets; PEG: polyethylene glycol.

### Table 3: Properties of metal nanoparticles [18].

| Nanoparticles       | Size (nm) | Shape               | Advantages                                      | Disadvantages                                        | Application                                                                 |
|---------------------|-----------|---------------------|-------------------------------------------------|-------------------------------------------------------|----------------------------------------------------------------------------|
| Gold nanoparticles  | 1–60      | Spherical rod polygonal floral | High stability low cytotoxicity in initial step possibility of high scale production | Relatively weak optical signal long-term cytotoxicity high price | Labeling and visualization diagnostics, therapeutics, catalysis, cancer cell treatment |
| Silver nanoparticles| 4–120     | Spherical wire oval polygonal rod | Antimicrobacterial high optical signal | Cytotoxicity low stability before surface treatment high price | Antimicrobial, gas/vapor sensing water sterilization, cancer cell treatment |
| Platinum nanoparticles| 10–100   | Spherical cuboidal floral | Catalysis high optical-signal high stability | High price cytotoxicity | Biosensing of molecules enhancement of bone strength, detection of cancer cells |
| Iron oxide nanoparticles | 4–45    | Tube spherical cluster | Superparamagnetic property low cytotoxicity economical | Weak strength low stability toxic solvent is needed | Gas sensing, magnetic resonance imaging |
| Zinc oxide nanoparticles | 20–600   | Flower rod wire sheet | Piezo- and pyro-electric wide range of UV absorption high optical signal economical antibacterial effect | Cytotoxicity low stability toxic solvent is needed | Photocatalyst, absorber of UV radiation, biosensors, gas sensing |
cell adhesion, hence creating biological signals and an environment for cell repair.

Roshanbinfar and colleagues [35] developed an electrochemical bio-mixed hydrogel composed of collagen, alginate, and conductive PEDOT: PSS, which incorporates ECM simulated fiber structure, enhanced electrical coupling, and myocardial cell maturation. This electrochemical bio-mixed hydrogel could increase the pulsation frequency to over 200 times the endogenous frequency of min−1. Cardiomyocytes exhibited better alignment and density in these constructs, improving sarcomere tissue. Jonathan and colleagues [64] mixed decellularized porcine myocardial extracellular matrix (dECM) and reduced graphene oxide (rGO) to prepare hybrid hydrogel. The experimental result demonstrated that engineered heart tissues constructed with dECM-RGO hydrogel scaffold and cardiomyocytes derived from human induced pluripotent stem cells (hiPSCs) significantly enhanced myocardial contractility and upregulated genes regulating systolic function. Also, these electrochemical bio-mixed hydrogels improved the maturation and beating properties of human induced pluripotent stem cell-derived cardiomyocytes. These cells exhibit 1.9 µm near-adult sarcomeric length, enhanced beating frequency, increased contraction speed, and larger contraction amplitude.

The myocardial’s dense uniaxial cardi cell structure and electrical and mechanical coupling between myocardium cells are critical factors of synchronous cardiac contractions. Navaei and colleagues [82] utilized a gelMA (gelatin methacrylate)-GNR hydrogel to develop homogeneous, dense, and highly aligned heart tissue that could provide electrical and topographic cues for simulating physiologically relevant cardiac activity. When the natural extracellular matrix is utilized to support cell growth and inoculation in vitro, it is inevitable that biophysical cues be destroyed during the decellularization process. Bai and colleagues prepared a hybrid hydrogel by incorporating single-walled carbon nanotubes (SWCNTs) into a heart-derived extracellular matrix (ECM). By interacting with ECM proteins, insoluble single-walled carbon nanotubes were dispersed uniformly throughout the mixed hydrogel system, activating integrin-related pathways such as biophysical cues and improving the system’s intercellular communication and bioactivity [66] (Figure 3). Modeling anisotropic cardiac architecture and controlling three-dimensional cell orientation are essential for developing cardiac tissue regeneration scaffolds [83]. Wu and colleagues [67] used a 3D hybrid scaffold that mimics the shape of native heart tissue in a hydrogel shell, using a permutation-based conductive nanofiber yarn network (NFFys-NET, composition: polycaprolactone, silk fibroin, and carbon nanotubes). They developed an endothelialized myocardial by coculturing the CM on the NFFys-NET layer and endothelial cells in a hydrogel shell. Thus, the hybrid approach of the NFFys-NET layer promotes cell orientation, maturation, and anisotropy, while the hydrogel shell offers a suitable three-dimensional environment for endothelialization, which has significant promise for designing three-dimensional cardiac anisotropy.

3.2. Tissue Engineering Scaffolds and Patches. A promising treatment option for ischemic cardiovascular disease is tissue engineering, a multidisciplinary collaborative strategy that combines materials engineering, life sciences, and computer modeling to ultimately produce artificial tissues or functional scaffolds for biomedicine and regenerative medicine [84]. The primary objective of cardiac tissue engineering is to provide artificial substitutes for damaged regions such as engineered scaffolds and/or patches [85, 86]. For therapeutic efficacy, these materials must have the same mechanical qualities and electrical conductivity as the original cardiac tissue in order to better fit into the beating heart. Additionally, the physical qualities of the scaffold/patch, such as porosity, pore size, and surface pattern, have a significant impact on the therapeutic efficacy [11, 82].

EHs have been shown to be an efficient component of cardiac tissue engineering scaffolds and patches [87, 88]. In myocardial infarction, ischemia damage results in an increase in tissue resistance in the infarct region, limiting heart synchronous electrical transmission. This asynchronous conduction between the myocardium and fibrotic tissue leads to asynchronous contractions that develop into ventricular dysfunction. He and colleagues synthesized electroconductive polypyrrole chitosan hydrogels (PPY:CHI) and discovered that they could improve electrical transmission in fibrotic tissues and resynchronize cardiac contraction to preserve cardiac function, and reduce susceptibility to arrhythmias by 30% following MI [36, 89]. Due to the decrease of electroconductive polymers’ electrical properties, their short working duration precludes their therapeutic use. Mawad and colleagues [37] demonstrated that the immobilization of phytic acid and other dopants in conductive scaffolds avoided electrical deterioration. Additionally, the water solubility and phase separation issues associated with PPY produced directly from the free pyrrole monomer may be overcome by sealing it to a hyperbranched polymer containing dopamine [38].

Carbon-based nanomaterials exhibit excellent electrical conductivity and mechanical properties, and previous research has demonstrated that they can be used as hydrogel scaffolds or patch materials for myocardial tissue engineering, as well as being favorable for myocardial cell adhesion, proliferation, and differentiation [65, 90, 91]. For example, Zhou and colleagues found that injected OPF (Oligo Poly (ethylene glycol) fumarate)/GO hydrogels could provide mechanical support and electrical connectivity to cardiomyocytes in normal myocardium and scars by activating typical Wnt signaling pathways. Additionally, they developed EHs with an acceptable structure, phenotype, and function using in vitro conductive SWNT and gelatin, which demonstrated significant structural fusion with infarcted myocardium following implantation, thereby enhancing remodeling and regeneration of infarcted myocardium [68]. Simultaneously, the integration of carbon nanotubes into
biocompatible materials such as collagen is one of the development strategies for cardiac patches [92]. Certain studies have shown that combining carbon nanofibers (CNF) and collagen hydrogel could repair injured myocardium, resulting in a reduction in fibrosis and an increase in vascular network and immature myocardial cell production in infarcted hearts [69]. The arrangement of cardiomyocytes is also essential in the design of cardiac patches, as the function of cardiac tissue is highly dependent on the linear arrangement of myofibrils and muscle bundles and the longitudinal shape and connections of ventricular myocytes [93]. The high resolution of 3D printing makes it ideal for cell patterning to provide terrain direction to cardiac muscle cells. Basara and colleagues [71] showed that the conductive characteristics of composite hydrogels could enhance the patch’s electrophysiological coupling to the infarcted region by utilizing a predesigned pattern on PEG hydrogels and 3D-printed conductive titanium carbide (Ti3C2Tx) MXene through aerosol injection. This research indicates that 3D-printed (Ti3C2Tx) MXene could be utilized to create an electrophysiologically relevant cardiac patch to treat MI. Besides, Sun and colleagues [70] polymerized nonclose-packed colloidal arrays on super-aligned carbon nanotube sheets (SACNTs) to achieve a new color hydrogel with electric conductivity and anisotropic structure, which was applied to visualizing and precisely constructing the heart-on-chip. The findings demonstrated that SACNTs’ anisotropic shape was capable of effectively promoting myocardial cell alignment. Additionally, its electrical conductivity might aid in the synchronization of heart cells, indicating that color hydrogels with electrical conductivity and structural anisotropy offer a wide range of application possibilities in cardiac engineering.

3.3. Delivery System. The cardiac muscle’s limited potential for regeneration raises delivery therapy (cellular, protein, or gene), a capable and promising approach for restoring injured heart tissue after myocardial infarction [94]. EHs could perform biological tasks by targeting particular tissue types using a combination of cells, growth factors, therapeutic peptides or chemical molecules, and genes. Unsurprisingly, many pieces of research have continued to innovate in cardiac tissue engineering. Different types of hydrogels were employed in cardiac repair and regeneration to mix diverse cardiac cells and stem cells, as well as therapeutic proteins and genes to achieve delivery, in order to adapt to the many functions and objectives of EHs, see Table 4. Human cells derived from various sources, including cardiac stem cells, bone marrow stem cells, mesenchymal stem cells, hematopoietic stem cells, and embryonic stem cells, have been used to regenerate cardiac tissue and are expected to be used in the future for cell delivery in the EHs system [95]. EHs’ porous characteristics, responsiveness to stimulus, and adjustable mechanical and physicochemical properties enable them to create a protected microenvironment conducive to cell activity. EHs stimuli responses include thermal, mechanical, electrical, temperature, light, and pH responses, among others [96–99]. Because of the response of EHs to external stimuli, the EHs system is capable of efficiently delivering biotherapeutic molecules such as proteins and genes in a controlled and local manner, as well as utilizing the cell’s mechanisms for continuous production of therapeutic proteins, which is not possible with mass protein delivery methods [100]. As a delivery platform, it is vital to consider the controlled release properties of EHs in order to fulfill particular drug release speed and duration requirements, as well as biodegradability.

How to employ stimulation to regulate the production, degradation, and release of therapeutic chemicals carried by EHs offers significant promise for future studies in heart repair and regeneration.
4. Challenges

Compared to conventional myocardial injury treatment strategies, cardiac tissue engineering utilizing EHs had the merits of enhancing the electrical conductivity of scar tissue and promoting heart regeneration. Prior to the clinical use of EHs, some difficulties must be resolved including the preparation of EHs, which relate to their electrical conductivity, biotoxicity, biocompatibility, and adequate mechanical strength. The present production of EHs requires further adjustment for the dispersion of conductive filler, as well as the synthesis technique and ambient conditions. Additionally, the physicochemical properties (e.g., size, surface area, surface properties, number of layers, and particle state) and surface functionalization of metal nanoparticles and carbon-based conductive fillers affect their in vitro and in vivo nanotoxicity, which is rarely well established and systematic. Despite the fact that, for injured cardiac tissue, the higher the conductivity of the biomaterial, the greater its ability to repair the electrical conduction of the scar site, and the higher the conductivity also increases the percentage of conductive material, resulting in increased bio toxicity. In some experiments, the majority of conductive materials were abandoned after the first cell experiment. Therefore, the conductivity and bio toxicity of all EHs must be in equilibrium [30, 35].

The mechanical compliance of conductive polymers remains unknown during implantation, and more research is needed to validate and enhance their effect in vivo [26]. Moreover, the electrically insulated macroporous matrix of hydrogels impairs cell-to-cell electrical connection and signal propagation within tissues, interfering the entire electrical integration of tissue structures with the normal heart and eventually resulting in unanticipated arrhythmias. The integration of micrometer- and nanometer-scale methods in hydrogel-based micropatterns may assist in overcoming this constraint 8. In contrast, the capacity of biomaterials to cross-link with the site of myocardial infarction is crucial to their therapeutic efficacy, independent of application. In cardiac tissue engineering, variations in patient age, infarct size, and other variables demand the exact individualization of EHs [107]. EHs are anticipated to have enormous promise in the realm of cardiac repair and regeneration, despite the challenges that need to be resolved.

5. Conclusions and Future Perspective

According to the present state of EHs production, dispersion of conductive fillers needs further improvement of synthesis techniques and conditions. The cell-loaded ECH organ model is still in its infancy, but it is a rapidly growing study area. This may be because current knowledge of cardiac biomechanics and electrophysiology is insufficient, and the structure of EHs has to be improved from cellular and molecular perspectives, as well as its long-term stability, function, and cytocompatibility. The ideal biodegradable EHs for cardiac tissue engineering have not yet been discovered [108, 109].

| Table 4: EHs for delivery systems to treat MI. |
|-----------------------------------------------|
| Hydrogel                                          | Delivered substance | Noticeable features                                                                 | References |
| Ti2C-cryogel                                      | CMs                 | Suitable mechanical properties and electrical conductivity to match natural myocardium and enhance angiogenesis | [101]      |
| Cardiac ECM and PPy hydrogel                     | Cardiac progenitor cell | Biocompatible microenvironment that supports CPC activity, adhesion and migration to scaffolds, and differentiation | [102]      |
| Cluster graphene oxide formed conductive silk hydrogel | Load growth factors by using endothelial progenitor cells | Positive effects of oxidative stress and ROS reprotoction and excellent cardiomyocyte survival and differentiation | [103]      |
| Ultrasmall graphene quantum dots/chitosan/collagen matrix hydrogel | hMSCs | Cell survival rate, expression of proinflammatory factors, and proangiogenic factors. | [104]      |
| ECM/Lapauhydrogel                                | ECM                 | Improved cytocompatibility and phenotypic maturation of heart-specific proteins       | [105]      |
| GO/GelMA hydrogel                                | DNA_{VEGF}          | Replenishing the supply of angiogenic genes also protects the captured DNA              | [106]      |
With the fast advancement of 3D printing in the biomedical field [110], the technology may now be utilized to rapidly create bespoke tissue-constructing frameworks, heal tissue damage in situ using cells, and even directly print tissues and organs. 3D printing in conjunction with external electrical stimulation may be a viable approach for engineering cardiac structures [111].

Delkash et al. [112] created an egg-white and sodium alginate-based natural bioink for bioprinting cell-laden patches utilized in endothelial tissue engineering. Their research indicated that the incorporation of these materials improved the printability and mechanical strength of cell-laden patches without impairing cell viability and with suitable degradation in a human-like environment. Using 3D printing technology, Bejleri et al. [113] printed cECM (cardiac extracellular matrix), hCPC (human cardiac progenitor cell), and GelMA into cardiac patches. They discovered that hCPCs in the patch showed enhanced differentiation and angiogenesis, which were effectively maintained in the rat heart for more than 14 days, and revealed vascularization. The research reveals the possibility of using 3D printing to heal injured cardiac muscles.

It is essential to investigate a conductive hydrogel that could endure the pulse while meeting the mechanical strength and electrical conductivity of the heart. Synergistic advances in medicine, biology, and materials science will continue to bridge the laboratory-clinic gap.

Data Availability
Data sharing is not applicable to this review as no datasets were generated or analyzed during the current review.

Conflicts of Interest
There are no conflicts of interest to declare.

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