

Review Article

Advancements in the Use of Hydrogels for Regenerative Medicine: Properties and Biomedical Applications

Andrea Revete ^{1,2} Andrea Aparicio ¹ Bruno A. Cisterna ³ Javier Revete ⁴
Luis Luis ⁴ Ernesto Ibarra ² Edwin A. Segura González ⁵ Jay Molino ¹
and Diego Reginensi ^{1,2,6,7}

¹Biological Engineering, Faculty of Biosciences and Public Health, Universidad Especializada de las Americas (UDELAS), Panama City, Panama

²Biomedical Engineering, Faculty of Health Sciences and Engineering, Universidad Latina de Panama (ULATINA), Panama City, Panama

³Department of Neuroscience and Regenerative Medicine, Medical College of Georgia, Augusta University, Augusta, GA, USA

⁴Experimentia S.A, Development of Innovative Strategies in Biomedicine and Sustainable Development, Panama, Panama

⁵Instituto Técnico Superior Especializado (ITSE), Panama, Panama

⁶Integrative Neurobiology, School of Medicine, Universidad de Panama (UP), Panama, Panama

⁷Center for Biodiversity and Drug Discovery, INDICASAT-AIP, City of Knowledge, Panama, Panama

Correspondence should be addressed to Jay Molino; jay.molino@udelas.ac.pa and Diego Reginensi; diego.reginensi@indicat.org.pa

Received 29 May 2022; Revised 29 August 2022; Accepted 5 October 2022; Published 7 November 2022

Academic Editor: Ravin Narain

Copyright © 2022 Andrea Revete et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Due to their particular water absorption capacity, hydrogels are the most widely used scaffolds in biomedical studies to regenerate damaged tissue. Hydrogels can be used in tissue engineering to design scaffolds for three-dimensional cell culture, providing a novel alternative to the traditional two-dimensional cell culture as hydrogels have a three-dimensional biomimetic structure. This material property is crucial in regenerative medicine, especially for the nervous system, since it is a highly complex and delicate structure. Hydrogels can move quickly within the human body without physically disturbing the environment and possess essential biocompatible properties, as well as the ability to form a mimetic scaffold *in situ*. Therefore, hydrogels are perfect candidates for biomedical applications. Hydrogels represent a potential alternative to regenerating tissue lost after removing a brain tumor and/or brain injuries. This reason presents them as an exciting alternative to highly complex human physiological problems, such as injuries to the central nervous system and neurodegenerative disease.

1. Introduction

Biomaterials are materials designed to interact with biological systems to evaluate, treat, or substitute any tissue, organ, or function in a living organism. These can interact with a biological system in various applications in biomedicine [1, 2]. The purpose of biomaterials is to interact with the living organism; that is, contact with the biological system. Thus, some biomechanical requirements must be met: (i) biocompatibility, which is the ability of the material to induce the least immunological rejection possible with the human body functioning harmoniously in synchronization

with the host; (ii) adequate durability related to function; (iii) capacity to be bioreabsorbed (the body can metabolize it); (iv) biodegradability, which is the capacity of biological degradation; (v) desired mechanical properties depending on stresses and deformations that may occur in it; and (vi) they must not show toxic effects, the material must not be toxic or carcinogenic since it will be in contact with living organisms [3].

Biomaterials can be classified into synthetic and natural [4]. Among synthetics, we can find metals, ceramics, polymers, and composite materials [5]. These materials can be produced under controlled conditions; therefore, their

mechanical and physical properties can be predicted. However, a disadvantage of synthetic biomaterials is their reduced biocompatibility and their low ability to induce tissue regeneration [6]. On the other hand, natural biomaterials present better scaffold-cell interactions due to their specific molecular domains but are more complex in their molecular architecture [7]. Natural biomaterials can be protein-based and generally obtained from animal and human sources. They include bioactive molecules that mimic the extracellular environment (e.g., collagen, fibrin, gelatin, and keratin) or polysaccharide-based, mainly obtained from algae (alginates, agarose, galactans, and carrageenan), higher plants (cellulose, pectin, guar gum, and starch), microorganisms (xanthan gum, dextran, gellan gum, pullulan, and bacterial cellulose), and animals (hyaluronan, chondroitin, heparin, chitin, and chitosan) [8–11].

Natural biomaterials present a crucial subset of biomaterials for use as tissue engineering scaffolds due to their high bioactivity, biocompatible character, mechanical kinetics, and degradation properties, and their intrinsic structural resemblance to the extracellular matrix (ECM) of native tissue; furthermore, in their application in biological systems, they do not release cytotoxic by-products during their degradation. In addition, one of the main advantages of natural biomaterials is their innate ability to promote biological recognition, as they can positively support various cellular processes [6]. There is evidence that natural biomaterials, based on decellularized extracellular matrix (dMEC), which preserve native tissue properties and promote functional regeneration of injured tissue, can be used in various preclinical applications [12–14]. The tissue decellularization process mainly eliminates a specific tissue's cellular content, preserving the extracellular matrix's structure and specific chemical signals of the extracellular matrix [15]. dMEC has been shown to provide tissue-specific properties that influence multiple cellular processes, such as chemotaxis, mitogenesis, and differentiation [16]. In addition, recent advances in this field have shown that the development of injectable decellularized biomaterials can serve as protective vehicles for cells and trophic factors and promote *in situ* regeneration of damaged tissue [17]. These new applications of decellularized biomaterials implanted at the site of trauma or disease can promote the generation of a reparative niche that could lead to local tissue repair [18].

The biocompatibility and biofunctionality of implantable biomaterials remain significant challenges for their wide use in biological applications. Furthermore, they should come into direct contact with tissues and fluids. Therefore, the processes of immunological and biological response must be considered (e.g., inflammation in the receiving organism) [19]. Cell-biomaterial interaction is critical in integrating implants based on biomaterials, as it precedes cell proliferation, cell migration, and cell differentiation [20]. Cell adhesion is mediated by serum proteins adsorbed on the surface of the material, such as immunoglobulins, vitronectin, fibrinogen, and fibronectin, in addition to the biomechanical characteristics of the material [21]. The interaction between the cells and the biomaterial implies a series of molecular events that occur both at the intracellular

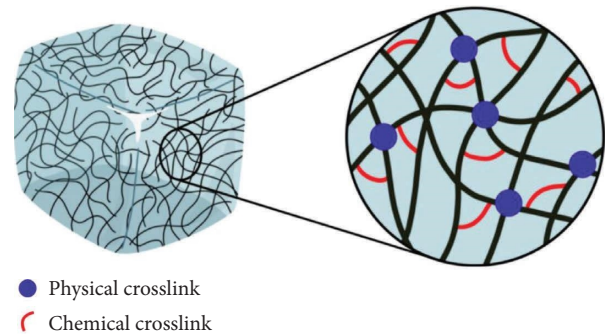


FIGURE 1: Hydrogel structure.

level that promote the expression of various transcription factors and gene regulation, as well as at the extracellular level mediated by multiple signals present in the ECM [22].

Cell adhesion is essential in cell viability studies since cell dispersion, migration, and differentiation depend on it. Therefore, controlling the interaction between cell receptors and the biomaterial surface is probably one of the most critical factors for designing biocompatible biomaterials in biomedical applications [23]. The process of cell adhesion to the surface of a biomaterial is thanks to adhesion proteins (fibronectin, laminin, and collagen) that use specific cell receptors found in the cell membrane (integrins). Integrins are responsible for recognizing adhesion proteins and facilitating their communication to achieve the adhesion process [24]. Biomaterials conditioned to meet specific topographical characteristics (porosity, stiffness, and roughness) allow cells to be guided or instructed in their expansion and development. Through cell studies, it has been possible to know that roughness is significant in the cell adhesion process, and it has been shown that this process, together with cell proliferation, is directly proportional to the level of roughness of the biomaterial surface [25].

Among the most widely used biomaterials in biomedical studies for tissue regeneration are hydrogels, which correspond to polymeric networks with high water absorption capacity; cross-linking changes a liquid polymer to a solid or gel by modifying the movement of the molecules that form the hydrogel. When polymer chains cross-link, they lose some of their ability to move as individual polymer chains. Their biomedical applications are diverse, highlighting their role as scaffolds in tissue injuries and sustained drug release systems. They are also three-dimensional scaffolds for various cell therapies, providing a microenvironment with biomimetic properties that promote the recovery of damaged tissue [26, 27] (Figure 1).

2. Basic Concepts of Hydrogels in Biomedicine

Hydrogels have been highly studied and used due to their many characteristics. First, we can refer to their capacity for high water content. Water must constitute at least 10 to 20% of the total weight (or volume) for a material to be a hydrogel; this property allows hydrogels a degree of flexibility similar to natural tissue in various applications in biomedicine [28]. This capacity is due to its hydrophilic

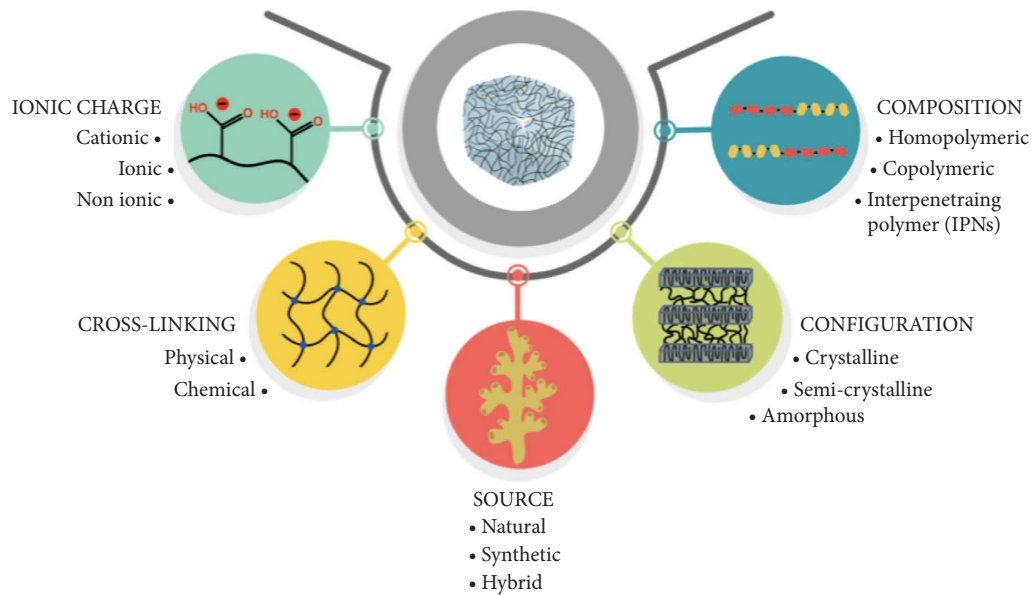


FIGURE 2: Hydrogel classification.

structure, which allows water to be conserved within its three-dimensional networks [29]. Indeed, hydrogels have the advantages of higher biocompatibility, biodegradability, adequate mechanical strength, a porous structure, and excellent ability for both adsorption and diffusion of water [30]. However, its potential in various biomedical applications is sometimes hampered by its low mechanical resistance and high electrical and thermal capacity [31]. Over the years, it has been possible to use scaffolds made from hydrogels to treat various types of tissues: cartilage, bone, muscle, fat, liver, and neurons [32].

2.1. Classification of Hydrogels. There are different ways of classifying a hydrogel; they can be through their (i) source, (ii) configuration of chains, (iii) polymeric composition, (iv) cross-linking type, and (v) network electrical charge [33] (Figure 2).

2.1.1. Source. Cross-linked polymers are referred to as hydrogels, whether derived from natural polymers, synthetic grafts, or both. Natural hydrogels (polymers of natural origin) have the characteristic of nontoxicity and are commercialized at a meager cost. They are generally extracted from natural sources such as seaweed, brown algae, bacterial culture, diverse polysaccharides (e.g., agarose, hyaluronic acid, and alginate), and proteins (e.g., collagen, gelatin, and fibrin) and decellularized extracellular matrix. Most are biocompatible, so they are widely used in tissue engineering. However, they lack the desired mechanical properties and can trigger immune responses when introduced into the human body [34]. In contrast, synthetic polymer hydrogels can be designed with established mechanical properties. However, they do not have any inherent bioactive properties; synthetic hydrogels encompass synthetic polymers that have more flexibility to couple the

mechanical properties of the hydrogel [35]. The most widely used synthetic polymers are polycaprolactone, poly(vinyl pyrrolidone) (PVP), poly(lactic acid) (PLA), poly(ethylene glycol) (PEG), and poly(vinyl alcohol) (PVA) [36].

2.1.2. Configuration of Chains. Synthetic hydrogels are generally amorphous in nature without any order at the molecular level, in contrast to biological gels containing ordered aggregates at the structural level [37]. Based on the structure composition, hydrogels have three types: amorphous, semicrystalline, and crystalline [38]. In crystalline hydrogels, the molecules are arranged in a three-dimensional order and have equal intermolecular forces. Crystalline hydrogels attribute exceptional mechanical strength and flexibility to various adverse conditions, including charged biopolymers, extreme acid/base environments, and unpredictable thermal shift conditions [39]. An irregular arrangement of molecules is observed in amorphous hydrogels, and the intermolecular forces are not equal and variable in the distance between the molecules that form the hydrogel. The hydrophilic polymer has not been cross-linked in the amorphous hydrogel and remains in a gel-like state. Various amorphous hydrogels contain additives such as collagen, calcium alginate, or CMC to be more absorbent [40]. Finally, semicrystalline hydrogels are a complex combination of amorphous and crystalline phases [41].

The hydrophilic nature of hydrogels is due to the presence of functional groups along the configuration of chains. When a hydrogel undergoes drying, the water evaporates, causing the structure to collapse. The gel passes from an expanded state, of maximum swelling, to a collapsed state with the consequent expulsion of the solvent. This process is reversible, in the dry state, called xerogel, the gel is a solid material, but in the presence of water, it expands until it reaches equilibrium swelling. This latter state results from a balance between the osmotic forces that cause water to

penetrate between the hydrophilic polymer chains and the cohesive forces between these chains that resist expansion [42].

2.1.3. Polymeric Composition. Based on the preparation method of a hydrogel, these can be divided into (a) homopolymeric hydrogels, (b) copolymeric hydrogels, and (c) interpenetrating hydrogels (IPN) [33]. Homopolymeric hydrogels are those hydrogels of polymeric networks created based on a particular monomer type, an essential structural element that encompasses any polymeric network. These hydrogels may comprise cross-linked skeletal structures depending on the character of the monomer and polymerization methods [43]. On the other hand, copolymeric hydrogels usually contain two or more distinct monomeric species with at least one hydrophilic monomeric constituent, assembled in a random, blocky, or alternating structural configuration along the red polymer chains. In addition to the cross-linking agent, these hydrogels are made up of two or more monomers that can be polymerized to form chains of random composition or structural blocks. This type of hydrogel can be synthesized when it is desired to incorporate or improve a specific property of one of the monomers in the resulting material, such as hydrophilic character and/or sensitivity to pH [44]. Finally, IPN hydrogels are defined as a polymer comprising two or more partially interlocked networks on a molecular scale with no covalent bonds between them and that cannot be separated except by breaking chemical bonds [45].

2.1.4. Cross-Linking Type. Depending on the cross-linking, they are distinguished physically and chemically as cross-linked hydrogels. Physical hydrogels are reversible and are formed by noncovalent bonds; chemical hydrogels are more stable and irreversible and are formed by covalent bonds between polymer chains. Polymer networks must obey certain conditions to form hydrogels: (a) interchain solid interactions to form stable coupling in the molecular network; and (b) the polymer network must encourage access and residence of water within the hydrogel [46]. Hydrogels that meet these demands can be prepared by noncovalent approaches such as electrostatic, hydrogen bonding, and hydrophobic forces between polymer chains. The hydrogels formed by these interactions are uniquely physical gels with high water sensitivity and thermo-reversibility [22].

Chemical or permanent hydrogels are covalently cross-linked; chemical cross-linking usually produces more stable hydrogels with better mechanical properties than physical hydrogels [25, 47]. Depending on the cross-linking type, chemical hydrogels can be obtained by radical polymerization, the reaction of functional groups, reagents, or enzymes [48, 49]. Chemical cross-linked hydrogel networks are easier to control than physical hydrogels because their synthesis and applications are not pH-dependent [50]. Furthermore, chemical cross-linking can transform the hydrogels' physical properties. Typically, swelling behavior, biodegradability, and mechanical strength have been modulated by covalent cross-linking, which can be carried

out by numerous approaches [51]. For example, chemical cross-linking of polysaccharides (e.g. starch, alginate, chitin, chitosan, cellulose, oligopeptides, and hyaluronic acid) and proteins (e.g., albumin and gelatin) is typically comprised of glycosidic and amino acid repeating units, respectively [25]. Therefore, there is a wide variety of well-defined hydrogels [52].

Physically cross-linked hydrogels present cross-links between polymer chains that are formed through attractive forces or interactions, such as hydrogen bonding or hydrophobic interactions. The formation of physical gels by the clustering of molecules causes the formation of free chain loops and thus inhomogeneities, which means short-lived lattice imperfections. This type of hydrogel has an advantage over chemical cross-linking methods in that they do not require chemical cross-linking agents, initiators, or photo-irradiation that could affect the integrity of cells or proteins. However, the main drawback of physically cross-linked hydrogels is their relative instability and possible rapid and unpredictable disintegration [53].

The cross-linked structure of the hydrogel can be achieved depending on the synthesis process or the raw materials used. Physical hydrogels present reversible networks due to the weakness of their interaction; meanwhile, chemical hydrogels present permanent networks, although with a minimum degree of swelling. Currently, the synthesis of both types of hydrogels has been widely reported because each of them shows favorable characteristics [52].

2.1.5. Network Electrical Charge. Hydrogels are also called "polyelectrolyte gels" when they have acidic or basic pendant groups such as carboxylic acid, sulfonic acid, primary amine, and quaternary ammonium salt [54]. Based on the network electrical charge, we have the following: (i) neutral hydrogels, also known as nonionic hydrogels. There is no charge on your spine or side meetings and due to the collaboration of water polymers, the nonionic hydrogel gradually swells in a liquid medium; (ii) anionic hydrogels have a negative charge. Hydrogel demonstrates more swelling in neutral to basic solutions due to dissociation at higher pH; and (iii) cationic hydrogels are positively charged cationic hydrogels. The predominant swelling is shown in acid media since its separation of chains is favored at low pH values [55, 56].

2.2. Hydrogel Swelling and pH-Sensitive Behavior and pH. Swelling is measured in terms of swelling ratio, the swelling weight ratio of swollen gel to dry gel. The swelling response in different matrix environments, such as water, pH, and ionic strength, is the characteristic of hydrogels to be used in various fields. The hydrogel responds to biological and environmental media, such as pH, ionic media, solvent, electric field, light exposure, and temperature [57]. The swelling kinetics and equilibrium are affected by different factors, such as the cross-linking ratio, the chemical nature of the polymers, the ionic media, and the synthesis state. The swelling of hydrogels is also affected by temperature and pH. pH-sensitive hydrogels swell due to the ionization of hydrophilic groups with variations in pH levels [58].

The pH-sensitive polymeric hydrogels restrict the pendant acidic and basic groups. Polymers containing acid groups, such as carboxylic acid and sulfonic acid, are known as anionic polymers, while polymers consisting of basic groups, such as amines, are cationic polymers. These groups accept or release protons and ionize with changes in pH [59]. Polymers that include a large number of such groups are recognized as polyelectrolytes. Furthermore, three-dimensional cross-linked polyelectrolytes show changes in swelling behavior with changes in pH. Pendant ionization in polyelectrolytes tends to cause differences in the corresponding acid or base's apparent dissociation constants (K_a). The swelling property of cross-linked polyelectrolytes is mainly due to the electrostatic repulsion of the ionized groups. Variations in pH, ionic strength, and electrostatic repulsion affect its properties. pH-sensitive hydrogels have been exploited for targeted and controlled oral drug release formulations [60].

For example, some studies have investigated the development of a new drug delivery system to decrease side effects and increase the efficiency of drug delivery based on the manufacture of hydrogel beads for use as a basil seed mucilage (BSM)-based drug delivery system and sodium alginate (SA) [61]; as well, another study developed a pH-sensitive hydrogel system based on fenugreek seed mucilage, extracted from *Trigonella foenum-graecum* seeds, to improve the oral bioavailability of methotrexate (MTX) [62]. In the same line of research, research has studied contact lenses as drug delivery media and the effect of physiological tear pH on drug release behavior [63]. pH-responsive dried hydrogels have been developed to indicate the healing degree of a wound [64]. Transdermal delivery systems for skin injury are being evaluated based on the physicochemical properties of pH-sensitive hydroxyethylcellulose (HEC)/hyaluronic acid (HA) complex hydrogels [65]. Various studies show how hydrogels can release, in a controlled manner, various drugs, factors, and physiological molecules in biomedical applications.

3. Hydrogel as an Alternative Biomaterial for Various Biomedical Purposes

In general, 2D cell cultures predominate in scientific research due to their relatively low cost (compared to others) and easy manipulation. In addition, they are not as complicated to work with as three-dimensional cultures. However, cell cultures based on three-dimensional structures are gaining popularity since they are more natural biochemical and biomechanical microenvironments [66]. Currently, there are challenges in three-dimensional cultures, such as the cellular extracellular matrix (ECM) interface, the mechanical microenvironment, spatiotemporal distributions of oxygen, and gradients of soluble factors and metabolic molecules [67], demonstrating that we are in the presence of a new and promising alternative for the biomedical research field. Actually, cell cultures, based on hydrogels, are used as three-dimensional scaffolds that provide structural integrity [68], serve as adhesive structures, tissue barriers [69], drug deposits [70], and deliver bioactive

agents that promote the tissue repair process [71]. Various studies have shown that hydrogel cell cultures represent 3D environments that allow cells to behave in a manner very similar to that observed *in vivo* conditions; thus, it would be a much more realistic model in physiological terms [72].

Hydrogels in regenerative medicine have been used as scaffolds to provide structural integrity and volume for cellular organization and morphological orientation, serve as tissue and bioadhesive barriers, act as drug reservoirs, deliver bioactive agents that foster the natural repair process, and encapsulate and deliver cells [73]. These cross-linked polymer chain structures possess high water content, easy transport of oxygen, nutrients, and waste, and realistic transport of soluble factors [74]. In addition, many hydrogels can be formed under mild, cytocompatibility conditions and are easily modified to possess ligands of cell adhesion, desired viscoelasticity, and degradability [75]. Although the water content is adjustable, as well as the gelation time and degradation due to the high water content and its physical and mechanical properties, hydrogels are very appropriate for applications in soft organs such as the brain [76].

A hydrogel has particular characteristics, highlighting its soft and elastic properties. They swell in the presence of water, considerably increasing their volume but maintaining their shape until reaching a physicochemical balance [77]. They are increasingly used as biomaterials because they are highly hydrophobic and can be loaded with different soluble molecules. Their biocompatibility is currently being studied in various human tissues [78, 79]. The unique physicochemical properties of hydrogels have aroused particular interest in their use for drug delivery applications and trophic factors [80]. The structure of the hydrogel is highly porous [81, 82]. With this, its hydrophilicity and the density of its intermolecular bonds can be easily adjusted, allowing it to be loaded with various specific molecules that are released systemically [77, 83].

Hydrogels share many fundamental physical properties with native tissues, such as high water content, the same range of elasticities, and mass transport [84]. Recent advances in hydrogel assembly and generation techniques have allowed the design of new three-dimensional (3D) scaffolds and microenvironments based on physiological microenvironments [85]. Moreover, many hydrogels are highly cytocompatible and easily adapted to possess cell adhesion ligands, stable viscoelasticity, and desired degradability [86]. The properties of hydrogels that must be considered in this postinjury environment are porosity, chemical composition, and mechanical properties. The hydrogel porosity is essential to stabilize the postinjury environment by allowing the flow of nutrients in and out of the scaffold. Porosity also affects cell infiltration [87], cell distribution, cell growth, proliferation, vascularization, and local angiogenesis [88]. Thus, hydrogels are injectable materials with *in situ* formation capacity; they are cytocompatible and support cell adhesion [89]. Today, hydrogels are employed for clinical applications such as wound healing and bone regeneration; more recently, they are used as scaffolds to provide a biomimetic 3D microenvironment for brain injuries [77, 90–92].

The mechanical properties that are sought in the design of these biomaterials are the appropriate integrity and strength because, for its application in tissue engineering, the hydrogel will have to provide functions of maintenance of loads or volumes. In addition to being able to transmit mechanical stimuli to the cells for their subsequent differentiation and development of tissues, the mechanical properties highlight viscoelasticity, which is essential in the design of hydrogels because hydrogels have shown unique abilities to mimic and interact positively with the injured tissue [93, 94]. Also, rigidity is considered a fundamental factor in cell viability, demonstrating that in cell cultures, the greater the rigidity of the hydrogel, the faster cell proliferation occurs [93], as well as the mechanosensing of the stiffness of their microenvironment, which affects cell differentiation through gene expression derived from the adhesion process of cytoskeleton proteins that are capable of tuning fates [95].

In addition, it should be considered that the mass transport properties are of great importance in the generation of hydrogels, as they must allow the appropriate transport of nutrients, metabolites, gases, and cells through the scaffold. The hydrogel design must be biocompatible, a fundamental requirement for promoting the adhesion of cells in scaffolding and the subsequent proliferation, migration, and cell differentiation [96]. Also, biodegradability is a fundamental property in the design of hydrogels for the release of drugs or particles; a hydrogel's biodegradability will define the degree of administration of the substance, as well as the degradation of the remaining hydrogel in the body [31]. In addition, hydrogels can encapsulate and deliver cells; this strategy is a technological procedure with the potential to treat a wide range of human diseases by replacing damaged or diseased cells. For this reason, cell encapsulation and delivery for cellular therapy have been proposed to treat different pathologies, including chronic skin lesions, bone damage, and brain injury [89].

Hydrogels are also used in the biomedical industry for therapeutic delivery; intraocular lenses, contact lenses, and corneal prostheses in ophthalmology; bone cement for orthopedics; wound dressings; 3D tissue scaffolds in regenerative medicine; self-healing materials; biosensors; and hemostasis bandages [26, 97], due to their excellent properties such as biocompatibility, water absorption, and adequate mechanical performance, among others [98]. Furthermore, when enhanced with nanofibers and peptides, they can be used as drug delivery systems. Recent research has been conducted on the feasibility of applying hydrogels in tissue engineering and drug delivery fields.

In most cases, hydrogels are used as homogeneous soft materials with uniform volume properties. To better mimic body tissues' anisotropic and complex structures, hierarchical hydrogels containing multiple layers with different biochemical signals and mechanical properties play a crucial role in biomedical applications. In addition, multilayer hydrogels, formulated by combining multiple cell types, drugs, or other exogenous factors, could account for controlled release behavior or cellular interactions [99]. Hydrogels are today among the most promising materials

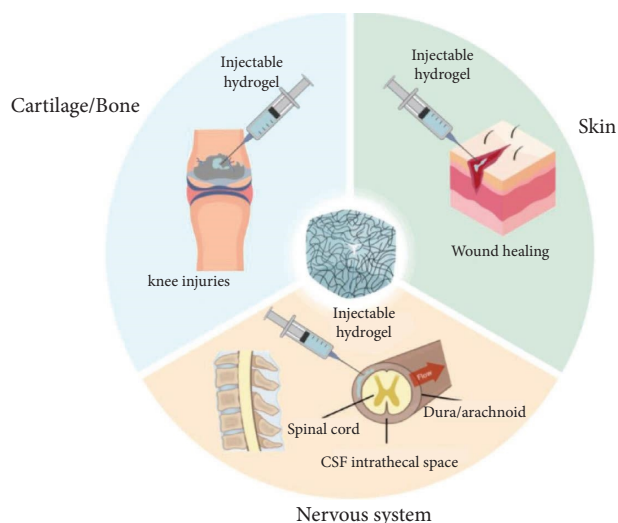


FIGURE 3: Applications of hydrogels.

for tissue engineering scaffolding (Figure 3). The development of hybrid hydrogels consisting of different polymers is based on numerous resources and has been applied to regenerative medicine, tissue engineering (including bone, cartilaginous, and meniscus regeneration, skin wound healing, and nervous system injuries), drug delivery, and bioelectronic interfaces [100, 101].

In summary, developing hydrogels for medical applications consists of three steps. The first step in the generation of hydrogels is the generation and characterization of the physicochemical cross-linking process; the second step is designing the response to specific stimuli (temperature, pH, ionic strength); and the third step is developing complex hybrid materials (e.g., PEG-PLA interaction) with a broad spectrum of tunable properties and trigger stimuli [82]. This last stage aimed to develop so-called “smart hydrogels” with various possible applications [102]. Hydrogel applications based on both natural and synthetic polymers offer endless possibilities to repair and regenerate a wide variety of tissues and organs [59], can respond to biological signals *in vivo* or remote triggers, and many other possible applications in biomaterials, biomedicine, and nanomedicine [82]. The ability of hydrogels to form *in situ* is advantageous for treating tissue lesions since, in their liquid phase, they can be administered through syringes (meaning a less invasive application) that allow them to fill areas with irregular lesions as opposed to solid biomaterials. This liquid-form administration can be accompanied by delivering soluble factors that directly restore tissue function to the injured area [29, 103]. Therefore, hydrogels can be particularly useful in complex environments that require advanced and invasive techniques to reach them, such as the central nervous system [104]. The main *in vivo* applications of hydrogels are in the controlled release of drugs in cartilage and bone diseases, the use of injectable hydrogels in wound healing and dressing, and the treatment of severe burns and ophthalmologic pathologies [105].

In this context, various applications in biomedicine are observed. For example, in bone regeneration, studies have

shown that hydrogels provide ideal environments for bone tissue to regenerate through cell therapy. Actually, the use of injectable hydrogels in bone injury allows for filling in the defective cavity; this is a great advantage from the biomedical point of view in irregular and large lesions [106]. It has been studied *in vivo* to improve bone density in sites of bone graft donations, which do not require a lot of mechanical strength. Biomolecule-loaded hydrogels have been demonstrated to promote bone regeneration, with gels loaded with chitosan, hydroxyapatite, and osteopontin. Due to its beneficial implantation methods (through injections), hydrogels have been designed to support fracture healing, long bone defects, cartilage defects, and osteoarthritis [90, 106].

Also, a series of studies of applications of hydrogels are in wound healing, burns/scalds, and diabetic foot. Wound healing is a complex physiological process broadly divided into four phases: hemostasis, inflammation, proliferation, and degeneration [107]. Injectable gels, both natural and synthetic, are being used for wound healing and skin regeneration for implantation purposes. Among the natural-based hydrogels, alginate is one of the main biomaterials used to heal damaged skin tissue. Composites with collagen, chitosan, and gelatin have been shown to improve skin regeneration processes [108]. Synthetic polymer-based hydrogels commonly used include poly (vinyl alcohol), poly (ethylene glycol), polycaprolactone, and polylactic acid. These are used to fabricate scaffolds capable of cell attachment and growth in cutaneous regeneration [109]. Currently, hydrogels are very popular as a therapeutic strategy in the delivery of antibiotics, antiseptics, antioxidants, and anti-inflammatories in the treatment of various skin wounds. In addition, hydrogels can be modified and studied to target wounds' specific pathophysiology since, depending on the type of wound, the origin, and the patient's condition and characteristics, the approach to wound dressing, healing, and repair must be different [91, 110]. Currently, several types of new hydrogel dressings are being continuously optimized, and their functions are progressively becoming ideal. However, there is still a gap in the ideal hydrogel depot, especially in treating chronic wounds.

According to various authors, the most challenging issue today is the generation of functional biomaterials to recover from nervous system injuries. The most crucial step in material bioengineering is brain repair by developing scaffolds that contain the mechanical, topological, and biochemical properties necessary to promote axonal regrowth in an injured brain [104]. The main advantage offered by hydrogels is that they have biomechanical and molecular properties that are compatible with the adjacent areas of injured tissue [18]. It is well known that the brain has a minimal capacity for tissue repair in the face of any damage (e.g., trauma, neurodegenerative diseases), thus resulting in a permanent loss of nervous tissue [111]; that is why one of the biggest challenges in the scientific field of research in biomedicine is to find solutions to brain injuries [112]. One strategy is the search for artificial supports, such as hydrogels, where cells can proliferate, migrate, and differentiate as if they were part of the original tissue. In addition,

various biomolecules, growth factors, and neurotrophins could be added to the biomaterial to help the recovery of injured brain tissue [34].

In the context of brain injuries, different hydrogel biomaterials based on materials such as alginate, gelatin, chitosan, methylcellulose, collagen, hyaluronic acid, and PLGA [113] have been used as microcarriers for the release of growth, angiogenic, and neurotrophic factors [114]. Currently, several well-documented studies show that stem cell-based therapy may be able to reduce the size of cortical infarction and increase blood vessel density [115]. However, cell transplant strategies often have low cell survival as their main drawback because the surrounding environment at the injury site has a series of signals capable of inhibiting the regenerative process [116]. Therefore, a possible way to address this problem is to encapsulate the cells to be transplanted into suitable biomaterials capable of protecting the cells in the implantation area, which can support cells [117].

Due to its many applications in the healthcare field (as shown in Table 1), this is the leading industry responsible for the increased market value of these biomaterials worldwide. Hydrogels have been a revolutionary option developed for contact lenses for the last 60 years, which is why they have become the biggest client for hydrogels, according to BCC Research. Moreover, it is expected that the wound-care field will become a rapid-growing representative for hydrogel applications in the next ten years, along with the cosmetic, skincare, and tissue engineering industries [118–120]. In 2016, the global hydrogel market reached a total of \$15.6 and was predicted to increase by a 6.3% compound annual growth rate (CAGR) (meaning a final value of \$22.3 billion), as described by BCC Research [120]. This prediction was proved correct by Precedence Research [118]. When the 2021 market value totaled \$22.45 billion by the end of that year and the beginning of 2022, the expected market value is set to maintain a 6% increase from 2022 to 2030. Exceptionally well-known companies dedicated to pharmaceuticals, medicine, and research are now some of the main producers and sellers of commercial hydrogels, such as Johnson & Johnson Services, Medtronic, Medline Industry, Advanced Biohealing, Inc., Organogenesis, Foryou Medical, Hisamitsu Pharmaceutical Co., Coloplast, and 3M Company, among many others [91, 121].

4. Discussion

Hydrogels are used in many fields of the biomedical industry, such as therapeutic administration [145, 146], bone cement in orthopedics [147], wound dressings in nursing [148], and tissue scaffolds in regenerative medicine [149], due to their excellent properties such as biocompatibility, water absorption, and adequate mechanical performance, among others [98]. In the pharmaceutical branch, hydrogels are being studied as drug delivery systems, consisting of hydrogels designed to load drugs inside for therapeutic administration. The design of hydrogels would specify their degradation characteristics depending on the type of drug release that is necessary; being hydrogels, the main advantage of this application is that the administration

TABLE 1: A summary of some of the main applications of hydrogels in biomedicine and regenerative medicine.

Hydrogel material	Applications	Ref.
<i>Synthetic</i>		
Polyvinyl alcohol (PVA)	(i) PVA hydrogel seeded with adipose-derived stem cells for wound dressing, promoting wound healing through stem cell delivery <i>in vitro</i> and <i>in vivo</i> .	[122]
Poly (ethylene glycol) (PEG)	(i) Tuning of alginate and PEG hydrogels allows fibroblast proliferation and increases osteogenic differentiation of MSCs. (ii) Photoclickable PEG hydrogels as a 3D cell culture scaffold for adult mouse cardiomyocytes, exhibiting biomimetic physiological and pathological microenvironments	[123, 124]
<i>Naturals</i>		
Hyaluronic acid (HA)	(i) Peptide-modified HA hydrogels to culture NSCs. Resulting in increased differentiation towards oligodendrocytes and neurons over 2D cultures on laminin-coated glass. (ii) Localized delivery of therapeutic cargo to CNS damage areas. (iii) Local delivery of BDNF on brain injury sites provoked by stroke.	[125–127]
Chitosan	(i) Transplantation of bone marrow mesenchymal stem cells and collagen-chitosan scaffolds to traumatic brain injury rats. (ii) Capacity to stand sufficient physiological activity of primary cultured neuronal cells. (iii) Skin infection control. Improved antimicrobial effect against <i>S. aureus</i> and <i>S. epidermidis</i>	[128, 129]
Collagen	(i) Three-dimensional collagen/silk fibroin scaffold (3D-CF) with cavities that simulate the anatomy of normal spinal cord. (ii) Wound dressing for refractory skin wounds accelerates the healing of deep second-degree burn wounds and the generation of new skin appendages. (iii) Nervous regeneration. <i>In vitro</i> study for peripheral nerve damage treatment. (iv) Bone tissue engineering. By developing a bone graft structure that can heal bone defects, having <i>in vitro</i> results of cellular proliferation and <i>in vivo</i> results of potential bone healing hydrogel. (v) Tissue regeneration in skin defects. Fabrication of bio-nano hydrogel systems demonstrating rapid tissue regeneration at the wound site in <i>in vivo</i> tests.	[130–133]
Alginate	(i) Neuroprotector for ischemic brain cells. (ii) Development of electroactive nanocomposite hydrogel. <i>In vitro</i> tests proved PC12 cells proliferate and spread evidently. (iii) Bone regeneration. Sustained delivery for bone regeneration in osteoporosis by <i>in vitro</i> and <i>in vivo</i> analysis	[134–136]
Fibrin	(i) Cavity repair resulting from a stroke. (ii) Neural progenitor cell delivery in spinal cord injury. Cell/neural tissue-compatible biomaterial for improving NPC <i>in vivo</i> survival.	[137, 138]
Gelatin	(i) Drug delivery. Improves wound healing and skin flap survival by the sustained release of basic fibroblast growth factor. (ii) Skin protection. Excellent UV protection properties and broad absorption of UV across UVA and UVB regions. (iii) Nerve regeneration scaffold. Ideal microstructure to prevent fibrous tissue ingrowth into the injury site.	[139–141]
Decellularized matrices	(i) Neural stem/progenitor cell microenvironment reconstruction, axonal regeneration, and spinal cord injury. (ii) Nervous regeneration. A hydrogel derived from porcine decellularized nerve tissue to repair peripheral nerve defects. (iii) Wound healing. The hydrogel yields significantly advanced wound closure in 24 h via the human dermal fibroblast scratch model.	[142–144]

of the hydrogel can be made by local injection, intravenous infusion, or surgical implantation, and once the drug is implanted and released, the hydrogel is designed to degrade in the body and prevent its extraction through additional clinical procedures [26, 97]. In most cases, hydrogels are used in tissue engineering to mimic the anisotropic and complex structure of body tissues through different biochemical signals and various mechanical properties that play a crucial role in various biomedical applications [149]. For example, there are studies in which hydrogels can act as implantable devices and be loaded with bioactive agents, allowing the controlled release of hormones, such as insulin [99].

Improving mechanical properties is one of the most desirable achievements in hydrogel engineering, and many researchers are currently working in this complex scientific area. However, most hydrogels possess only shallow mechanical properties, especially in a swollen state [150]. More recent studies have demonstrated new procedures to improve the mechanical properties of hydrogels by incorporating nanomaterials, such as graphene and its derivatives (e.g., carbon nanotubes and graphene oxide) [26, 98]. Several techniques have been developed to manufacture hydrogels that include microscale ordered particles (1–500 μm), called microgels or microparticle-based hydrogels (HMP) [96].

HMPs can be made from natural or synthetic polymers and manufactured in a variety of shapes and sizes using techniques that are often compatible with the encapsulation of biologics (e.g., cells and drugs) [151], and they can be administered by intra-articular injection or direct injection into tissues [152]. For many years, effective and reliable oral insulin delivery strategies have been sought to treat diabetes. Currently, hydrogels are being explored in oral insulin administration as it protects and prevents the degradation of the peptide during its passage through the stomach and allow its release into the bloodstream [153].

Hydrogels are used in many fields of the biomedical industry, such as therapeutic delivery, intraocular lenses, contact lenses, corneal prostheses in ophthalmology, bone cement for orthopedics, wound dressings, and 3D tissue scaffolds in regenerative medicine, due to their excellent properties such as biocompatibility, water absorption, and adequate mechanical performance, among others [98]. In most cases, hydrogels are used as homogeneous soft materials with uniform bulk properties. However, hierarchical hydrogels containing multiple layers with different biochemical signals and various mechanical properties play a crucial role in biomedical applications to better mimic the anisotropic and complex structure of body tissues.

Besides the already-known characteristics of hydrogels and their current uses, plenty of upcoming investigations promise to reach the full potential of these materials. For example, we can mention the use of chitosan for the administration of growth factors; a hybrid material made from chitosan-polyvinyl alcohol-epichlorohydrin with high regenerative prospects for elastic cartilage [154]. Similarly, these novel hydrogels can be used as fibers for actuators, artificial adhesives, transplantable tissue organs, and soft tissue recovery treatments, which is crucial to counteract the limitations of standard treatment to more effectively promote reparative dentinogenesis [155]. In summary, hydrogels can provide different biological enhancement insights in designing rigid tissue scaffolds for orthopedic insertion injuries. Thus, injectable hydrogels are promising scaffolds for cartilage and bone tissue engineering, owing to their minimal invasive properties and ability to match irregular defects.

Various methods for treating chronic wounds include debridement, hyperbaric oxygen therapy, ultrasound, electromagnetic therapies, negative pressure wound therapy, skin grafts, and hydrogel dressings. The intrinsic characteristics of hydrogels allow them to benefit from cutaneous healing essentially by supporting a moist environment. Hydrogel-based systems offer tremendous potential in skin regeneration for several reasons: they have long been recognized as the standard treatment for necrotic and sloughy wounds [156]; they offer sustained and/or stimuli-responsive delivery of antiseptics or antibiotics [157]; they can modulate the local inflammatory environment or incorporate antioxidants or anti-inflammatories [158]; and incorporating bioactive agents and different types of cells have been proposed as the future of advanced therapies [110]. Hydrogel dressings are more advantageous for chronic wound treatment because they can be conveniently designed

to meet the specific needs of the treatment of chronic wounds. Hydrogel dressings can promote wound healing by improving autolytic debridement, tissue hydration, and wound oxygenation. This helps to recover lost skin capacity after tissue damage. The main hydrogels used in skin regeneration are derived from chitosan, agar, gelatin, and methylcellulose [108]. Conversely, ethnomedicinal plants can treat wounds as they have no side effects, while in the case of chemical drugs, side effects are increasing. Based on this knowledge, the increase in applications of hydrogels of vegetable origin has now begun, for example, *Moringa oleifera*, *Aloe vera*, and others [159–161].

Another notable advance in biomedicine is photo-cross-linkable hydrogels since their properties can be manipulated in space-time through exposure to light to achieve desirable parameters translated into multiple biomedical applications (critical in tissue engineering), regenerative medicine, and drug delivery [162]. Hydrogels have become the allies of regenerative medicine recently. The advantages of the different rigidities of the different hydrogels and their impact on various treatments and applications, significantly influencing the treatment of stem cells (BMSC), are being studied [163]. Additionally, researchers propose simulating muscle, skin, and dermis tissue with the help of 3D hydrogels to maximize the rigidity qualities of the hydrogel [164]. It can be concluded that although the applications of hydrogels have been attenuating for a few years, there is still an extensive breakdown of possibilities for using hydrogels for multiple applications in areas such as regenerative medicine, tissue engineering, and many others.

An interesting approach to hydrogels has been their use to repair CNS injuries, mainly due to the properties mentioned before and their ability to be implanted through minimally invasive procedures for drug delivery purposes. To try to imitate the unique composition of tissues, several techniques have been developed to capture the microenvironment *in vivo* of tissues by employing the decellularization technique [165]. In addition, decellularized tissues and organs have become increasingly frequent in studies in cell culture and animal models [166]. The technology of hydrogels based on the decellularized extracellular matrix is an attractive approach for the treatment of CNS lesions because it has multiple positive effects, such as biocompatibility, immunomodulation, and tissue integration capacity, which provides a mimetic, minimally invasive platform that can be adjusted both mechanically and biochemically to deliver to the environment where various bioactive, angiogenic, and growth factors are implanted [167], as well as cells [168].

Recent studies integrate stem cells into neural cells by embedding them into native tissue hydrogels, such as ECM hydrogels. ECM-based hydrogels implanted in the brain cavity that have suffered tissue loss have demonstrated the ability to attract endogenous cells. Furthermore, these 3D gels can be formulated at different concentrations of proteins, allowing the control of their rheological and inductive properties [169]. All this will enable us to infer that, in the case of nervous system regeneration, the components that make up the brain

microenvironment may be necessary for neuronal maturation and differentiation [170, 171].

Several techniques have been developed to mimic the unique composition of tissues. That closely captures the microenvironment *in vivo* using decellularized tissues or cell-derived ECM proteins. Using decellularized tissues and organs has become increasingly prevalent in preclinical animal studies and human clinical applications [172]. ECM hydrogel technology is an attractive approach for treating CNS disease and trauma. Two fundamental steps are required for ECM hydrogel formation: (i) ECM material solubilization into monomeric protein components and (ii) neutralization controlled by temperature and/or pH to provoke instinctive reformation of the intramolecular bonds of the monomeric components in a hydrogel [173]. The water content, gelation time, and the degradation rate are all adjustable. Due to their high water content and physical and mechanical properties, hydrogels are highly appropriate for soft organs such as the brain [3].

In addition to the favorable biocompatibility, immunomodulation, and tissue remodeling effects of naturally derived ECM scaffolds, ECM's hydrogel technology provides a flexible platform that can be adjusted mechanically and biochemically to multiple implantation environments [127, 174]. Factors, including cells, growth factors, and other bioactive factors can be delivered through minimally invasive injections. Initial studies have shown upbeat delivery and remodeling of tissues in animal models of CNS injury [174, 175]. In addition, decellularized brain ECM from animal models is reported to be compatible with neural cells as induced pluripotent stem cell-derived neurons grow and mature on such scaffolds. In recent work, cortex-derived neural networks were more abundant when implanted within decellularized brain ECM scaffolds than type I collagen and Matrigel controls [176, 177].

There has been a growing interest in transplanting different stem cells to restore neurological functions and improve behavioral recovery after an ischemic attack. Several well-documented studies show that transplanted stem cells can enhance ischemic stroke by reducing the cortical infarct size and increasing the blood vessels' density. However, cell transplantation strategies often suffer from poor cell survival due to the toxicity of the surrounding environment at the injury site. One possible way to address this problem is by encapsulating the cells to be transplanted in suitable microenvironments that protect the cells during and after implantation and support cell growth and survival. In addition, the engineering and design of the biomaterials to be used can influence transplanted or endogenous stem cells' subsequent fate by directing their differentiation; this is when hydrogels are studied and designed as scaffolds for stem cell implantation and their subsequent differentiation [175].

Thus, hydrogel studies' future is going towards regenerative medicine through stem cells in various organ systems. Even though it is uncertain that these applications will be suitable for clinical trials, the available literature suggests that the road researchers are taking to study and develop hydrogels is the right one. So far, the results make them a

promising biomaterial for future research concerning bioengineering and regenerative medicine.

5. Conclusions

Hydrogels are an essential tool for regenerative medicine and biomedical engineering; their applications have been and are still being tested in most organ systems due to the promising results already obtained. These biomaterials are so widely studied that their properties include water absorption, biocompatibility, and the ability to mimic native tissue for cell proliferation and differentiation. Some promising biomaterials are light-sensitive hydrogels that have been researched for possible application in drug delivery, microlenses, and biosensors due to the remote and non-invasive nature of their activation process. This hydrogel type has promising roles in bioengineered applications to release molecular and cellular species. These materials offer real advantages to the organizational engineering community and will likely attract increasing attention in the coming years. In the future, researchers hope to explore the functions of various hydrogel derivatives in biomaterial formulations, which will be an excellent opportunity to develop new materials with new properties.

Furthermore, different hydrogel materials can be specially modified and functionalized to achieve better performance. Hydrogels' exploitation is constantly increasing after evidence of their even broader therapeutic potential due to their ability to induce tissue regeneration. The innovation in advanced tissue repair is further directed to the development of so-called smart hydrogels, which combine hydrogels with components that enhance the primary purpose of providing a beneficial environment for tissue regeneration.

Hydrogels have shown the advantage of allowing researchers to modify their physical and chemical properties to meet each study's needs. Thus, hydrogels are great candidates for vastly different applications besides the hundreds of known commercial applications that are responsible for their exponential growth in different markets. In addition, many newly developed hydrogels perform well *in vitro* tests but not so well *in vivo*. From *in vitro* experiments to *in vivo*, we need a more systematic strategy to develop strategies for advanced biomaterials.

Disclosure

The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Conflicts of Interest

DR was supported by the SENACYT, Panamá: (Grant Nos. FID17-078 and FID18-042), PFID-INF-2020-22 and IDDS22-09; SENACYT, Panamá, supported JR: (Grant No. FID18-042). JM was supported by SENACYT, Panamá:

(Grant Nos. APY19-009 and MINBUZA-2020.926889) from the Department of European Integration, Netherlands. The authors declare that there are no conflicts of interest.

Authors' Contributions

Original draft preparation was performed by AR and DR. Review and editing were performed by AR, AA, JR, LL, BC, ES, EI, DR, and JM. Visualization was carried out by JM. Funding acquisition and final editing were performed by DR, JM, and EI.

Acknowledgments

The support of the Panamanian National System of Researchers (SNI) is appreciated in this research.

References

- [1] G. Orive, E. Anitua, J. L. Pedraz, and D. F. Emerich, "Biomaterials for promoting brain protection, repair and regeneration," *Nature Reviews Neuroscience*, vol. 10, no. 9, pp. 682–692, 2009.
- [2] J. M. Singelyn, J. A. DeQuach, S. B. Seif-Naraghi, R. B. Littlefield, P. J. Schup-Magoffin, and K. L. Christman, "Naturally derived myocardial matrix as an injectable scaffold for cardiac tissue engineering," *Biomaterials*, vol. 30, no. 29, pp. 5409–5416, 2009.
- [3] M. J. Hernandez, R. Gaetani, V. M. Pieters et al., "Decellularized extracellular matrix hydrogels as a delivery platform for MicroRNA and extracellular vesicle therapeutics," *Advanced Therapeutics*, vol. 1, no. 3, Article ID 1800032, 2018.
- [4] D. D. Kiradzhyska and R. D. Mantcheva, "Overview of biocompatible materials and their use in medicine," *Folia Medica*, vol. 61, no. 1, pp. 34–40, 2019.
- [5] M. Alizadeh-Osgouei, Y. Li, and C. Wen, "A comprehensive review of biodegradable synthetic polymer-ceramic composites and their manufacture for biomedical applications," *Bioactive Materials*, vol. 4, no. 1, pp. 22–36, 2019.
- [6] F. M. Chen and X. Liu, "Advancing biomaterials of human origin for tissue engineering," *Progress in Polymer Science*, vol. 53, pp. 86–168, 2016.
- [7] L. P. Datta, S. Manchineella, and T. Govindaraju, "Biomolecules-derived biomaterials," *Biomaterials*, vol. 230, Article ID 119633, 2020.
- [8] F. López-Gallego and A. I. Benítez-Mateos, "Manufacturing of protein-based biomaterials coupling cell-free protein synthesis with protein immobilization," *Methods in Molecular Biology*, vol. 2100, pp. 335–343, 2020.
- [9] A. Ounkaew, P. Kasemsiri, K. Jetsrisuparb et al., "Synthesis of nanocomposite hydrogel based carboxymethyl starch/polyvinyl alcohol/nanosilver for biomedical materials," *Carbohydrate Polymers*, vol. 248, Article ID 116767, 2020.
- [10] F. G. Torres, S. Commeaux, and O. P. Troncoso, "Starch-based biomaterials for wound-dressing applications," *Starch—Stärke*, vol. 65, no. 7–8, pp. 543–551, 2013.
- [11] S. Tiwari, R. Patil, and P. Bahadur, "Polysaccharide based scaffolds for soft tissue engineering applications," *Polymers*, vol. 11, no. 1, p. 1, 2018.
- [12] A. T. Rowley, R. R. Nagalla, S. W. Wang, and W. F. Liu, "Extracellular matrix-based strategies for immunomodulatory biomaterials engineering," *Advanced Healthcare Materials*, vol. 8, no. 8, Article ID e1801578, 2019.
- [13] D. E. Heath, "A review of decellularized extracellular matrix biomaterials for regenerative engineering applications," *Regenerative Engineering and Translational Medicine*, vol. 5, no. 2, pp. 155–166, 2019.
- [14] Y. Jiang, R. Li, C. Han, and L. Huang, "Extracellular matrix grafts: from preparation to application (review)," *International Journal of Molecular Medicine*, vol. 47, no. 2, pp. 463–474, 2020.
- [15] R. Guruswamy Damodaran and P. Vermette, "Tissue and organ decellularization in regenerative medicine," *Biotechnology Progress*, vol. 34, no. 6, pp. 1494–1505, 2018.
- [16] T. Hoshiba, H. Lu, N. Kawazoe, and G. Chen, "Decellularized matrices for tissue engineering," *Expert Opinion on Biological Therapy*, vol. 10, no. 12, pp. 1717–1728, 2010.
- [17] L. Yu, Z. J. Sun, Q. C. Tan et al., "Thermosensitive injectable decellularized nucleus pulposus hydrogel as an ideal biomaterial for nucleus pulposus regeneration," *Journal of Biomaterials Applications*, vol. 35, no. 2, pp. 182–192, 2020.
- [18] L. R. Nih, S. T. Carmichael, and T. Segura, "Hydrogels for brain repair after stroke: an emerging treatment option," *Current Opinion in Biotechnology*, vol. 40, pp. 155–163, 2016.
- [19] L. P. Frazão, J. Vieira De Castro, and N. M. Neves, "In vivo evaluation of the biocompatibility of biomaterial device," *Advances in Experimental Medicine and Biology*, vol. 1250, pp. 109–124, 2020.
- [20] Y. Kang, "Cell biological techniques and cell-biomaterial interactions," *Cells*, vol. 9, no. 9, 2020.
- [21] F. Karimi, A. J. O'Connor, G. G. Qiao, and D. E. Heath, "Integrin clustering matters: a review of biomaterials functionalized with multivalent integrin-binding ligands to improve cell adhesion, migration, differentiation, angiogenesis, and biomedical device integration," *Advanced Healthcare Materials*, vol. 7, no. 12, Article ID e1701324, 2018.
- [22] X. Li, R. Li, Z. Liu, X. Gao, S. Long, and G. Zhang, "Integrated functional high-strength hydrogels with metal-coordination complexes and H-bonding dual physically cross-linked networks," *Macromolecular Rapid Communications*, vol. 39, no. 23, Article ID e1800400, 2018.
- [23] S. Gonçalves, F. Dourado, and L. R. Rodrigues, "Overview on cell-biomaterial interactions," in *Advanced Polymers in Medicine*, F. Puoci, Ed., Springer International Publishing, Berlin, Germany, 2015.
- [24] H. S. Dhowre, S. Rajput, N. A. Russell, and M. Zelzer, "Responsive cell-material interfaces," *Nanomedicine*, vol. 10, no. 5, pp. 849–871, 2015.
- [25] E. M. Ahmed, "Hydrogel: preparation, characterization, and applications: a review," *Journal of Advanced Research*, vol. 6, no. 2, pp. 105–121, 2015.
- [26] Q. Chai, Y. Jiao, and X. Yu, "Hydrogels for biomedical applications: their characteristics and the mechanisms behind them," *Gels (Basel, Switzerland)*, vol. 3, no. 1, p. 6, 2017.
- [27] H. Cao, L. Duan, Y. Zhang, J. Cao, and K. Zhang, "Current hydrogel advances in physicochemical and biological response-driven biomedical application diversity," *Signal Transduction and Targeted Therapy*, vol. 6, no. 1, p. 426, 2021.
- [28] N. A. Peppas and A. S. Hoffman, "1.3.2E—hydrogels," in *Biomaterials Science*, W. R. Wagner, S. E. Sakiyama-Elbert, G. Zhang, and M. J. Yaszemski, Eds., Academic Press, Cambridge, MA, USA, 2020.
- [29] V. Gradinaru, J. Treweek, K. Overton, and K. Deisseroth, "Hydrogel-tissue chemistry: principles and applications,"

- Annual Review of Biophysics*, vol. 47, no. 1, pp. 355–376, 2018.
- [30] Y. Zhu, Q. Zhang, X. Shi, and D. Han, “Hierarchical hydrogel composite interfaces with robust mechanical properties for biomedical applications,” *Advanced Materials*, vol. 31, no. 45, Article ID e1804950, 2019.
 - [31] A. Chyzy and M. E. Plonska-Brzezinska, “Hydrogel properties and their impact on regenerative medicine and tissue engineering,” *Molecules*, vol. 25, no. 24, p. 5795, 2020.
 - [32] C. Gazia, R. Tamburrini, A. Asthana et al., “Extracellular matrix-based hydrogels obtained from human tissues: a work still in progress,” *Current Opinion in Organ Transplantation*, vol. 24, no. 5, pp. 604–612, 2019.
 - [33] M. R. Singh, S. Patel, and D. Singh, “Chapter 9—natural polymer-based hydrogels as scaffolds for tissue engineering,” in *Nanobiomaterials in Soft Tissue Engineering*, A. M. Grumezescu, Ed., pp. 231–260, William Andrew Publishing, Norwich, NY, USA, 2016.
 - [34] M. C. Catoira, L. Fusaro, D. Di Francesco, M. Ramella, and F. Boccafroschi, “Overview of natural hydrogels for regenerative medicine applications,” *Journal of Materials Science: Materials in Medicine*, vol. 30, no. 10, p. 115, 2019.
 - [35] S. Vijayavenkataraman, N. Vialli, J. Y. H. Fuh, and W. F. Lu, “Conductive collagen/polypyrrole-b-polycaprolactone hydrogel for bioprinting of neural tissue constructs,” *International Journal of Bioprinting*, vol. 5, 2019.
 - [36] M. Müllner, “Functional natural and synthetic polymers,” *Macromolecular Rapid Communications*, vol. 40, no. 10, Article ID e1900151, 2019.
 - [37] O. Okay, “Semicrystalline physical hydrogels with shape-memory and self-healing properties,” *Journal of Materials Chemistry B*, vol. 7, no. 10, pp. 1581–1596, 2019.
 - [38] P. B. Mohite and S. Adhav, “A hydrogels: methods of preparation and applications,” *International Journal of Advances in Pharmaceutics*, vol. 6, no. 3, pp. 79–85, 2017.
 - [39] Y. You, R. Xing, Q. Zou, F. Shi, and X. Yan, “High-tolerance crystalline hydrogels formed from self-assembling cyclic dipeptide,” *Beilstein Journal of Nanotechnology*, vol. 10, pp. 1894–1901, 2019.
 - [40] S. Tripathi, S. J. Patel, R. D. Patel et al., “A review on bio-compatible hydrogel: formulation aspect and evaluation,” *Research Journal of Pharmaceutical Dosage Forms and Technology*, vol. 10, no. 2, pp. 119–122, 2018.
 - [41] V. Vachhrajani and P. Khakhkhar, “Moisturising dressings,” in *Science of Wound Healing and Dressing Materials*, V. Vachhrajani and P. Khakhkhar, Eds., pp. 69–71, Springer, Singapore, 2020.
 - [42] H. P. S. Abdul Khalil, E. B. Yahya, H. A. Tajarudin, V. Balakrishnan, and H. Nasution, “Insights into the role of biopolymer-based xerogels in biomedical applications,” *Gels (Basel, Switzerland)*, vol. 8, no. 6, p. 334, 2022.
 - [43] P. Vinchi, S. U. Rawal, and M. M. Patel, “Chapter 19—biodegradable hydrogels,” in *Drug Delivery Devices and Therapeutic Systems*, E. Chappel, Ed., pp. 395–419, Academic Press, Cambridge, MA, USA, 2021.
 - [44] M. Formanek, L. Rovigatti, E. Zaccarelli, F. Sciortino, and A. J. Moreno, “Gel formation in reversibly cross-linking polymers,” *Macromolecules*, vol. 54, no. 14, pp. 6613–6627, 2021.
 - [45] C. O. Crosby, B. Stern, N. Kalkunte, S. Pedahzur, S. Ramesh, and J. Zoldan, “Interpenetrating polymer network hydrogels as bioactive scaffolds for tissue engineering,” *Reviews in Chemical Engineering*, vol. 38, no. 3, pp. 347–361, 2022.
 - [46] L. Lu, S. Yuan, J. Wang et al., “The formation mechanism of hydrogels,” *Current Stem Cell Research and Therapy*, vol. 13, no. 7, pp. 490–496, 2018.
 - [47] M. F. Akhtar, M. Hanif, and N. M. Ranjha, “Methods of synthesis of hydrogels—a review,” *Saudi Pharmaceutical Journal*, vol. 24, no. 5, pp. 554–559, 2016.
 - [48] B. Elham, M. Hosseini, M. Mohajer et al., “Enzymatic crosslinked hydrogels for biomedical application,” *Polymer Science—Series A*, vol. 63, 2021.
 - [49] U. S. K. Madduma-Bandarage and S. V. Madihally, “Synthetic hydrogels: synthesis, novel trends, and applications,” *Journal of Applied Polymer Science*, vol. 138, no. 19, Article ID 50376, 2021.
 - [50] D. Ye, C. Chang, and L. Zhang, “High-strength and tough cellulose hydrogels chemically dual cross-linked by using low- and high-molecular-weight cross-linkers,” *Biomacromolecules*, vol. 20, no. 5, pp. 1989–1995, 2019.
 - [51] J. Ahn, J. Ryu, G. Song, M. Whang, and J. Kim, “Network structure and enzymatic degradation of chitosan hydrogels determined by crosslinking methods,” *Carbohydrate Polymers*, vol. 217, pp. 160–167, 2019.
 - [52] M. Bustamante-Torres, D. Romero-Fierro, B. Arcentales-Vera, K. Palomino, H. Magaña, and E. Bucio, “Hydrogels classification according to the physical or chemical interactions and as stimuli-sensitive materials,” *Gels (Basel, Switzerland)*, vol. 7, no. 4, p. 182, 2021.
 - [53] W. Hu, Z. Wang, Y. Xiao, S. Zhang, and J. Wang, “Advances in crosslinking strategies of biomedical hydrogels,” *Biomaterials Science*, vol. 7, no. 3, pp. 843–855, 2019.
 - [54] N. Wanasingha, P. Dorishetty, N. K. Dutta, and N. R. Choudhury, “Polyelectrolyte gels: fundamentals, fabrication and applications,” *Gels (Basel, Switzerland)*, vol. 7, no. 3, p. 148, 2021.
 - [55] Z. Ahmad, S. Salman, S. A. Khan et al., “Versatility of hydrogels: from synthetic strategies, classification, and properties to biomedical applications,” *Gels (Basel, Switzerland)*, vol. 8, no. 3, p. 167, 2022.
 - [56] O. Erol, A. Pantula, W. Liu, and D. H. Gracias, “Transformer hydrogels: a review,” *Advanced Materials Technologies*, vol. 4, no. 4, Article ID 1900043, 2019.
 - [57] T. Jayaramudu, H. U. Ko, H. C. Kim, J. W. Kim, and J. Kim, “Swelling behavior of polyacrylamide-cellulose nanocrystal hydrogels: swelling kinetics, temperature, and pH effects,” *Materials*, vol. 12, no. 13, 2019.
 - [58] S. Hollingshead and J. C. Liu, “pH-sensitive mechanical properties of elastin-based hydrogels,” *Macromolecular Bioscience*, vol. 20, no. 4, Article ID e1900369, 2020.
 - [59] H. Zhao, K. Xu, P. Zhu, C. Wang, and Q. Chi, “Smart hydrogels with high tunability of stiffness as a biomimetic cell carrier,” *Cell Biology International*, vol. 43, no. 2, pp. 84–97, 2019.
 - [60] X. Bai, Z. Bao, S. Bi et al., “Chitosan-based thermo/pH double sensitive hydrogel for controlled drug delivery,” *Macromolecular Bioscience*, vol. 18, no. 3, Article ID 1700305, 2018.
 - [61] N. Srikhao, K. Chirochapas, N. Kwansanei et al., “Multi-responsive optimization of novel pH-sensitive hydrogel beads based on basil seed mucilage, alginate, and magnetic particles,” *Gels*, vol. 8, no. 5, p. 274, 2022.
 - [62] H. R. Hussain, S. Bashir, A. Mahmood et al., “Fenugreek seed mucilage grafted poly methacrylate pH-responsive hydrogel: a promising tool to enhance the oral bioavailability of methotrexate,” *International Journal of Biological Macromolecules*, vol. 202, pp. 332–344, 2022.

- [63] G. Kim, H. J. Kim, and H. Noh, "pH sensitive soft contact lens for selective drug-delivery," *Macromolecular Research*, vol. 26, no. 3, pp. 278–283, 2018.
- [64] A. Tamayol, M. Akbari, Y. Zilberman et al., "Flexible pH-sensing hydrogel fibers for epidermal applications," *Advanced Healthcare Materials*, vol. 5, no. 6, pp. 711–719, 2016.
- [65] S. S. Kwon, B. J. Kong, and S. N. Park, "Physicochemical properties of pH-sensitive hydrogels based on hydroxyethyl cellulose-hyaluronic acid and for applications as transdermal delivery systems for skin lesions," *European Journal of Pharmaceutics and Biopharmaceutics*, vol. 92, pp. 146–154, 2015.
- [66] C. Jensen and Y. Teng, "Is it time to start transitioning from 2D to 3D cell culture?" *Frontiers in Molecular Biosciences*, vol. 7, p. 33, 2020.
- [67] D. Gonzalez-Nieto, L. Fernandez-Garcia, J. Perez-Rigueiro, G. V. Guinea, and F. Panetsos, "Hydrogels-assisted cell engraftment for repairing the stroke-damaged brain: chimera or reality," *Polymers*, vol. 10, no. 2, p. 184, 2018.
- [68] A. Yosef, O. Kossover, I. Mironi-Harpaz et al., "Fibrinogen-based hydrogel modulus and ligand density effects on cell morphogenesis in two-dimensional and three-dimensional cell cultures," *Advanced Healthcare Materials*, vol. 8, no. 13, Article ID e1801436, 2019.
- [69] K. Zhang and A. Manninen, "3D cell culture models of epithelial tissues," *Methods in Molecular Biology*, vol. 1926, pp. 77–84, 2019.
- [70] A. Shehzad, V. Ravinayagam, H. AlRumaih et al., "Application of three-dimensional (3D) tumor cell culture systems and mechanism of drug resistance," *Current Pharmaceutical Design*, vol. 25, no. 34, pp. 3599–3607, 2019.
- [71] B. S. Kim, Y. W. Kwon, J. S. Kong et al., "3D cell printing of in vitro stabilized skin model and in vivo pre-vascularized skin patch using tissue-specific extracellular matrix bioink: a step towards advanced skin tissue engineering," *Biomaterials*, vol. 168, pp. 38–53, 2018.
- [72] J. C. Fontoura, C. Viezzer, F. G. Dos Santos et al., "Comparison of 2D and 3D cell culture models for cell growth, gene expression and drug resistance," *Materials Science and Engineering: C*, vol. 107, Article ID 110264, 2020.
- [73] B. V. Slaughter, S. S. Khurshid, O. Z. Fisher, A. Khademhosseini, and N. A. Peppas, "Hydrogels in regenerative medicine," *Advanced Materials*, vol. 21, no. 32–33, pp. 3307–3329, 2009.
- [74] K. T. Nguyen and J. L. West, "Photopolymerizable hydrogels for tissue engineering applications," *Biomaterials*, vol. 23, no. 22, pp. 4307–4314, 2002.
- [75] M. P. Lutolf and J. A. Hubbell, "Synthetic biomaterials as instructive extracellular microenvironments for morphogenesis in tissue engineering," *Nature Biotechnology*, vol. 23, no. 1, pp. 47–55, 2005.
- [76] G. Potjewyd, S. Moxon, T. Wang, M. Domingos, and N. M. Hooper, "Tissue engineering 3D neurovascular units: a biomaterials and bioprinting perspective," *Trends in Biotechnology*, vol. 36, no. 4, pp. 457–472, 2018.
- [77] J. Kopecek, "Hydrogel biomaterials: a smart future?" *Biomaterials*, vol. 28, no. 34, pp. 5185–5192, 2007.
- [78] I. M. El-Sherbiny and M. H. Yacoub, "Hydrogel scaffolds for tissue engineering: progress and challenges," *Global Cardiology Science and Practice*, vol. 2013, no. 3, pp. 38–42, 2013.
- [79] M. Navarro and J. A. Planell, "Is nanotechnology the key to unravel and engineer biological processes?" *Methods in Molecular Biology*, vol. 811, pp. 1–16, 2012.
- [80] C. J. Medberry, P. M. Crapo, B. F. Siu et al., "Hydrogels derived from central nervous system extracellular matrix," *Biomaterials*, vol. 34, no. 4, pp. 1033–1040, 2013.
- [81] M. Navarro, S. D. Valle, S. Martinez et al., "New macroporous calcium phosphate glass ceramic for guided bone regeneration," *Biomaterials*, vol. 25, no. 18, pp. 4233–4241, 2004.
- [82] L. L. Palmese, R. K. Thapa, M. O. Sullivan, and K. L. Kiick, "Hybrid hydrogels for biomedical applications," *Current Opinion in Chemical Engineering*, vol. 24, pp. 143–157, 2019.
- [83] M. Sheikhpour, L. Barani, and A. Kasaean, "Biomimetics in drug delivery systems: a critical review," *Journal of Controlled Release*, vol. 253, pp. 97–109, 2017.
- [84] N. Martin and G. Youssef, "Dynamic properties of hydrogels and fiber-reinforced hydrogels," *Journal of the Mechanical Behavior of Biomedical Materials*, vol. 85, pp. 194–200, 2018.
- [85] M. Gonzalez Gonzalez, I. Cichon, A. Scisłowska-Czarnecka, and E. Kolaczowska, "Challenges in 3D culturing of neutrophils: assessment of cell viability," *Journal of Immunological Methods*, vol. 457, pp. 73–77, 2018.
- [86] A. Kirschning, N. Dibbert, and G. Dräger, "Chemical functionalization of polysaccharides-towards biocompatible hydrogels for biomedical applications," *Chemistry—A European Journal*, vol. 24, no. 6, pp. 1231–1240, 2018.
- [87] J. T. S. Pettikiriachchi, C. L. Parish, M. S. Shoichet, J. S. Forsythe, and D. R. Nisbet, "Biomaterials for brain tissue engineering," *Australian Journal of Chemistry*, vol. 63, no. 8, p. 1143, 2010.
- [88] Z. Z. Khaing, R. C. Thomas, S. A. Geissler, and C. E. Schmidt, "Advanced biomaterials for repairing the nervous system: what can hydrogels do for the brain?" *Materials Today*, vol. 17, no. 7, pp. 332–340, 2014.
- [89] G. D. Nicodemus and S. J. Bryant, "Cell encapsulation in biodegradable hydrogels for tissue engineering applications," *Tissue Engineering Part B Reviews*, vol. 14, no. 2, pp. 149–165, 2008.
- [90] J. Nallusamy and R. K. Das, "Hydrogels and their role in bone tissue engineering: an overview," *Journal of Pharmacy and BioAllied Sciences*, vol. 13, 2021.
- [91] K.-H. Jeong, D. Park, and Y.-C. Lee, "Polymer-based hydrogel scaffolds for skin tissue engineering applications: a mini-review," *Journal of Polymer Research*, vol. 24, no. 7, p. 112, 2017.
- [92] J. George, C.-C. Hsu, L. T. B. Nguyen, H. Ye, and Z. Cui, "Neural tissue engineering with structured hydrogels in CNS models and therapies," *Biotechnology Advances*, vol. 42, Article ID 107370, 2020.
- [93] H. Jo, M. Yoon, M. Gajendiran, and K. Kim, "Recent strategies in fabrication of gradient hydrogels for tissue engineering applications," *Macromolecular Bioscience*, vol. 20, no. 3, Article ID e1900300, 2020.
- [94] A. Vedadghavami, F. Minooei, M. H. Mohammadi et al., "Manufacturing of hydrogel biomaterials with controlled mechanical properties for tissue engineering applications," *Acta Biomaterialia*, vol. 62, pp. 42–63, 2017.
- [95] L. R. Smith, S. Cho, and D. E. Discher, "Stem cell differentiation is regulated by extracellular matrix mechanics," *Physiology*, vol. 33, no. 1, pp. 16–25, 2018.
- [96] G. Chen, W. Tang, X. Wang, X. Zhao, C. Chen, and Z. Zhu, "Applications of hydrogels with special physical properties in biomedicine," *Polymers*, vol. 11, no. 9, p. 1420, 2019.
- [97] S. R. Singh, V. Komal, and R. S. Shree, "Advanced hydrogels for biomedical applications," *Biomedical Journal of Scientific & Technical Research*, vol. 5, no. 1, 2018.

- [98] A. Serrano-Aroca, J. F. Ruiz-Pividal, and M. Llorens-Gomez, "Enhancement of water diffusion and compression performance of crosslinked alginate films with a minuscule amount of graphene oxide," *Scientific Reports*, vol. 7, no. 1, Article ID 11684, 2017.
- [99] G. Liu, Z. Ding, Q. Yuan, H. Xie, and Z. Gu, "Multi-layered hydrogels for biomedical applications," *Frontiers of Chemistry*, vol. 6, p. 439, 2018.
- [100] M. Maisani, D. Pezzoli, O. Chassande, and D. Mantovani, "Cellularizing hydrogel-based scaffolds to repair bone tissue: how to create a physiologically relevant micro-environment?" *Journal of Tissue Engineering*, vol. 8, Article ID 204173141771207, 2017.
- [101] Y. Wang, H. Tan, and X. Hui, "Biomaterial scaffolds in regenerative therapy of the central nervous system," *BioMed Research International*, vol. 2018, Article ID 7848901, 19 pages, 2018.
- [102] X. Li and X. Su, "Multifunctional smart hydrogels: potential in tissue engineering and cancer therapy," *Journal of Materials Chemistry B*, vol. 6, no. 29, pp. 4714–4730, 2018.
- [103] W. Wei, H. Li, C. Yin, and F. Tang, "Research progress in the application of in situ hydrogel system in tumor treatment," *Drug Delivery*, vol. 27, no. 1, pp. 460–468, 2020.
- [104] G. D. Mahumane, P. Kumar, L. C. Du Toit, Y. E. Choonara, and V. Pillay, "3D scaffolds for brain tissue regeneration: architectural challenges," *Biomaterials Science*, vol. 6, no. 11, pp. 2812–2837, 2018.
- [105] C. Vasile, D. Pamfil, E. Stoleru, and M. Baican, "New developments in medical applications of hybrid hydrogels containing natural polymers," *Molecules*, vol. 25, no. 7, p. 1539, 2020.
- [106] Y. Zhang, Z. Li, J. Guan, Y. Mao, and P. Zhou, "Hydrogel: a potential therapeutic material for bone tissue engineering," *AIP Advances*, vol. 11, no. 1, Article ID 010701, 2021.
- [107] L. Cañedo-Dorantes and M. Cañedo-Ayala, "Skin acute wound healing: a comprehensive review," *International Journal of Inflammation*, vol. 2019, Article ID 3706315, 15 pages, 2019.
- [108] F. Fan, S. Saha, and D. Hanjaya-Putra, "Biomimetic hydrogels to promote wound healing," *Frontiers in Bioengineering and Biotechnology*, vol. 9, 2021.
- [109] W. Shu, Y. Wang, X. Zhang, C. Li, H. Le, and F. Chang, "Functional hydrogel dressings for treatment of burn wounds," *Frontiers in Bioengineering and Biotechnology*, vol. 9, 2021.
- [110] L. P. da Silva, R. L. Reis, V. M. Correlo, and A. P. Marques, "Hydrogel-based strategies to advance therapies for chronic skin wounds," *Annual Review of Biomedical Engineering*, vol. 21, no. 1, pp. 145–169, 2019.
- [111] S. Grealish, J. Drouin-Ouellet, and M. Parmar, "Brain repair and reprogramming: the route to clinical translation," *Journal of Internal Medicine*, vol. 280, no. 3, pp. 265–275, 2016.
- [112] L. Edgar, T. Pu, B. Porter et al., "Regenerative medicine, organ bioengineering and transplantation," *British Journal of Surgery*, vol. 107, no. 7, pp. 793–800, 2020.
- [113] M. Bordononi, E. Scarian, F. Rey et al., "Biomaterials in neurodegenerative disorders: a promising therapeutic approach," *International Journal of Molecular Sciences*, vol. 21, no. 9, p. 3243, 2020.
- [114] X. Ma, A. Agas, Z. Siddiqui et al., "Angiogenic peptide hydrogels for treatment of traumatic brain injury," *Bioactive Materials*, vol. 5, no. 1, pp. 124–132, 2020.
- [115] A. C. Boese, Q. S. E. Le, D. Pham, M. H. Hamblin, and J. P. Lee, "Neural stem cell therapy for subacute and chronic ischemic stroke," *Stem Cell Research & Therapy*, vol. 9, no. 1, p. 154, 2018.
- [116] A. Gamble, A. R. Pepper, A. Bruni, and A. M. J. Shapiro, "The journey of islet cell transplantation and future development," *Islets*, vol. 10, no. 2, pp. 80–94, 2018.
- [117] D. R. Arifin, M. Kulkarni, D. Kadayakkara, and J. W. M. Bulte, "Fluorocapsules allow in vivo monitoring of the mechanical stability of encapsulated islet cell transplants," *Biomaterials*, vol. 221, Article ID 119410, 2019.
- [118] Precedence-Research, "Hydrogel market (by raw material type: synthetic hydrogels, natural hydrogels, and hybrid hydrogels; by composition: polyacrylate, polyacrylamide, silicone-modified hydrogels, agar-based, and others; by form: amorphous hydrogels and semi crystalline hydrogels; by product; by end user)—global industry analysis, size, share, growth, trends, regional outlook, and forecast 2022–2030," *Chemical and Material*, 2021.
- [119] S. H. Aswathy, U. Narendrakumar, and I. Manjubala, "Commercial hydrogels for biomedical applications," *Heliyon*, vol. 6, no. 4, Article ID e03719, 2020.
- [120] BCC-Research, *Hydrogels: Applications and Global Markets to 2022*, BCC Publishing, Boston, MA, USA, 2017.
- [121] T. M. Research, *Global Hydrogel Market 2019–2028*, Business Wire, San Francisco, CA, USA, 2020.
- [122] T. Gao, M. Jiang, X. Liu et al., "Patterned polyvinyl alcohol hydrogel dressings with stem cells seeded for wound healing," *Polymers*, vol. 11, no. 1, p. 171, 2019.
- [123] S. Nam, R. Stowers, J. Lou, Y. Xia, and O. Chaudhuri, "Varying PEG density to control stress relaxation in alginate-PEG hydrogels for 3D cell culture studies," *Biomaterials*, vol. 200, pp. 15–24, 2019.
- [124] C. Crocini, C. J. Walker, K. S. Anseth, and L. A. Leinwand, "Three-dimensional encapsulation of adult mouse cardiomyocytes in hydrogels with tunable stiffness," *Progress in Biophysics and Molecular Biology*, vol. 154, pp. 71–79, 2020.
- [125] S. K. Seidlits, J. Liang, R. D. Bierman et al., "Peptide-modified, hyaluronic acid-based hydrogels as a 3D culture platform for neural stem/progenitor cell engineering," *Journal of Biomedical Materials Research Part A*, vol. 107, no. 4, pp. 704–718, 2019.
- [126] R. J. Miller, C. Y. Chan, A. Rastogi et al., "Combining electrospun nanofibers with cell-encapsulating hydrogel fibers for neural tissue engineering," *Journal of Biomaterials Science*, vol. 29, no. 13, pp. 1625–1642, 2018.
- [127] J. M. Obermeyer, A. Tuladhar, S. L. Payne, E. Ho, C. M. Morshead, and M. S. Shoichet, "Local delivery of brain-derived neurotrophic factor enables behavioral recovery and tissue repair in stroke-injured rats," *Tissue Engineering Part A*, vol. 25, no. 15–16, pp. 1175–1187, 2019.
- [128] E. A. Grebenik, A. M. Surin, K. N. Bardakova et al., "Chitosan-g-oligo (L, L-lactide) copolymer hydrogel for nervous tissue regeneration in glutamate excitotoxicity: in vitro feasibility evaluation," *Biomedical Materials*, vol. 15, no. 1, Article ID 015011, 2020.
- [129] L. M. Hemmingsen, K. Julin, L. Ahsan, P. Basnet, M. Johannessen, and N. Skalko-Basnet, "Chitosomes-in-chitosan hydrogel for acute skin injuries: prevention and infection control," *Marine Drugs*, vol. 19, no. 5, p. 269, 2021.
- [130] G. Ge, Y. Lu, X. Qu et al., "Muscle-inspired self-healing hydrogels for strain and temperature sensor," *ACS Nano*, vol. 14, no. 1, pp. 218–228, 2020.

- [131] H. Samadian, H. Maleki, A. Fathollahi et al., "Naturally occurring biological macromolecules-based hydrogels: potential biomaterials for peripheral nerve regeneration," *International Journal of Biological Macromolecules*, vol. 154, pp. 795–817, 2020.
- [132] M. H. Nabavi, M. Salehi, A. Ehterami et al., "A collagen-based hydrogel containing tacrolimus for bone tissue engineering," *Drug Delivery and Translational Research*, vol. 10, no. 1, pp. 108–121, 2020.
- [133] M. Ragothaman, A. Kannan Villalan, A. Dhanasekaran, and T. Palanisamy, "Bio-hybrid hydrogel comprising collagen-capped silver nanoparticles and melatonin for accelerated tissue regeneration in skin defects," *Materials Science and Engineering: C*, vol. 128, Article ID 112328, 2021.
- [134] S. Homaeigohar, T. Y. Tsai, T. H. Young, H. J. Yang, and Y. R. Ji, "An electroactive alginate hydrogel nanocomposite reinforced by functionalized graphite nanofilaments for neural tissue engineering," *Carbohydrate Polymers*, vol. 224, Article ID 115112, 2019.
- [135] T. Distler, E. Schaller, P. Steinmann, A. R. Boccaccini, and S. Budday, "Alginate-based hydrogels show the same complex mechanical behavior as brain tissue," *Journal of the Mechanical Behavior of Biomedical Materials*, vol. 111, Article ID 103979, 2020.
- [136] P. García-García, R. Reyes, E. Pérez-Herrero, M. R. Arnau, C. Évora, and A. Delgado, "Alginate-hydrogel versus alginate-solid system Efficacy in bone regeneration in osteoporosis," *Materials Science and Engineering: C*, vol. 115, Article ID 111009, 2020.
- [137] L. R. Nih, S. Gojgini, S. T. Carmichael, and T. Segura, "Dual-function injectable angiogenic biomaterial for the repair of brain tissue following stroke," *Nature Materials*, vol. 17, no. 7, pp. 642–651, 2018.
- [138] T. Sudhadevi, H. S. Vijayakumar, E. V. Hariharan, S. Sandhyamani, and L. K. Krishnan, "Optimizing fibrin hydrogel toward effective neural progenitor cell delivery in spinal cord injury," *Biomedical Materials*, vol. 17, no. 1, Article ID 014102, 2021.
- [139] R. Ardhani, I. D. Ana, and Y. Tabata, "Gelatin hydrogel membrane containing carbonate hydroxyapatite for nerve regeneration scaffold," *Journal of Biomedical Materials Research Part A*, vol. 108, no. 12, pp. 2491–2503, 2020.
- [140] T. Kushibiki, Y. Mayumi, E. Nakayama et al., "Photo-crosslinked gelatin hydrogel improves wound healing and skin flap survival by the sustained release of basic fibroblast growth factor," *Scientific Reports*, vol. 11, no. 1, Article ID 23094, 2021.
- [141] X. Lu, Y. Si, S. Zhang, J. Yu, and B. Ding, "In situ synthesis of mechanically robust, transparent nanofiber-reinforced hydrogels for highly sensitive multiple sensing," *Advanced Functional Materials*, vol. 31, no. 30, Article ID 2103117, 2021.
- [142] C. Xu, L. Liu, S. Renneckar, and F. Jiang, "Chemically and physically crosslinked lignin hydrogels with antifouling and antimicrobial properties," *Industrial Crops and Products*, vol. 170, Article ID 113759, 2021.
- [143] T. Lin, S. Liu, S. Chen et al., "Hydrogel derived from porcine decellularized nerve tissue as a promising biomaterial for repairing peripheral nerve defects," *Acta Biomaterialia*, vol. 73, pp. 326–338, 2018.
- [144] C. Savitri, S. S. Ha, E. Liao, P. Du, and K. Park, "Extracellular matrices derived from different cell sources and their effect on macrophage behavior and wound healing," *Journal of Materials Chemistry B*, vol. 8, no. 42, pp. 9744–9755, 2020.
- [145] D. Lin, L. Lei, S. Shi, and X. Li, "Stimulus-responsive hydrogel for ophthalmic drug delivery," *Macromolecular Bioscience*, vol. 19, no. 6, Article ID e1900001, 2019.
- [146] R. Narayanaswamy and V. P. Torchilin, "Hydrogels and their applications in targeted drug delivery," *Molecules*, vol. 24, no. 3, p. 603, 2019.
- [147] X. Han, H. Xu, L. Che et al., "Retracted: application of inorganic nanocomposite hydrogels in bone tissue engineering," *iScience*, vol. 23, no. 12, Article ID 101845, 2020.
- [148] X. Zhang, X. Kang, L. Ji, J. Bai, W. Liu, and Z. Wang, "Stimulation of wound healing using bioinspired hydrogels with basic fibroblast growth factor (bFGF)," *International Journal of Nanomedicine*, vol. 13, pp. 3897–3906, 2018.
- [149] S. Pina, V. P. Ribeiro, C. F. Marques et al., "Scaffolding strategies for tissue engineering and regenerative medicine applications," *Materials*, vol. 12, no. 11, p. 1824, 2019.
- [150] E. Fennell and J. M. Huyghe, "Chemically responsive hydrogel deformation mechanics: a review," *Molecules*, vol. 24, no. 19, p. 3521, 2019.
- [151] J. P. Newsom, K. A. Payne, and M. D. Krebs, "Microgels: modular, tunable constructs for tissue regeneration," *Acta Biomaterialia*, vol. 88, pp. 32–41, 2019.
- [152] M. H. Chen, J. J. Chung, J. E. Mealy et al., "Injectable supramolecular hydrogel/microgel composites for therapeutic delivery," *Macromolecular Bioscience*, vol. 19, no. 1, Article ID e1800248, 2019.
- [153] A. C. Daly, L. Riley, T. Segura, and J. A. Burdick, "Hydrogel microparticles for biomedical applications," *Nature Reviews Materials*, vol. 5, no. 1, pp. 20–43, 2020.
- [154] S. O. Ebhodaghe, "Hydrogel—based biopolymers for regenerative medicine applications: a critical review," *International Journal of Polymeric Materials and Polymeric Biomaterials*, vol. 71, no. 3, pp. 155–172, 2022.
- [155] A. K. M. Ayatullah Hosne Asif, M. Rahman, P. Sarker, M. Z. Hasan, and D. Paul, "Hydrogel fibre: future material of interest for biomedical applications," *Journal of Textile Science and Technology*, vol. 5, no. 4, pp. 92–107, 2019.
- [156] L. Zhang, H. Yin, X. Lei et al., "A systematic review and meta-analysis of clinical effectiveness and safety of hydrogel dressings in the management of skin wounds," *Frontiers in Bioengineering and Biotechnology*, vol. 7, p. 342, 2019.
- [157] A. Surowiecka, J. Strużyna, A. Winiarska, and T. Korzeniowski, "Hydrogels in burn wound management-A review," *Gels (Basel, Switzerland)*, vol. 8, no. 2, p. 122, 2022.
- [158] I. P. Harrison and F. Spada, "Hydrogels for atopic dermatitis and wound management: a superior drug delivery vehicle," *Pharmaceutics*, vol. 10, no. 2, p. 71, 2018.
- [159] E. Ahmadian, S. M. Dizaj, A. Eftekhari et al., "The potential applications of hyaluronic acid hydrogels in biomedicine," *Drug Research*, vol. 70, no. 1, pp. 6–11, 2020.
- [160] K. Z. Meza-Valle, R. A. Saucedo-Acuña, K. L. Tovar-Carrillo, J. C. Cuevas-González, E. A. Zaragoza-Contreras, and J. Melgoza-Lozano, "Characterization and topical study of Aloe vera hydrogel on wound-healing process," *Polymers*, vol. 13, no. 22, p. 3958, 2021.
- [161] R. Mohammadinejad, H. Maleki, E. Larrañeta et al., "Status and future scope of plant-based green hydrogels in biomedical engineering," *Applied Materials Today*, vol. 16, pp. 213–246, 2019.
- [162] J. R. Choi, K. W. Yong, J. Y. Choi, and A. C. Cowie, "Recent advances in photo-crosslinkable hydrogels for biomedical applications," *Biotechniques*, vol. 66, no. 1, pp. 40–53, 2019.
- [163] T. Luo, B. Tan, L. Zhu, Y. Wang, and J. Liao, "A review on the design of hydrogels with different stiffness and their effects

- on tissue repair," *Frontiers in Bioengineering and Biotechnology*, vol. 10, 2022.
- [164] A. Urciuolo, E. Serena, R. Ghua et al., "Engineering a 3D in vitro model of human skeletal muscle at the single fiber scale," *PLoS One*, vol. 15, no. 5, Article ID e0232081, 2020.
 - [165] E. García-Gareta, Y. Abduldaiem, P. Sawadkar, C. Kyriakidis, F. Lali, and K. V. Greco, "Decellularised scaffolds: just a framework? current knowledge and future directions," *Journal of Tissue Engineering*, vol. 11, Article ID 204173142094290, 2020.
 - [166] T. T. Tiemann, A. M. Padma, E. Sehic et al., "Towards uterus tissue engineering: a comparative study of sheep uterus decellularisation," *Molecular Human Reproduction*, vol. 26, no. 3, pp. 167–178, 2020.
 - [167] H. Ghuman, C. Mauney, J. Donnelly, A. R. Massensini, S. F. Badylak, and M. Modo, "Biodegradation of ECM hydrogel promotes endogenous brain tissue restoration in a rat model of stroke," *Acta Biomaterialia*, vol. 80, pp. 66–84, 2018.
 - [168] B. S. Kim, S. Das, J. Jang, and D. W. Cho, "Decellularized extracellular matrix-based bioinks for engineering tissue- and organ-specific microenvironments," *Chemical Reviews*, vol. 120, 2020.
 - [169] P. Micheels and M. O. Eng, "Rheological properties of several hyaluronic acid-based gels: a comparative study," *Journal of Drugs in Dermatology*, vol. 17, no. 9, pp. 948–954, 2018.
 - [170] D. Lam, H. Enright, J. Cadena et al., "Tissue-specific extracellular matrix accelerates the formation of neural networks and communities in a neuron-glia co-culture on a multi-electrode array," *Scientific Reports*, vol. 9, 2019.
 - [171] M. J. Sawkins, L. T. Saldin, S. F. Badylak, and L. J. White, "ECM hydrogels for regenerative medicine," in *Extracellular Matrix for Tissue Engineering and Biomaterials*, A. C. Berardi, Ed., pp. 27–58, Springer International Publishing, Berlin, Germany, 2018.
 - [172] M. Parmaksiz, A. Dogan, S. Odabas, A. E. Elçin, and Y. M. Elçin, "Clinical applications of decellularized extracellular matrices for tissue engineering and regenerative medicine," *Biomedical Materials*, vol. 11, no. 2, Article ID 022003, 2016.
 - [173] L. T. Saldin, M. C. Cramer, S. S. Velankar, L. J. White, and S. F. Badylak, "Extracellular matrix hydrogels from decellularized tissues: structure and function," *Acta Biomaterialia*, vol. 49, pp. 1–15, 2017.
 - [174] L. E. Fitzpatrick and T. C. McDevitt, "Cell-derived matrices for tissue engineering and regenerative medicine applications," *Biomaterials Science*, vol. 3, no. 1, pp. 12–24, 2015.
 - [175] J. D. Tang and K. J. Lampe, "From de novo peptides to native proteins: advancements in biomaterial scaffolds for acute ischemic stroke repair," *Biomedical Materials*, vol. 13, no. 3, Article ID 034103, 2018.
 - [176] D. Reginensi, D. Ortiz, A. Pravia et al., "Role of region-specific brain decellularized extracellular matrix on in vitro neuronal maturation," *Tissue Engineering Part A*, vol. 26, no. 17–18, pp. 964–978, 2020.
 - [177] P. M. Crapo, S. Tottey, P. F. Slivka, and S. F. Badylak, "Effects of biologic scaffolds on human stem cells and implications for CNS tissue engineering," *Tissue Engineering Part A*, vol. 20, no. 1–2, pp. 313–323, 2014.