Journal of
Composites Science

MDPI

Review

Hydrogel Composites for Multifunctional Biomedical Applications

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Abstract: Hydrogel composites are pivotal in biomedical research, showing promise across various applications. This review aims to thoroughly examine their significance and versatile roles in regenerative medicine, tissue engineering, and drug delivery systems. Key areas of investigation include integrating growth factor delivery systems, overcoming structural limitations in tissue engineering, exploring innovations in clinical applications, and addressing challenges in achieving bioactivity and biomechanical compatibility. Furthermore, the review will discuss controlled release mechanisms for drug delivery, advancements in biocompatibility and mechanical stability, recent progress in tissue regeneration and wound healing, and future prospects such as smart hydrogels, personalized treatments, and integration with wearable technology. Ultimately, the goal is to provide a comprehensive understanding of how hydrogel composites impact biomedical research and clinical practice.

Keywords: hydrogel composites; biomedical applications; regenerative medicine; drug delivery; tissue engineering

Citation: Omidian, H.; Akhzarmehr, A.; Dey Chowdhury, S. Hydrogel Composites for Multifunctional Biomedical Applications. *J. Compos. Sci.* **2024**, *8*, 154. https://doi.org/10.3390/jcs8040154

Academic Editor: Francesco Tornabene

Received: 19 February 2024
Revised: 5 April 2024
Accepted: 16 April 2024
Published: 19 April 2024

1. Introduction

In the field of medical and scientific research, hydrogel composites have emerged as a pivotal element in advancing various areas, including regenerative medicine, tissue engineering, and drug delivery systems. Despite their potential, the application of these materials is not without challenges, necessitating ongoing innovation to unlock their full capabilities.

In regenerative medicine and tissue engineering, the quest to mimic natural healing processes has led to the exploration of complex biomaterial strategies. This includes integrating growth factor delivery systems that operate over different timescales [1], addressing the structural limitations of traditional hydrogels [2], and crafting microstructures that replicate the intricacies of natural skin [3]. These efforts aim to improve the reliability of tissue constructs for essential medical procedures, such as facial reconstructions and skin grafts. Moreover, there's a focused drive to enhance specific tissues like dermal papilla cells for hair regeneration [4], as well as bone [5,6], cartilage [7], and dental tissues [8–10], each demanding solutions that enhance viability, proliferation, and integration.

The development of materials for clinical applications faces its own set of hurdles. Innovations such as shape-recoverable hydrogels for cosmetic procedures [11] and chitin hydrogel/nanocomposite scaffolds for periodontal health [12,13] seek to extend the boundaries of current therapeutic effectiveness and application simplicity. Furthermore, the challenge of creating materials that exhibit both bioactivity [14] and biomechanical compatibility [15] with bodily tissues is critical for seamless integration and functionality within the human body.

In the area of drug and growth factor delivery systems, achieving precise, effective, and patient-friendly methodologies remains a significant challenge. This involves the controlled release of substances like BMP-2 for bone regeneration [5] and the formulation of

systems for rhBMP-2 [16], along with other therapeutic agents [17–20]. These innovations aim to optimize regenerative potential while minimizing adverse effects, marking a crucial area for technological advancement.

Biocompatibility and mechanical stability are paramount in ensuring that bioengineered tissues and materials can endure physiological conditions while providing optimal functionality. This is evident in the efforts to enhance the biocompatibility and mechanical properties of artificial articular cartilage [21] and to develop hydrogels for skull defect repair with improved mechanical stability [22].

Improving drug solubility [23], such as with efavirenz, and optimizing oral delivery mechanisms to increase the efficacy of treatments, as demonstrated with alginate-based composite capsules for antioxidants [24], highlight the need for formulations that enhance bioavailability and absorption.

Targeted and controlled drug delivery techniques strive for localized, precise therapies that minimize systemic exposure and side effects. This includes developing topical delivery systems for nitric oxide [25] and injectable nanoparticle–hydrogel composites for liver cancer treatment [26], along with graphene oxide/chitosan hydrogels for targeted chemotherapy delivery [27].

Addressing specific health challenges, such as effectively targeting tumors in colorectal cancer therapy with biodegradable microspheres in thermosensitive hydrogels [28] and advancing wound care solutions with bi-layer dressings [29] and nanoparticle-encapsulated growth factor co-loaded with chitosan-based hydrogels for diabetic wounds [30], showcases the need for multifunctional solutions that offer both antimicrobial properties and support tissue regeneration.

Minimally invasive treatment methods, like hydrogel-forming microneedles for skin infections [31], and improvements in cardiovascular treatments through hydrogel–tissue composites [32], highlight a broader goal of reducing patient discomfort and enhancing the integration and functionality of medical implants.

Moreover, ensuring the biocompatibility of new materials for implants [33,34] and developing responsive materials that adapt to changes in environmental stimulus [35,36] is critical for safe, long-term success and dynamic treatment responses, respectively.

This review aims to examine hydrogel composites in general, with a specific focus on novel hydrogel composites. These composites have been engineered to exhibit customized properties aimed at enhancing performance in various fields such as tissue engineering and regeneration, orthopedic and bone regeneration and repair, advanced drug delivery systems, dental and oral health management, wound healing and skin repair, cardiovascular applications, transplantation and immunomodulation, ophthalmic applications, as well as biomedical devices and sensors.

2. Hydrogel Composites

Hydrogels are crosslinked polymers that swell in water, utilized extensively in biomedical applications due to their biocompatibility and tunable properties. These materials can mimic the extracellular matrix (ECM), making them ideal for a range of medical uses, including drug delivery, tissue engineering, and regenerative medicine. Hydrogel composites, which incorporate materials like nanohydroxyapatite or clays, offer enhanced mechanical properties and functionality, broadening their application scope. Advances in hydrogel technology have led to intelligent hydrogels that respond to environmental stimuli, such as temperature and pH, adapting their properties accordingly. This adaptability, combined with their ability to closely mimic biological tissues, positions hydrogels as a cornerstone in developing innovative medical treatments and devices, ranging from injectable hydrogels for targeted therapy to superabsorbent hydrogel composites for advanced medical applications [37–41].

The development and application of hydrogel composites have emerged as pivotal areas of interest within biomedical science. These composites incorporate a diverse range of primary components, including natural polymers such as gelatin, chitosan, hyaluronic acid,

and alginate, which are selected for their biocompatibility and bioactivity. Notably, gelatin methacrylate (GelMA) is frequently used [3,4,16,42,43] due to its versatility and the ease with which it can be modified to suit various applications. Similarly, synthetic polymers like polyethylene glycol (PEG), polyvinyl alcohol (PVA), and poly(lactic-co-glycolic acid) (PLGA) [6,17,21] are also widely employed. These materials are chosen for their ability to be tailored in terms of mechanical properties and degradation rates, making them suitable for specific biomedical applications. In addition, inorganic components such as hydroxyapatite, bioactive glass, and metallic nanoparticles [12,44–47] are integrated into hydrogels for their osteoconductivity and antibacterial properties, indicating a strong focus on composites designed for bone tissue engineering and infection control.

In terms of applications, there is a significant emphasis on bone tissue engineering, with many composites designed to enhance osteoinduction, osteoconduction, and osteogenesis by utilizing materials like tricalcium phosphate and bioactive glass [8,12]. Another major area of focus is wound healing and skin regeneration, where composites are developed to accelerate the healing process and promote skin regeneration through the inclusion of antibacterial agents, growth factors, or cell-laden systems [4,48,49]. Additionally, the trend toward developing injectable hydrogels [4,47,50] points to an increasing interest in creating minimally invasive therapeutic options. The use of 3D printing technology and scaffold designs [46,51] further highlights the growing interest in producing customized, patient-specific structures for regenerative medicine.

Innovation within this field also extends to the development of hydrogels with unique functionalities. For instance, some composites are designed for combination therapies by incorporating bioactive molecules, drugs, or cells [22,52], aiming for synergistic effects to enhance healing and regeneration. Furthermore, certain composites are engineered to respond to environmental stimuli [53], which suggests an interest in creating smart materials for targeted therapy and controlled drug release. The mechanical strength and durability of hydrogels are also being improved through the inclusion of fibers, nanoparticles, and crosslinking agents [54,55].

Recent studies have placed a considerable emphasis on drug delivery systems, with hydrogel composites being developed for the controlled release of a variety of pharmaceuticals, such as efavirenz, doxorubicin, paclitaxel, and dexamethasone [23,27,56–58]. This highlights the ongoing interest in enhancing the efficacy and specificity of drug delivery. The integration of bioactive and therapeutic agents, including growth factors, enzymes, and antibiotics [1,31,59–63], reflects a focus on promoting healing and regeneration while combating infection. The field is also leveraging advanced functional materials like graphene oxide, mesoporous silica nanoparticles, and metal–organic frameworks [27,64,65] to improve composite properties such as mechanical strength, bioactivity, and drug loading capacity.

Moreover, the development of stimuli-responsive hydrogels [53,61,62] for targeted therapeutic applications remains a key area of interest. These materials can respond to changes in the environment, enabling the controlled release of drugs or active agents in response to specific physiological conditions. Innovative combinations of materials, such as injectable nanoparticle–hydrogel systems and micelle–hydrogel composites [26,66], suggest a move toward more complex, multifunctional systems. This indicates a demand for therapies that can be administered directly to the site of injury or disease, highlighting the continued development of injectable hydrogel systems [23,26,27]. The integration of nanotechnology, through the inclusion of nanoparticles and nanozymes [64,67–69], plays a critical role in enhancing the functionality of hydrogel composites, particularly for targeted drug delivery and antibacterial applications.

In conclusion, the dynamic evolution of hydrogel composites within biomedical science highlights a profound commitment to innovation and advancement. From tailored mechanical properties to targeted drug delivery and smart responsiveness, the multifaceted nature of these materials promises a transformative impact on regenerative medicine, drug delivery, and infection control.

3. Tissue Engineering and Regeneration

In the field of tissue engineering and regeneration, recent studies have shown significant advancements through the development and application of hydrogel composites. One innovative approach involves the creation of a composite by blending short fibers derived from electrospun scaffolds with tissue-specific self-assembling peptide (SAP) hydrogel, forming a nanofiber structure reminiscent of the extracellular matrix, ranging from 10 to 300 nm in diameter. This combination facilitates both immediate and sustained release of growth factors, enhancing the regeneration process starting from a burst release by the SAP hydrogel followed by a gradual release from the nanofibers beginning six days post-application [1].

Furthermore, the use of polysaccharide hydrogel composites, incorporating elements such as nanocellulose, agarose, and sodium alginate, alongside seeded cells and employing polyvinyl alcohol as a sacrificial material, has shown promise in 3D bioprinting personalized, large-scale, vascularized tissue-engineered constructs, including facial structures, without structural collapse during the printing process [2]. Similarly, a patterned GelMA-PEGDA hydrogel, enhanced with acryloylated Arg-Gly-Asp (RGD) peptides, has been developed to support the growth of keratinocytes, thus facilitating the creation of an epidermal model that fosters stem cell maintenance and relevant signaling pathways for skin regeneration [3].

Innovations extend to the development of an implantable, shape-recoverable hydrogel composite crafted from hyaluronic acid and TEMPO-oxidation cellulose nanofiber, which adapts to extracellular moisture to shrink and regain its shape in vivo, a property enhanced by the introduction of ethylene glycol diglycidyl ether to increase the elastic modulus [11]. Additionally, gelatin methacryloyl (GelMA) and chitosan hydrogels have been employed to produce interpenetrating network microcarriers loaded with platelet-rich plasma and seeded with dermal papilla cells (DPC), promoting hair follicle regeneration when combined with an epidermal cell-laden (EPCs) GelMA in a co-cultured system [4]. Figure 1 illustrates that PRP-loaded DPC/EPC co-cultured hydrogel system (DECHS) enhances hair follicle inductive ability as demonstrated by improved DIO-labeled cell retention, increased regenerative hair follicles, and blood vessel formation compared to control and DECHS groups in nude mice.

A composite hydrogel incorporating nickel-chelated nitrilotriacetic acid microparticles with genetically engineered BMP-2 fused to a polyhistidine tag-T4 Lysozyme, blended into a novel gelatin-based hydrogel, has demonstrated improved mechanical properties and controlled, long-term BMP-2 delivery through its in situ injectability, thermosensitivity, and adhesiveness [5]. The development of a biodegradable, thermosensitive hydrogel composite bone cement, merging PLGA-polyethylene glycol-PLGA hydrogel with calcium silicate-based bioactive bone cement, aims at enhancing bone repair and osteogenesis, showing promising results in rabbit femoral defect models [6].

The design of a composite system for partial-thickness cartilage defect regeneration, combining an electrospun gelatin-incorporated scaffold with an injectable heparin-based hydrogel for chondrocyte delivery, has shown to significantly enhance chondrogenic gene expression and glycosaminoglycan production, facilitating considerable in vitro and in vivo cartilage regeneration [7]. Similarly, the evaluation of three different 3D-bioplotted composite scaffolds for bone repair has identified the superior performance of HYDR (TCP/Col/chitosan) and TCP/Col scaffolds in enhancing bone regeneration, particularly highlighting the relative density of new bone formation with HYDR scaffolds [70].

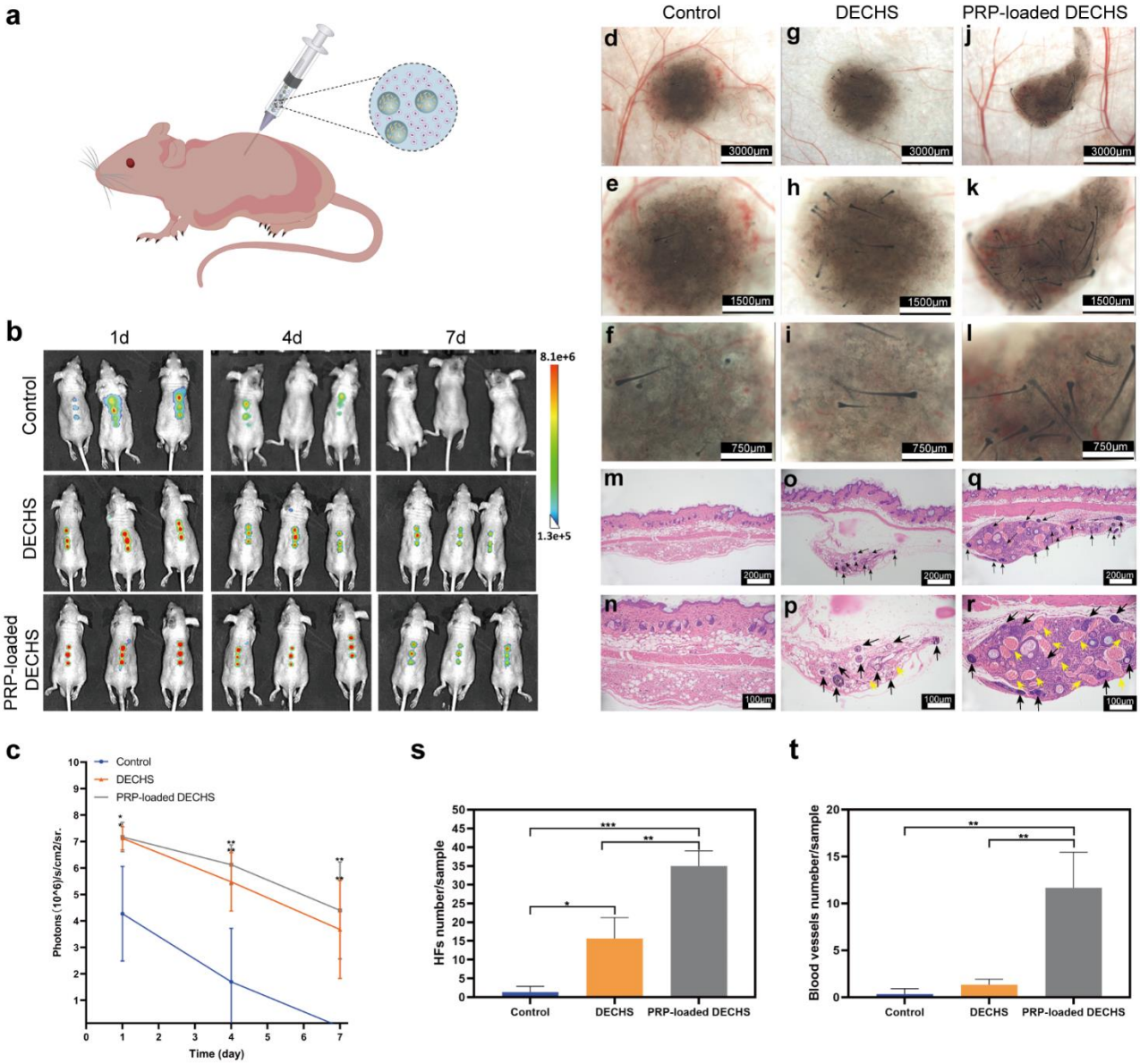

Figure 1. PRP-loaded DECHS improves the HF inductive ability. (**a**) Schematic diagram of injecting PRP-loaded DECHS into a nude mouse; (**b**) in vivo fluorescence imaging following subcutaneous injection of DIO-labeled cells in the control group, DECHS group, and PRP-loaded DECHS group. (**c**) Quantitative diagram of the DIO signal intensity expressed as photons/s/cm^2/sr. Stereomicroscopy images of injection sites in the control group (**d**–**f**), DECHS group (**g**–**i**), and PRP-loaded DECHS group (**j**–**l**). HE-stained images of the injection site in the control group (**m**,**n**), DECHS group (**o**,**p**), and PRP-loaded DECHS group (**q**,**r**). Black arrows: regenerative HFs, yellow: regenerative blood vessels. Statistical diagrams of HF numbers/sample (**s**); and blood vessel numbers/sample (**t**) among the three groups. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; statistical significance was analyzed using unpaired independent-samples *t*-test [4].

Research into the use of beta-tricalcium phosphate microsphere–hydrogel composites loaded with recombinant human bone morphogenetic protein-2 for the healing of dental implant sites has indicated a marked improvement in bone healing and osseointegration, a finding that extends to the use of similar composites in rabbit tibial defect models for enhancing peri-implant bone formation [8,9]. Further studies have investigated the efficacy of rhBMP-2-loaded hydrogel composites in mandible bone defects alongside dental

implants in minipigs, aiming to promote osteogenesis and improve osseointegration under challenging conditions [10].

The development of an antibacterial and bioactive composite scaffold, utilizing alpha- and beta-chitin hydrogel with bioactive glass ceramic and silver nanoparticles, has shown promise in periodontal regeneration through its porosity, mechanical properties, antibacterial activity, and support for cell viability and proliferation [12]. Injectable composite hydrogels, such as the one made of silanized hydroxypropyl methyl cellulose and biphasic calcium phosphate, have been evaluated for their effectiveness in bone formation around periodontal defects, offering ease of use for filling periodontal lesions [13].

In osteogenesis, a GelMA/MBGNs-rhBMP-2 hydrogel membrane, designed for controlled release of rhBMP-2 followed by calcium and silicon ions, aligns with the stages of bone healing, promising enhanced outcomes [16]. The development of a PVA-BG composite hydrogel as a bionic artificial articular cartilage/bone implant has explored the effects of preparation processes on its mechanical properties, aiming to improve the interface strength between artificial cartilage and bone [14].

For dental applications, a mesoporous silica hydrogel nanocomposite has been created for human dental pulp stem cell proliferation, incorporating metronidazole to inhibit bacterial growth, thus supporting cell proliferation for pulpitis therapy [71]. A $SrCuSi_4O_{10}$/GelMA composite hydrogel has been developed for vital pulp therapy, combining antibacterial properties and pulp regeneration activity, showcasing improved repair of the dentine–pulp complex [42].

In the context of spinal repair, a chemically stabilized elastin-glycosaminoglycan-collagen composite hydrogel has been introduced for nucleus pulposus regeneration, mimicking the resilient and hydrophilic nature of the target tissue [72]. Furthermore, a comprehensive strategy employing hydrogel and scaffold composites has been evaluated for annulus fibrosus repair, aiming to restore biomechanics and reduce the risk of herniation in a bovine injury model [15]. A novel approach for nucleus pulposus replacement involves the use of photo-polymerizable nanofibrillated cellulose in a hydrogel, showing significant potential in maintaining disc height post-surgery [73].

Furthermore, the evaluation of a pectin/polyvinyl alcohol composite hydrogel as an artificial nucleus material has demonstrated its ability to preserve disc height and delay histological degeneration in a rabbit model, offering insights into non-invasive treatments for disc degeneration [74]. These advancements highlight the diverse and innovative approaches being explored in the regeneration and repair of various tissues, leveraging the unique properties of hydrogel composites to address specific clinical challenges.

4. Orthopedic and Bone Regeneration

In the domain of orthopedic and bone regeneration, the exploration and development of hydrogel composites has been pivotal. A notable advancement includes leveraging the natural hydrogel properties of blood clots to handle biphasic calcium phosphate microparticles, creating a moldable composite with inherent osteogenic properties. This material has shown promising results in repairing critical femoral defects and fostering bone formation in ectopic sites [75]. Similarly, the formulation of an injectable composite paste, combining calcium phosphate cement with hydrogel microbeads encapsulating human umbilical cord mesenchymal stem cells, targets the enhancement of bone tissue engineering by maintaining high mechanical strength and cell viability after injection [50].

The use of gelatin/hydroxyapatite scaffolds, enriched with human placental extracts through 3D printing, represents another innovative approach. These scaffolds achieve a porous matrix that, when supplemented with glycerol and immersed in human placental extracts, becomes biologically activated, thus serving as a promising platform for bone tissue engineering [44]. Moreover, the development of chitosan–hydroxyapatite biocomposites combines the bioceramic properties of hydroxyapatite with the bioactivity of chitosan in various forms, such as scaffolds and films, catering to both bone tissue engineering and environmental bioremediation [45].

The creation of Cu-doped bioactive glass composite scaffolds through 3D printing, which integrates tyramine-modified gelatin/silk fibroin with copper-doped bioactive glass, is aimed at bone defect repairs. This composite foster angiogenesis and osteogenesis, showcasing the multifaceted approach toward improving bone regeneration [46]. In a similar vein, the formulation of a MgO nanoparticle-coordinated phosphate-functionalized chitosan injectable hydrogel (CSMP-MgO) utilizes a supramolecular approach to form an injectable matrix that promotes osteogenesis and angiogenesis, marking a significant step forward in bone regeneration applications [47].

The fabrication of injectable thermosensitive hydrogel nanocomposites, incorporating nanohydroxyapatite into a biodegradable triblock copolymer, maintains the thermoresponsive nature of the base hydrogel while enhancing its mechanical properties. This makes it an ideal candidate for injectable orthopedic tissue engineering [76]. Another inventive strategy includes the synthesis of an injectable thermosensitive composite blending acellular bone matrix granules with a triblock copolymer. This material overcomes the limitations associated with acellular bone matrix by offering a moldable solution that can fit various defects and potentially reduce inflammation and pain, highlighting its suitability for minimally invasive orthopedic applications [77].

The construction of a non-toxic, biodegradable double-network hydrogel composed of polyethylene glycol and kartogenin-conjugated chitosan stands out for cartilage repair. This hydrogel facilitates specific gene expression and extracellular matrix secretion by mesenchymal stem cells, pointing towards significant advancements in cartilage regeneration [78]. Research on polyvinyl alcohol hydrogels for orthopedic implants, particularly as an artificial cartilage, underlines the ongoing efforts to enhance clinical applications, mechanical properties, and the development of orthopedic implants, including artificial articular cartilage, intervertebral discs, and artificial menisci [21].

Surface modification techniques have also seen innovations, such as the application of a bioactive gelatin methacrylate/polyacrylamide hydrogel composite coating on long carbon fiber reinforced polyether ether ketone for orthopedic implant applications. This enhances osteogenicity and bone tissue integration, demonstrating the potential for improved implant success [43]. The creation of hydrogel stents for cartilage construction using gelatin sodium alginate and nanohydroxyapatite via 3D printing indicates improved mechanical strength and biodegradability, offering a new approach to treating traumatic thoracolumbar fractures [54].

Injectable double network hydrogels reinforced with mesoporous silica nanoparticles and loaded with BMP-4 for skull defect repair have been developed. These hydrogels feature a dual-network structure that enhances mechanical stability and facilitates controlled BMP-4 release, proving effective in promoting bone regeneration in irregular skull defects [22]. The fabrication of a thermosensitive injectable hydrogel based on chitosan integrated with hydroxyapatite nanoparticles demonstrates pH-sensitive drug release and significant growth inhibition of Staphylococcus aureus, marking a step forward in preventing infections related to orthopedic procedures [48].

The development of DAC®, a fast-resorbable, antibacterial-loaded hydrogel coating, has been tested in vivo for highly contaminated implant surgeries, showing a significant reduction in bacterial colonization without adverse effects. This innovation offers a promising avenue for reducing post-operative infections [49]. Comparative studies, such as the evaluation of i-Factor Bone Graft versus local autograft in anterior cervical discectomy and fusion, have shown high fusion rates and significant improvements in patient outcomes, illustrating the potential of advanced materials in clinical settings. The i-Factor Bone Graft is a composite bone substitute material that incorporates the P-15 synthetic collagen fragment adsorbed onto an organic bone mineral and suspended in an inert biocompatible hydrogel carrier. This hydrogel carrier is integral in delivering the synthetic collagen fragment and an organic bone mineral effectively to the surgical site, contributing to the overall success of the treatment [79].

Reviews on stimulus-responsive hydrogels and magnesium-enriched materials for bone tissue engineering provide a comprehensive overview of the current state of research. These materials, responsive to various stimuli, offer new possibilities for bone defect repair by facilitating cell adhesion, proliferation, and differentiation. Magnesium-enriched materials, in particular, have been identified for their potential to enhance vascularized osteogenesis, highlighting the importance of future research in this area [53,80].

Further developments include the mixing of collagen with thermosensitive hydrogels and calcium phosphate, evaluated for their osteoinductive abilities and suitability for weight-bearing bone defects [81]. Innovative approaches also include the creation of injectable, self-crosslinkable bone substitutes and the utilization of cuttlefish bone as a biogenous bone filler for 3D printed scaffolds, aiming to improve mechanical properties and support healing in bone defects [51,82].

Analytical techniques, such as the use of Synchrotron X-ray radiation for analyzing bioglass-enriched hydrogels, provide insights into particle size and distribution within hydrogels, showing the importance of precision in scaffold design [83]. The development of single-unit trilayer scaffolds, consisting of a bottom layer mimicking the bone environment, a middle layer with a specialized pore structure, and a top layer made of hydrogel for osteochondral tissue engineering, signifies a significant step forward in creating integrated solutions for complex tissue regeneration [84].

Injectable calcium phosphate cement scaffolds containing hydrogel fibers encapsulating various stem cells point to a minimally invasive approach to bone engineering, offering a conducive environment for stem cell proliferation and differentiation [85]. Moreover, the fabrication of an aspirin-loaded hydrogel composite coating on zinc surfaces aims to enhance the corrosion resistance, osteogenic, anti-inflammatory, and antibacterial properties of orthopedic implants, illustrating the multifaceted approach to improving implant performance and patient outcomes [52].

5. Drug Delivery Systems

In the advancement of drug delivery systems, hydrogel composites have emerged as a versatile and innovative solution, addressing a broad spectrum of therapeutic applications with enhanced efficacy and patient compliance. For instance, superporous hydrogel composite (SPHC) polymers have been evaluated for their retention time within the human intestinal tract through scintigraphy. Enteric-coated gelatin capsules containing radiolabeled SPHC demonstrated the ability of these polymers to adhere to the upper part of the small intestine for durations of 45 to 60 min without causing discomfort, highlighting their safety and potential as oral drug delivery systems [86].

In pain management, a programmed drug delivery system that integrates a collagen-based injectable hydrogel with PLGA particles has been developed to facilitate the controlled release of bupivacaine. By adjusting the composition ratios, researchers have been able to manage the release of bupivacaine from rapid release within a single day to delayed release extending up to nine days, showcasing its applicability for customizable pain management solutions [17].

A notable innovation is the "Natural Self-Emulsifying Reversible Hybrid Hydrogel (NSERH)", crafted by embedding resveratrol micelles within a fenugreek galactomannan hydrogel scaffold. This composite has significantly improved the oral bioavailability of free resveratrol in human subjects, indicating superior absorption and sustained delivery compared to its unformulated counterpart [18]. Moreover, a composite hydrogel system designed for the oral delivery of insulin comprises glucose-responsive nanocarriers loaded with insulin, encapsulated within a hyaluronic acid hydrogel. This system is tailored to navigate the challenges of oral insulin delivery, providing protection to insulin and demonstrating an effective hypoglycemic effect in diabetic rats post-oral administration [19]. Figure 2 depicts the hypoglycemic effects of insulin-loaded nanocarriers (INCs), as well as the evaluation of a hyaluronic acid (HA) hydrogel system containing insulin-loaded nanocarriers (INCs-HA) in diabetic rats following oral administration.

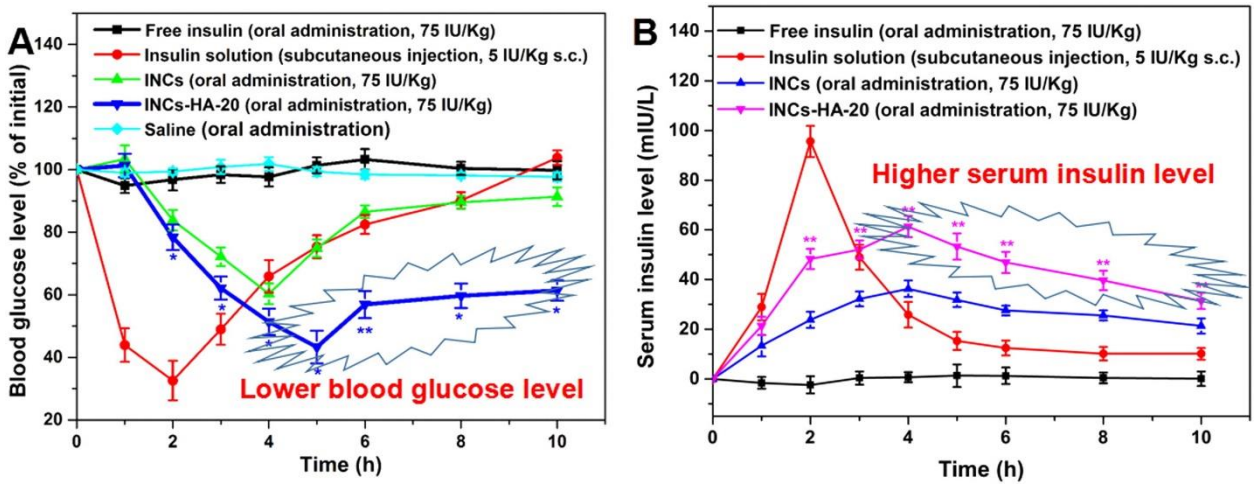

Figure 2. Blood glucose levels in diabetic rats following oral administration of insulin-loaded nanocarriers, HA hydrogel system containing insulin-loaded nanocarriers, saline, and insulin solution (**A**). Serum insulin level in diabetic rats following oral administration of insulin-loaded nanocarriers, HA hydrogel system containing insulin-loaded nanocarriers, and insulin solution (**B**). Data are presented as the average ± standard deviation ($n = 5$, * $p < 0.05$, ** $p < 0.01$) [19].

The development of a pH-sensitive, sustained-release oral drug delivery system employs a xanthan gum-graft-poly(acrylic acid)/graphene oxide composite hydrogel for the delivery of diclofenac potassium. This hydrogel, synthesized via in situ polymerization, displays pH sensitivity, enhanced mechanical strength, and improved bioavailability under physiological conditions [20]. Another innovative approach involves the preparation of a Crosslinked Hydrogel Composite (CHC) for the solubility enhancement of efavirenz, utilizing a blend of hydroxyethylcellulose, poly(acrylic acid), and poly(vinyl alcohol) under lyophilization. This formulation significantly boosts the solubility of efavirenz and offers a sustained release mechanism [23].

Composite capsules based on alginate hydrogel, gum arabic, and gelatin have been developed for the oral delivery of the antioxidant Perinereis aibuhitensis extract, ensuring protection from gastric acid and enhancing absorption efficiency and in vivo efficacy [24]. Furthermore, a gentamicin hydrogel infused with Tetracarpidium conophorum extract has been optimized to enhance gentamicin's permeation for topical delivery, leveraging permeation enhancers and optimal stirring rates [59]. The design of a nanoclay-polyamine composite hydrogel for the topical delivery of nitric oxide gas utilizes Laponite nanoclay and pentaethylenehexamine, forming a macromolecular structure aimed at localized NO gas release at the site of application, showing promise for biomedical uses [25].

Innovations extend to the development of dry reservoir-hydrogel-forming microneedles composites, fabricated from Gantrez®S-97 and Carbopol® 974P NF crosslinked with PEG 10,000, for the minimally invasive delivery of cefazolin, blending hydrogel-forming microneedles with dry reservoirs to achieve significant drug delivery through the stratum corneum into the epidermis [31]. A camptothecin-loaded microsphere within a thermosensitive hydrogel has been designed for the therapy of colorectal peritoneal carcinomatosis. This injectable and biodegradable composite combines polymeric microspheres with a thermosensitive hydrogel, resulting in a significant anti-tumor effect by increasing apoptosis and inhibiting tumor microvessel density [28].

An injectable nanoparticle–hydrogel composite system aims to deplete intratumoral lactate in combination with immunotherapy against hepatocellular carcinoma recurrence. This system slowly releases lactate oxidase-loaded hollow mesoporous MnO_2 nanoparticles, transforming the immunosuppressive tumor environment into an immunocompetent setting [26]. Moreover, a graphene oxide/chitosan injectable composite hydrogel has been prepared for the controlled release of doxorubicin, optimizing local bioavailability for the treatment of solid tumors [27].

A glycol chitin/poly(acrylic acid) hydrogel composite, incorporating biofunctionalized PLGA microspheres, has been designed for the sustained release of paclitaxel through intratumoral injection. This composite aims to offer prolonged drug release and a potent inhibitory effect on hepatoma cells, marking a promising approach for cancer therapy [56]. Additionally, an optimized transdermal ethosomal hydrogel containing carvedilol demonstrates sustained release and an enhanced anti-hypertensive effect, proposing a novel administration route [87].

Improved topical delivery systems have also been developed for psoriasis and rheumatoid arthritis treatments. A composite hydrogel made of Carbopol®, incorporating tacrolimus-loaded polymeric nanocarriers has shown enhanced skin delivery and treatment efficacy in psoriasis models [60], while a sulfasalazine-loaded solid lipid nanoparticle-based hydrogel optimized for rheumatoid arthritis management significantly reduces paw thickness and pro-inflammatory cytokines [88]. For osteoarthritis, a colchicine mesoporous silica nanoparticles/hydrogel composite applied to cotton patches has enhanced drug flux and permeation, with its therapeutic efficacy validated in rat models [64].

Emerging therapies include a composite hydrogel delivering CuS nanoparticles and sulfo-N-succinimidyl oleate for spatiotemporal lipid intervention in the tumor milieu, enhancing immunogenic cell death and engaging the immune system to counteract tumor growth and metastasis [67]. Additionally, a nanocomposite-based hydrogel loaded with methotrexate into ZnO/Ag for psoriasis therapy utilizes ZnO hybrid mesoporous microspheres for drug delivery and reactive oxygen species scavenging, alongside Ag nanoparticles for immunoregulatory properties [68]. Furthermore, a composite thermoresponsive hydrogel with auranofin-loaded nanoparticles has been developed for the topical treatment of vaginal trichomonad infection, designed for intravaginal administration to maximize local drug concentrations while minimizing systemic exposure [89]. These advancements feature multifaceted approaches in hydrogel composite development, offering targeted and efficient drug delivery solutions across various therapeutic domains.

6. Dental and Oral Health and Disease Management

In the field of dental and oral health, recent advancements have focused on the development of hydrogel composites for various therapeutic applications, demonstrating promising results in biocompatibility and efficacy. A notable example includes the creation of a pectin/polyvinyl alcohol composite (CoPP) hydrogel, specifically developed for potential use as a prosthetic nucleus material. This hydrogel underwent a comprehensive array of biocompatibility tests, such as cytotoxicity assessments, sensitization evaluations, the Ames test, mice marrow micronucleus and chromosome aberration tests, and implantation studies. These investigations collectively indicated that the CoPP hydrogel possesses excellent biocompatibility, positioning it as a viable candidate for implant materials [33].

Further evaluation of the CoPP hydrogel's biocompatibility was conducted with a focus on its potential as a prosthetic nucleus pulposus material. This involved both in vitro cytotoxicity testing on NCTC L929 cells and in vivo biocompatibility assessments through the implantation of dehydrated CoPP and PVA hydrogel into Sprague Dawley (SD) rats. The in vivo studies particularly aimed to observe the processes of wound healing, the infiltration of inflammatory cells, and the formation of fibrous capsulation around the implants. The results from these studies reaffirmed the CoPP hydrogel's suitability as an implant material, highlighting its excellent biocompatibility profile [34].

Innovations in hydrogel composites extend to the treatment of oral ulcers, with the design of an intelligent composite hydrogel supported with compound 3J. This hydrogel formulated using sodium alginate, carboxymethyl chitosan, and chitosan quaternary ammonium salt, demonstrated significant anti-inflammatory activity and pH sensitivity. These characteristics are particularly beneficial for oral ulcer treatments, offering a responsive approach to therapy that can potentially improve patient outcomes [35]. Figure 3 demonstrates the efficacy of CMCS-SA-AmCS-SA and 3J on oral ulcer healing in vivo. Over time, the ulcer area decreased in all groups. However, CMCS-SA-AmCS-SA hydrogel

and CMCS-SA-AmCS-SA-3J (20 kg/mg) hydrogel exhibited superior therapeutic effects compared to other groups.

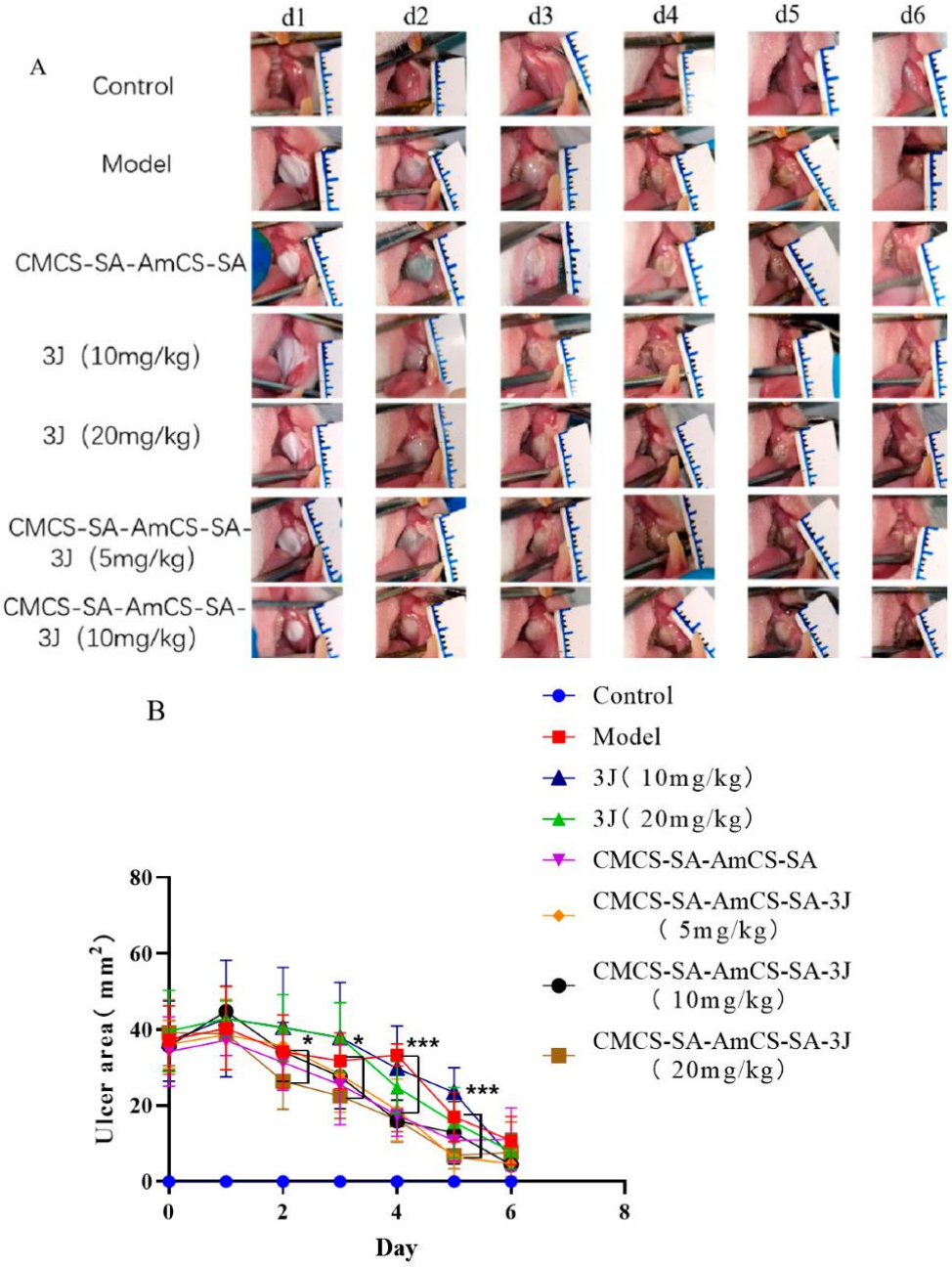

Figure 3. Analysis of the effect of treating oral ulcer in vivo. (**A**) Changes in ulcer area in each group at 0−6 days after establishing oral ulcer model induced by phenol (mean ± SD, $n = 8$). (**B**) Quantitative results of oral ulcer area at different time points (mean ± SD, $n = 8$), * $p < 0.05$, *** $p < 0.001$ [35].

Another development is the injectable sodium hyaluronate/45S5 bioglass composite hydrogel (BG/HA), which has been tailored for the treatment of oral submucous fibrosis (OSF). This innovative hydrogel releases biologically active silicate ions, which are known to inhibit collagen deposition and inflammation, while also promoting angiogenesis and epithelial regeneration. The BG/HA composite hydrogel represents a novel therapeutic approach for OSF, a condition that has historically been challenging to treat effectively [90].

These advancements highlight the diverse and impactful applications of hydrogel composites in dental and oral health care. Through meticulous development and rigorous testing, these materials are proving to be invaluable in addressing a range of dental and

oral conditions, offering new avenues for treatment that prioritize biocompatibility, efficacy, and patient comfort.

7. Wound Healing and Skin Repair

In the field of wound healing and skin repair, recent advancements have been made through the development of hydrogel composites designed to optimize the delivery of therapeutic agents and support tissue regeneration. One such innovation is a controlled release system for stratifin, aimed at stimulating matrix metalloproteinase-1 (MMP-1) expression in dermal fibroblasts during the latter stages of wound healing. This system comprises stratifin complexed with chitosan particles, encapsulated within PLGA microspheres, and integrated into crosslinked hyaluronic acid films. The design of this composite hydrogel ensures a delayed release of stratifin for three days, with a subsequent controlled release over 30 days, effectively enhancing MMP-1 expression while maintaining cell viability [91].

Another research involves the development of a non-biodegradable bacterial nanocellulose/acrylic acid (BNC/AA) hydrogel, specifically engineered to deliver human dermal fibroblasts to wound sites in athymic mice. This hydrogel successfully transferred over 50% of the fibroblasts to the wound within the first 24 h, facilitating accelerated wound healing and the formation of a more mature skin microstructure by the seventh day (Figure 4) [92].

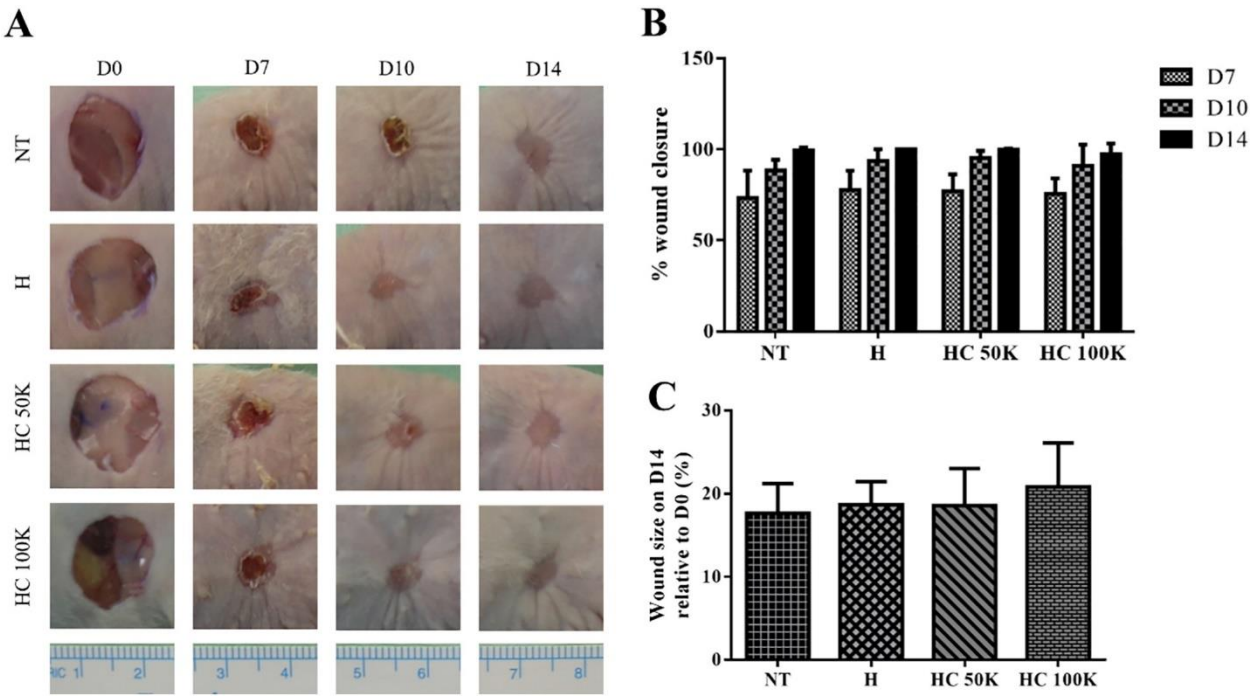

Figure 4. Wound closure and wound contraction. (**A**) Representative visual appearance of the wound for different treatment groups on day 0, 7, 10, and 14; (**B**) percentage wound closure for different treatment groups on day 7, 10, and 14 ($p > 0.05$); and (**C**) wound size, i.e., wound contraction on day 14 relative to day 0 ($p > 0.05$). (NT) stands for no treatment group; (H) hydrogel alone, HC 50 K and HC 100 K stands for hydrogel with different amount of HDF [92].

A micelle–hydrogel composite, loaded with amphotericin B and curcumin, was evaluated in a full-thickness excision wound model in rats. This innovative composite promoted wound healing by initially eliminating infection and subsequently reducing inflammation, achieving up to 80% wound closure. It also facilitated high collagen deposition and improved re-epithelialization and granulation, demonstrating its efficacy in wound management [66].

Further studies have explored the interaction between human dermal fibroblasts and a bacterial nanocellulose/acrylic acid hydrogel for tissue regeneration. The hydro-

gel's properties were found to significantly influence fibroblast behavior at both cellular and molecular levels, highlighting its potential as a wound dressing material capable of incorporating fibroblasts to expedite wound healing [93].

A bimetal–organic framework-loaded composite hydrogel (PCbM) composed of PVA, chitosan and AgCu@MOF, used in wound dressings, characterized by its antibacterial and adhesive hemostatic properties. The inclusion of AgCu@MOF within the hydrogel enhances water retention and permeability, enabling the hydrogel to bind with wet tissue effectively. As a wound adhesive, PCbM hydrogel not only improved tissue adhesion but also supported wound recovery effectively and with a high biocompatibility [65].

An innovative chitosan-based composite hydrogel, incorporating a vasoconstrictor (potassium aluminum sulfate) and a coagulation activator (calcium chloride), was developed to improve hemostatic properties. This injectable, shear-thinning hydrogel demonstrated compatibility with both cells and blood, effectively inducing rapid blood clotting and showing promise for application in low-pressure bleeding sites [94].

A bi-layer dressing, combining a gelatin nanofibrous mat loaded with epigallocatechin gallate and a polyvinyl alcohol hydrogel, was devised to enhance wound healing. This dressing significantly improved healing rates in experimental rats, through mechanisms such as enhanced angiogenesis, re-epithelialization, and a reduction in inflammatory responses [29].

Moreover, a chitosan-based composite hydrogel incorporating silver ions and nanoparticle-encapsulated epidermal growth factor (EGF) was tailored for diabetic wound healing. This hydrogel facilitated sustained release of Ag^{+} and EGF, provided enhanced hydration in an ion-rich environment, and demonstrated significant wound healing efficacy in a diabetic rat model [30]. These advancements highlight the pivotal role of hydrogel composites in advancing wound healing and skin repair, offering novel solutions that combine therapeutic efficacy with targeted delivery and biocompatibility.

8. Cardiovascular Applications

In the domain of cardiovascular health, hydrogel composites have emerged as a significant area of innovation, offering new strategies for the treatment and management of heart-related conditions. These materials have been engineered to address various challenges, from post-surgical recovery to the restoration of heart function after myocardial infarction.

A notable advancement involves the use of a poly(2-hydroxyethyl methacrylate) (pHEMA) hydrogel, which has been reinforced with a polyethylene terephthalate (PET) mesh for use as a pericardial substitute. This composite material was specifically tested to assess its ability to reduce adhesion formation following cardiac surgery. The results were promising, showing no adhesions, only a thin layer of fibrous tissue development, and no significant mechanical changes post-implantation, indicating its potential as an effective solution for enhancing recovery and outcomes after cardiac procedures [95].

Exploring the potential of nanotechnology in cardiovascular treatments, a nanocomposite hydrogel stent implantation technique was evaluated for its effectiveness in treating coronary artery disease in relation to cardiovascular diseases. This approach demonstrated both safety and efficacy, optimizing blood flow rates as observed in coronary angiography and improving perfusion in cases of coronary artery disease. Such advancements offer hope for patients with coronary conditions, providing a minimally invasive option to restore blood flow and heart function [96].

Innovations extend to regenerative therapies, where a composite combining bone marrow-derived mesenchymal stem cells (BMSCs) with a hydrogel was injected into patients after myocardial infarction. This treatment aimed to preserve left ventricular function and showed significant improvements in ventricular diameter, wall thickness, and ejection fraction. This approach highlights the potential of regenerative medicine in recovering heart function and improving local systolic and diastolic function after acute myocardial infarction (AMI) [97].

Further, a hydrogel–tissue composite loaded with a nitroxide radical and vascular endothelial growth factor (VEGF) was developed for use in cardiovascular implants. This composite targets several key areas: anti-coagulation, endothelialization, anti-inflammation, and anti-calcification. It features an inflammation-triggered dual release mechanism, demonstrating a sophisticated approach to addressing multiple challenges in cardiovascular implantation and therapy. This innovation stresses the potential of hydrogel composites in creating multifunctional, responsive treatments for cardiovascular diseases [32].

These advancements in hydrogel composite technology for cardiovascular applications represent significant steps forward in the treatment and management of heart diseases. Through the development of materials that can reduce post-surgical adhesions, improve blood flow, preserve heart function, and enhance the efficacy of cardiovascular implants, these innovations offer new hope for patients with cardiovascular conditions, pointing to a future where heart disease management is more effective, less invasive, and tailored to the needs of each individual patient.

9. Transplantation and Immunomodulation

In the field of transplantation and immunomodulation, hydrogel composites have played a transformative role, offering innovative solutions to enhance graft survival and minimize the adverse effects associated with systemic immunosuppression. These advancements are particularly significant in the context of transplant medicine, where managing the immune response without compromising the recipient's overall health is a delicate balance.

An important development in this area is the creation of a self-assembled hydrogel that is engineered to release tacrolimus (tacrolimus–hydrogel), a potent immunosuppressive drug, in response to proteolytic enzymes that are overexpressed during inflammatory responses. This hydrogel was designed for a one-time local injection and has demonstrated a significant extension in graft survival within a rat hindlimb transplantation model. The localized delivery system offers a targeted approach to immunosuppression, aiming to prolong graft viability while potentially reducing the side effects associated with systemic administration of immunosuppressive drugs which is capable of preventing vascularized composite allotransplantation (VCA) rejection [61].

Further innovation is seen in the development of an inflammation-responsive hydrogel specifically designed for local immunosuppression. This hydrogel, which also contains tacrolimus, was developed to address the health comorbidities associated with immunosuppression in the context of vascularized composite allotransplantation. Administered subcutaneously within the graft site every 70 days, this approach has shown promise in maintaining long-term graft survival while significantly reducing the toxicity related to systemic immunosuppression. This strategy underlines the potential of localized drug delivery systems in improving outcomes for transplant recipients [62].

The efficacy and tolerability of a tacrolimus-eluting hydrogel platform were also evaluated within a large animal forelimb vascularized composite allotransplantation model. This enzyme-responsive, tacrolimus-eluting hydrogel was implanted directly into the graft site, aiming to achieve long-term graft survival with minimal systemic drug exposure. This study's findings suggest that such hydrogel composites can offer a viable alternative to conventional systemic immunosuppression, potentially reducing the risk of toxicity while maintaining the immune system's tolerance to the transplanted tissue [63].

These advancements in hydrogel composites for transplantation and immunomodulation represent a significant leap forward in transplant medicine. By focusing on localized and targeted drug delivery systems, these innovations not only aim to improve graft survival rates but also seek to enhance the quality of life for transplant recipients by minimizing the adverse effects associated with long-term systemic immunosuppression. The development of these hydrogel composites highlights the potential for more personalized and precise immunomodulatory therapies in the future of transplantation.

10. Ophthalmic Applications

In ophthalmic applications, hydrogel composites are being explored for their potential to change treatments across a range of eye conditions. From enhancing drug delivery to providing scaffolds for tissue regeneration, these materials are at the forefront of innovative solutions in eye care.

One example involves the development of rod-shaped mucoadhesive ophthalmic inserts composed of a silicone elastomer base, oxytetracycline HCl (OXT), and sodium chloride. These inserts are notable for their surface, which is grafted with either a polyacrylic acid (PAA) or polymethacrylic acid (PMA) interpenetrating polymer network (IPN). The effectiveness of these inserts, particularly in terms of mucoadhesion, improves with the increased thickness of the IPN layer. Additionally, the rate at which oxytetracycline is released from the inserts is modulated by the composition of the IPN and the concentration of NaCl, offering a tailored approach to drug delivery directly to the ocular surface [98].

Another advancement is the creation of a porous nanohydroxyapatite/poly(vinyl alcohol) hydrogel composite designed to mimic the structure and function of an artificial cornea. This composite features a porous skirt surrounding a transparent central region, mimicking the natural cornea's anatomy to facilitate integration and interlocking with host tissues. When implanted in rabbit eyes, this artificial cornea demonstrated excellent biocompatibility, marking a significant step forward in corneal transplantation and repair [99].

The development of a thermosensitive in situ gelling formulation that incorporates solid lipid nanoparticles (SLNs) loaded with Resina Draconis into a poloxamer-based hydrogel represents an innovative approach to ocular drug delivery. Utilizing a melt-emulsion ultrasonication method for preparing the SLNs and a central composite design for optimizing the hydrogel formulation, this system offers a novel method for delivering therapeutic agents directly to the eye, with potential implications for a wide range of ocular conditions [100].

A composite drug delivery system, featuring drug-loaded poly(lactide-co-glycolide) (PLGA) nanoparticles embedded within a chemically crosslinked hyaluronan hydrogel, has been designed to extend the dosing interval in the treatment of posterior eye diseases such as wet Age-related Macular Degeneration (wet AMD). This system is capable of sustaining the release of the model drug bovine serum albumin (BSA) for over two months, suggesting a promising approach to reducing the frequency of treatments for such chronic conditions [101].

Further, a collagen hydrogel containing protein-encapsulated alginate microspheres has been developed specifically for ocular applications. With Bovine serum albumin (BSA) serving as a model drug, this hydrogel aims to achieve sustained drug release while also supporting the growth of human corneal epithelial cells, indicating its potential for corneal repair and regeneration [102].

In the fight against ocular infections, tannin-coordinated Co_3O_4/Ag nanozyme composite-based hybrid hydrogels have been developed for the prophylactic treatment of Pseudomonas aeruginosa keratitis. Demonstrating broad-spectrum antibacterial activity and biocompatibility, this approach offers a new strategy for managing and preventing infectious keratitis, a serious condition that can lead to vision loss [69].

A composite hydrogel combining chitosan nanoparticles loaded with deoxyribonuclease (DNase I) and silk fibroin has been designed to sustainably regulate neutrophil extracellular traps (NETs) and reduce neovascularization, critical for ocular surface reconstruction following corneal chemical injuries. This innovative solution shows the potential of hydrogel composites in ocular surface healing and reconstruction, offering hope for patients suffering from severe corneal injuries [103].

Furthermore, the development of a fast-forming nanocomposite hydrogel incorporating diclofenac micelles into a poloxamer-based matrix is intended for ocular delivery. This hydrogel is designed to provide sustained drug release while resisting tear flushing, all without causing irritation to the eye. This advancement in ocular drug delivery systems

promises to improve the management of ocular inflammation and pain, enhancing patient comfort and treatment efficacy [104].

These examples highlight the significant potential of hydrogel composites in addressing a broad spectrum of ophthalmic issues, from improving drug delivery mechanisms to supporting tissue regeneration and fighting infections. As research in this area progresses, these innovative materials are set to play an increasingly central role in advancing eye care and treatment methodologies.

11. Biomedical Devices and Sensors

In the rapidly evolving field of biomedical devices and sensors, hydrogel composites have emerged as a cornerstone for innovation, offering unprecedented solutions that integrate functionality with biocompatibility. These materials have been meticulously engineered to meet the diverse needs of medical applications, ranging from implantable devices to wearable sensors, highlighting their versatility and potential in advancing health care technologies.

A significant development in this domain is the preparation of a composite material that blends silicone rubber with poly(2-hydroxyethyl methacrylate) p(HEMA) hydrogel. This composite yields a hydrophilic material that exhibits swelling in water. Rigorous testing has confirmed its non-toxic, non-irritant properties, and crucially, it elicits no significant tissue reaction, highlighting its suitability for a wide range of biomedical applications [105].

Aquavene, a poly(ethylene oxide)/polyurethane composite hydrogel, has been evaluated for its use as a ureteral stent biomaterial. This composite hydrogel demonstrated superior resistance to encrustation and blockage in a simulated urine flow model, outperforming traditional materials such as silicone and polyurethane. This advancement suggests a promising avenue for reducing common complications associated with ureteral stents [106].

The synthesis of a carbon nanotube-reduced graphene oxide hydrogel integrated into a fabric composite represents a leap forward in the development of flexible, stretchable supercapacitor electrodes. This technology is specifically aimed at wearable devices, offering excellent charge/discharge rates and durability under mechanical stress, thereby enhancing the reliability and lifespan of wearable electronics [55].

An implantable bladder volume sensor employing a resistor ladder network made from a conductive hydrogel composite has been developed. This sensor provides discrete resistance values for accurate bladder volume estimation, with an emphasis on biocompatibility and mechanical compatibility with bladder tissue, offering a novel solution for monitoring bladder health [107].

The preparation of poly(lactide-co-glycolide) (PLGA) microsphere/poly(vinyl alcohol) (PVA) hydrogel coatings for glucose biosensors has been undertaken to evaluate their impact on sensor functionality, including linearity, response time, and sensitivity. This approach assesses glucose permeability through the coatings, aiming to optimize biosensor performance for diabetes management [57].

Dexamethasone-loaded PLGA microsphere/PVA hydrogel composites have been developed for coating implantable devices. Utilizing USP apparatus 4 for accelerated in vitro release testing under various conditions, this methodology aims to predict "real-time" release outcomes, facilitating the controlled delivery of therapeutics from implantable devices [58].

A pH-sensitive molecularly imprinted polymer (MIP) nanospheres/hydrogel composite has been created for the controlled release of dexamethasone-21 phosphate disodium. Employing UV-initiated precipitation polymerization and UV polymerization for the hydrogel matrix, this composite targets implantable biosensor coatings, enabling responsive drug release based on pH changes [108].

The incorporation of hydrogel polymers into silicone rubber tubing to produce composite materials has been tested as ex vivo arteriovenous (A-V) shunts in dogs. This research focused on observing blood cell adhesion and predicting shunt success, demon-

strating the composite's potential to improve the compatibility and functionality of vascular shunts [109].

Soft composite hydrogel objects, formed from sodium alginate, urease, and oil droplets through a gelation procedure, represent autonomous bodies with predefined spatial and temporal responses to environmental stimuli like urea. This innovation opens new possibilities for creating responsive biomedical devices that can adapt to changing physiological conditions [36].

Furthermore, the development of a nanometallic conductive composite–hydrogel core–shell microneedle skin patch for real-time monitoring of glucose levels combines an inner conductive silver paste core with an outer bioactive hydrogel layer. This design facilitates biomarker extraction and sensing, offering a minimally invasive solution for continuous glucose monitoring, thereby enhancing diabetes management [110].

These advancements in hydrogel composites for biomedical devices and sensors highlight the field's dynamic nature, with researchers continually pushing the boundaries of what's possible. By integrating these innovative materials into medical technologies, the potential for improving patient care and treatment outcomes is vast, showcasing the critical role of hydrogel composites in the future of medicine.

12. Hydrogel Composite Testing and Evaluation

In the rapidly evolving field of biomedical engineering, hydrogel composites have emerged as versatile and highly promising materials for a wide range of applications, from drug delivery systems to tissue engineering scaffolds. This section aims to provide an overview of the critical tests and evaluations essential for the development and characterization of hydrogel composites for biomedical applications, ensuring these materials meet the stringent requirements necessary for clinical use.

The foundational step in hydrogel composite development involves assessing their mechanical properties, such as elastic modulus, shape recovery capability, mechanical resistance, and biomechanical restoration. These properties are crucial for ensuring the materials can withstand physiological conditions while providing the necessary support to biological tissues [11,15,73]. Additionally, evaluating the compression strain rate, shear strength, and the material's ability to support cell viability after injection offers insights into the composite's potential for tissue engineering and regenerative medicine applications [14,50]. Elastic recovery properties and mechanical stability are also assessed to determine the hydrogel's suitability for various biomedical applications [22,44].

At the molecular level, understanding gene and protein expression within hydrogel composites is essential for predicting their interaction with biological systems. Techniques such as RT-PCR, Western blot, and immunofluorescence staining, along with RNA sequencing, provide comprehensive data on gene expression profiles, enabling researchers to tailor hydrogel compositions for specific applications [3]. The evaluation of specific biomarkers, including alkaline phosphatase, dentin matrix protein 1, and dentin sialophosphoprotein, further informs the hydrogel's bioactivity and potential for promoting tissue regeneration [71].

For hydrogel composites designed for drug delivery, controlled and long-term sustained release of therapeutic agents is a critical characteristic. Tests to determine the pH-sensitive drug release patterns and the hydrogel's capacity for swelling and sustained growth factor release are conducted to optimize delivery profiles and therapeutic efficacy [5,20,48].

Developing hydrogel composites involves synthesizing materials with specific properties, such as sol-gel phase transition behavior and porous three-dimensional structures. Characterization techniques, including scanning electron microscopy (SEM), are employed to assess the material's morphology and structure [51,76,77]. This step is crucial for ensuring the hydrogel's functionality and performance in biomedical applications.

Evaluating the biocompatibility and therapeutic effectiveness of hydrogel composites involves a series of in vitro and in vivo tests. These include cell viability, adhesion, and

proliferation assays, as well as implantation studies to assess the material's performance in promoting tissue repair and regeneration in clinically relevant models [8–10,70,78].

For applications in bone and vascular tissue engineering, hydrogel composites must promote angiogenesis and osteogenesis. Tests to assess the enhanced expression of chondrogenic genes, production of glycosaminoglycans (GAGs), and the material's osteogenic properties provide valuable data for optimizing hydrogel formulations for these specific applications [7,46,75,80].

This guide highlights the comprehensive testing framework required to develop hydrogel composites for biomedical applications. Through careful evaluation of mechanical and biological properties, gene and protein expression, drug delivery capabilities, and biocompatibility, researchers can tailor hydrogel composites to meet the needs of various medical applications, paving the way for innovative treatments and therapies.

13. Benefits and Outcomes

Recent advances in regenerative medicine, particularly in tissue engineering, include the development of self-assembling peptide hydrogels, electrospun nanofibers, and composite hydrogels, enabling targeted growth factor delivery and complex tissue reconstruction [1,2]. Notable progress in skin and bone regeneration has been made using GelMA-PEGDA hydrogels and biodegradable thermosensitive hydrogels, enhancing tissue model accuracy and regenerative efficacy [3,6]. Innovations in cartilage repair and dental implants, like PLCL scaffolds and hydrogel composites, have significantly improved outcomes [7,8]. Advances in mechanically robust injectable composites cater to orthopedic demands [50,76,77], while enhanced hydrogel composites offer improved integration and strength for trauma and orthopedic applications [21,54,81]. Multifunctional biomaterials now incorporate antibacterial and anti-inflammatory properties, aiding in infection control and tissue integration [48,49,52]. Enhanced drug delivery systems, like smart nanocarriers and hydrogel-based microneedles, facilitate controlled drug release and improve treatment efficacy [17–20,31]. Wound healing and surgical advancements include dual-drug-releasing composites and nanocellulose hydrogels, promoting rapid healing and tissue development [29,30,66,94]. Integration of medical devices with wearable technology has led to innovations in drug delivery and health monitoring, offering potential in chronic condition management and biosensing [55,98,100,104,107,110].

14. Limitations

Translating hydrogel composites from lab to clinical use faces challenges in scalability, reproducibility, and mechanical-biological balance [13,70]. Achieving controlled, stable release of therapeutic agents remains a priority, with ongoing efforts to enhance material stability and functionality [5,16]. Manufacturing complexities and regulatory compliance present significant barriers to large-scale production and market entry. Variability in patient responses stresses the need for personalized treatment approaches, further complicated by regulatory hurdles, especially in transplantation and personalized therapies.

15. Future Directions

Advancements in smart hydrogels indicate a move towards precision medicine, with materials responsive to physiological changes enabling better drug delivery and tissue integration [53]. Personalized treatment, facilitated by 3D and bioprinting technologies, promises enhanced treatment efficacy through customized implants and therapies [2,51,84]. Research on hybrid hydrogel composites seeks to improve material performance and sustainability [12,14]. The integration of hydrogels with wearable devices and sensors could revolutionize real-time health monitoring and responsive care [85]. Overcoming regulatory and environmental challenges is essential for advancing hydrogel technologies in regenerative healing and personalized medicine, with AI and ML integration offering prospects for improved diagnostics and treatment personalization.

16. Conclusions

In the context of regenerative medicine and tissue engineering, hydrogel composites have been recognized for their potential to initiate a transformative era in medical science. This review highlighted the suitability of hydrogel composites, including tissue-specific self-assembling peptide hydrogels and electrospun nanofibers, for their role in enhancing growth factor delivery, bioprinting, and tissue reconstruction with remarkable precision and efficacy. Despite these advantages, challenges such as scale-up production, long-term stability, biocompatibility, and regulatory complexities remain. Future research should focus on developing smart and responsive hydrogels, personalized treatment modalities through 3D printing, and hybrid composites to improve sustainability. The integration of these materials with wearable technology and AI-driven solutions is poised to transform healthcare delivery. As we navigate the future, striking a balance between innovation, regulatory compliance, and environmental responsibility will be critical to fully harness the potential of hydrogel composites in advancing patient care and medical outcomes.

Author Contributions: The authors confirm contributions to the paper as follows: conceptualization, writing, review, and editing, H.O.; investigation, review, and editing, A.A. and S.D.C. All authors have read and agreed to the published version of the manuscript.

Funding: This review article received no external funding.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflicts of interest.

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