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REVIEW

A Comprehensive Review on the Utilization of Biomaterials for Bio-Based Hydrogel in Therapeutic Applications

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Abstract

A bio-based hydrogel is a complex compound that consists of natural biomaterials and is widely applied for various therapeutic purposes. The modification from traditional biomaterials to reformulated bio-based hydrogels has gained a place at biomedical field due to the growth of therapeutic benefits such as drug delivery, tissue engineering, and regenerative medicine. Moreover, the increasing global demand for bio-based hydrogels has resulted in a worldwide shortage of mass formulations and has raised environmental awareness. By using natural biomaterials instead of synthetic ones, these hydrogels minimize their negative effects on the environment while simultaneously maximizing the successful execution of the product. However, the mechanisms governing degradation and bioactivity in bio-based hydrogels, which dictate drug release profiles, hydrogel stability, and therapeutic effectiveness, are not yet comprehensively understood. Therefore, by analyzing recent progress and ongoing challenges, this review will reveal how advanced bio-based hydrogels are quietly transforming the future of healthcare and offering novel solutions to pressing health problems.

Keywords Biomaterials · Bio-based · Hydrogels · Therapeutics · Polysaccharides

Introduction

Biomaterials are consciously designed substances that have potential in repairing, replacing, or enhancing tissue functions within biological systems. In addition, the fabrication of biomaterials involves two fundamental processes: either from natural resources or through synthetic methodologies [1]. Consequently, they are safe for the body because they don't cause bad reactions and are strong and flexible like the tissues they help or replace. Moreover, various biomaterials, including metals, polysaccharides, ceramics, and proteins, are strategically selected by doctors and scientists based on the specific demands of the therapeutic intervention [2]. In other words, each biomaterial interacts with organismal systems for medical purposes, including diagnostic, therapeutic, or tissue engineering applications [3].

Bio-based hydrogels (BBHs), as naturally derived biomaterials, are characterized by extensively hydrated, three-dimensional networks, designed to create adaptable, sustainable platforms for diverse therapeutic and biomedical applications. In essence, biomaterials and bio-based hydrogels exhibit a synergistic relationship, since bio-based hydrogels exploit the natural biomaterials' qualities such as biocompatibility, biodegradability, and bioactivity to form matrices that closely align with the human tissue extracellular matrix [4, 5]. A notable trait of bio-based hydrogels is their capacity to self-repair [6]. This feature is particularly advantageous for dynamic conditions where mechanical stress is common, including soft tissue replacement and wound healing [7]. Furthermore, it can be exploited to create advanced drug delivery mechanisms because it is sensitive to changes in pH, temperature, and ionic strength [8]. Additionally, bio-based hydrogels, which are made by natural sources like chitosan, alginate, collagen, cellulose, dextrose, hyaluronic acid, pectin, and agar, have inherent antimicrobial activity, making them ideal for wound dressings and infection control [9–12]. Besides providing therapeutic benefits, bio-based hydrogels work for sustainability by utilizing renewable resources and decreasing the need for nonbiodegradable synthetic materials [13]. As shown in Fig. 1 various biopolymers are summarized with their properties and therapeutic uses. Notably, prominent features

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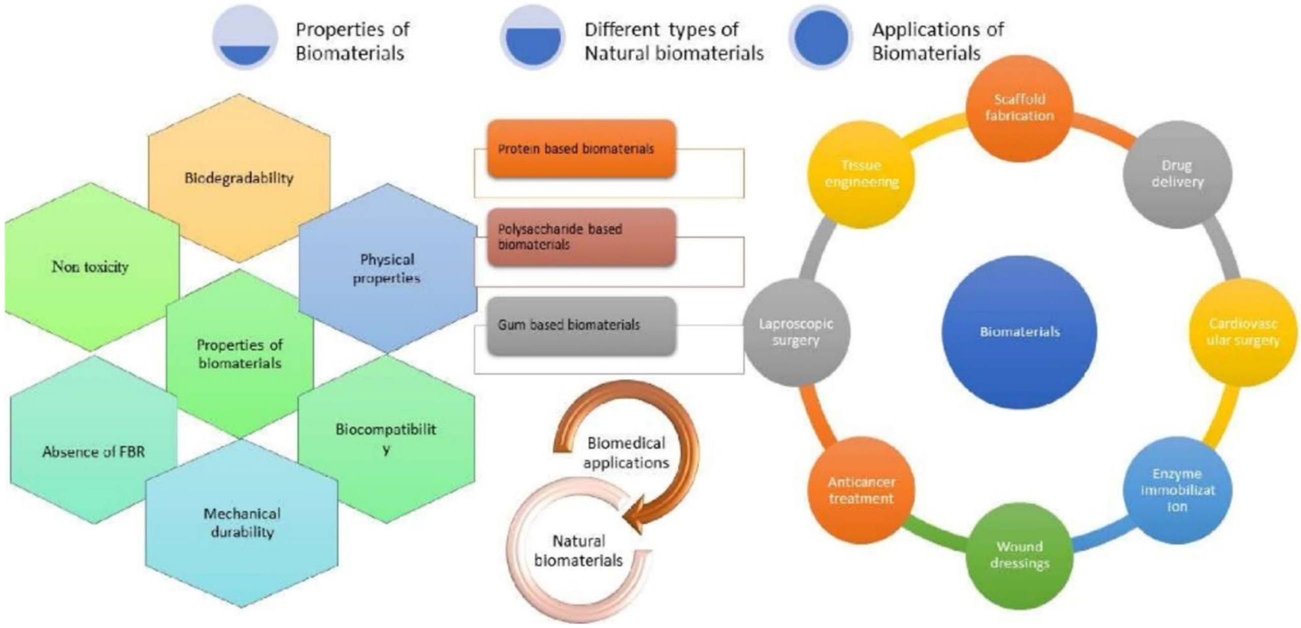

Fig. 1 Properties, types, and applications of biomaterials [14]

of these biomaterials are their capacity for biodegradation, absence of toxic effects, mechanical strength, biocompatibility, beneficial physical characteristics, and reduced risk of foreign body reactions. Thus, applications of biomaterials cover areas like tissue engineering and scaffold fabrication to drug delivery, cardiovascular surgery, enzyme immobilization, wound dressings, cancer treatment, and laparoscopic procedures [14].

Despite the extensive research on biomaterials for bio-based hydrogels in therapeutic settings, there are still important areas that need additional study. Most studies have concentrated on designing new materials and advancing their fundamental features. However, there is insufficient knowledge of how these materials interact with the human body over long durations. Moreover, producing these hydrogels on a large scale and at a reasonable cost for common medical use remains a significant problem. Additionally, not all biomaterials used in hydrogels are fully compatible with the human body. Advanced investigation is necessary to identify materials that are safe and do not produce adverse effects. To address deficiencies in strength and flexibility observed in many bio-based hydrogels, there is a need for more research. Furthermore, to achieve better drug delivery outcomes, it is crucial to refine hydrogels' targeting capabilities. Typically, hydrogels are utilized without the combination of other therapeutic approaches. Incorporating hydrogels into other treatments might boost their performance and deliver more complete patient solutions.

This review offers a comprehensive and accessible summary of recent progress and challenges in bio-based hydrogels for therapeutic uses. By reviewing current studies, this paper showcases how different biomaterials amplify the effectiveness of hydrogels in therapeutic uses. over and above, the review will highlight the challenges and limitations faced by researchers and practitioners, suggesting potential solutions and future directions.

Classification of Biomaterials for BBHs

While not all biomaterials can be used to produce BBHs [5], it is important to note that BBHs are formulated from natural or synthetic polymers, which form a gel structure upon contact with water [15]. In nature, there are numerous materials but only a few biomaterials have active compounds, which are called bioactive compounds. These biomaterials have sourced goods widely that originated from a variety of genesis such as bacteria, minerals, plants, and animals. For illustration, AL-dabbagh, Salman et al., and EL-Ghwas et al. (2022) have pointed out that Acetobacter xylinum is the primary source of cellulose, as opposed to dextran has been derived from Leucistic mesenteries [16, 17].

Naturally, biomaterials are classified into three types, polysaccharides-based, protein-based, and gum-based. This review provides a comprehensive overview of the biomaterials used to produce BBHs for therapeutic applications, according to their types, origin, and active compounds as shown in Table 1 [14, 18].

Besides these natural biomaterials, a new compound existing biomaterial, modified from polysaccharides and

Table 1 Classification of biomaterials for BBHs production into polysaccharide-based, protein-based and gum-based

Type	Biomaterial	Natural resource	Active compounds	Therapeutic properties	Ref
Polysaccharide-based	Cellulose	Bacterial sources (e.g., *Acetobacter xylinum*) Plant cell walls (e.g., cotton, wood)	β-D-glucose units	Biocompatibility, ability to form a gel, high mechanical Strength	[19–21]
	Chitosan	Shrimp, crabs (Exoskeleton of crustaceans)	N-acetylglucosamine, Glucosamine	Healing capability, antimicrobial and cell proliferation ability, homeostatic agent	[22–24]
	Alginate	Brown seaweed (e.g., Laminaria, Ascophyllum)	Guluronic acid, Mannuronic acid	Anti-inflammatory, gel-forming ability, biocompatibility	[25, 26]
	Dextran	Bacterial fermentation (e.g., Leucon Stoc mesenteroides)	Glucose units (linked by α-1,6 glycosidic bonds)	Immunomodulation due to its high-water solubility, biodegradability, and relative biocompatibility	[16, 27, 28]
	Hyaluronic Acid	Synovial fluid, rooster combs, and bacterial fermentation	D-glucuronic acid, N-acetyl-D-glucosamine	Anti-aging properties due to its ability to retain moisture and enhance tissue repair, joint lubrication, wound healing, anti-inflammatory	[29, 30]
	Collagen	Animal connective tissues (skin, bones, cartilage, tendons	Hydroxyproline, glycine, proline	skin elasticity, regeneration of tissue, healing capability	[31–33]
	Gelatin	Denatured collagen (animal connective tissue)	Proline, hydroxyproline, glycine	Hemostasis, healing capability, drug delivery	[34–36]
Protein- based	Fibrin/fibronectin	Blood plasma (human, animal)	Fibrinogen, Thrombin, Fibronectin	Cell adhesion, tissue repair, healing properties	[37, 38]
	Elastin	Animal connective tissue (skin, arteries)	Trophoblastic, Desmosine, Iso-desmosine	Skin elasticity, tissue repair, vascular health	[39–41]
	Fibroin	Silk (Bombyx mori silkworm)	Alanine, Glycine, Serine	Tissue engineering, drug delivery	[42–44]
	Whey proteins	Milk (bovine)	Beta-lactoglobulin, Alpha-lactalbumin, Immunoglobulins	Antioxidant activity, immune modulation, muscle repair	[45–47]
	Guar Gum	Seeds of guar plants (*Cyamopsis tetragonoloba*)	Galactomannan	Anti-diabetic, laxative, and cholesterol-lowering effects due to its high fiber content and ability to modulate blood sugar levels	[48, 49]
Gum- based	Gellan Gum	Sphingomonas elodea Fermentation	Glucuronic acid, rhamnose, glucose	Biocompatibility and mechanical strength, stabilizer in drug formulations	[50, 51]
	Gum Arabic	Acacia tree sap (*Acacia senegal*, *Acacia seyal*)	Arabinogalactan	Ability to stabilize emulsions and their high biocompatibility, probiotic, anti-inflammatory	[52, 53]
	Carrageenan	Red seaweed (*Chondrus crispus*)	Sulfated polysaccharides (e.g., kappa, iota, lambda carrageenan)	Anticoagulant, gel-forming properties, antiviral, anticoagulant	[54–56]
	Xanthan Gum	Fermentation of sugars by *Xanthomonas campestris*	Glucuronic acid, mannose, glucose	Anti-inflammatory properties, Stabilizer in drug formulations	[57, 58]

gum-based biomaterials has been explored, named after Oligo-alginate which has significant biological properties and therapeutical potentiality like antitumor, anticoagulant, antihypertensive, antidiabetic, neurogenerative, and antiallergic properties, immunomodulatory, antimicrobial, and antioxidant. Moreover, it can fight neurodegenerative diseases (e.g., Alzheimer's disease). That's why it has achieved substantial attention in the field of pharma [59, 60]. Furthermore, Exopolysaccharides (EPSs) which are isolated from microorganisms from extreme niches like hot springs, cold waters, halophilic environments, and salt marshes, have antitumor and antioxidant properties, nutraceuticals usage, cosmetics, and insecticide application [61, 62].

Characteristics of Biomaterials for BBHs

Biomaterials are natural composites utilized in the formulation of BBHs that have some principal characteristics that recommend them as a promising catalyst for diverse therapeutic oriented. Figure 2 simplifies the characteristics of biomaterials to produce BBHs.

Biocompatibility

Biomaterials have been utilized as vectors in biocompatible drug delivery systems that conduct directly with biological tissues and develop any organ, tissue, or body function. Although advanced biomaterials can give instant filling effects and stimulate tissue regeneration, they can avoid additional damage to the donor site, while minimizing the risk of prosthetic rejection and long-term infection. For example, Gelatin, chitosan, calcium phosphate, alginate, and xanthan gum, all-natural polymers are used to formulate diverse delivery systems. However, the transition of advanced biomaterials into clinical is experiencing great difficulties. In-depth and long-term research is crucial to explore the interaction between biomaterials and host tissues, the biocompatibility, safety, and biodegradability of implanted biomaterials [63, 64].

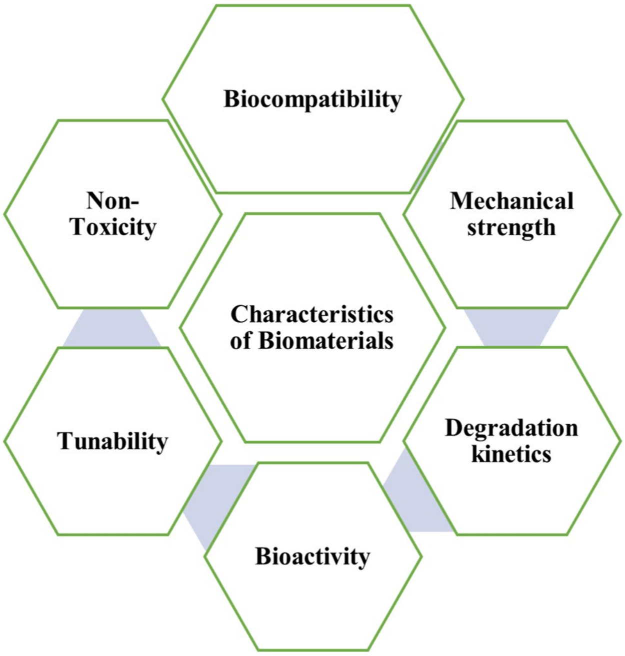

Fig. 2 The characteristic of biomaterials for BBHs production

Mechanical Strength

The mechanical strength of BBHs mainly depends on the breaking of bonds and unfolding of proteins under light. That's why this is a crucial application in the biomedical field. Like, for wound dressing or injectable preparation, soft hydrogel is perfect. On the other hand, for tissue engineering, rigid hydrogel is utilized as scaffolds. Scientists have explored some strategies to enhance mechanical strength for instance using double-network frameworks, dynamic crosslinking strategies, and integrating reinforcing fibers [65, 66].

Degradation Kinetics

Degradation kinetics is the term that means the biomaterial that is taken into the body for medical purposes and how much time it will take to break. It is a fully biological process inside the body where the biomaterials are broken gradually. The advantages of these properties are mainly utilized in tissue engineering, improved cell integration, developed resorbable devices, and controlled-release drug as it is designed to degrade into non-toxic by-products that can be safely absorbed or excreted by the body temporarily. However, the material's chemical composition, molecular structure, and environmental conditions such as pH and temperature are capable of influencing the degradation rate [67, 68].

Bioactivity

To promote healing and integration, by supporting cell adhesion, proliferation, and differentiation, biomaterials that interact with the biological system of the body are known as bioactive materials. For example, collagen or chitosan have latent potential because of their ability to interact with cells, thereby promoting tissue regeneration. However, facilitating cellular interactions is always dependent on surface characteristics, mechanical properties, and the material's inherent capabilities. Therefore, researchers have been working to understand and optimize these properties to explore better therapeutic applications [69].

Tunability

The use of knowledge-based tools to manipulate the properties of biomaterials according to the desired direction is defined as tunability [70]. For example, to respond to environmental stimuli, making them suitable for drug delivery and tissue engineering, hydrogel can be modified and engineered in living tissue. Moreover, precise control over drug release profiles, enhancing the efficacy of therapeutic agents, another class of tunable biomaterials, polyurethanes are utilized. Additionally, sequence-controlled synthetic polymers can improve biomaterials that can reproduce natural biopolymers, developing their functionality in medical applications. In regenerative medicine and other biomedical fields, the characteristics of biomaterials are significantly important [71, 72].

Non-Toxicity

BBHs are biocompatible and do not generate toxic substances, as they are manufactured from natural sources. For example, in drug delivery systems, wound healing applications, tissue engineering scaffolds, and ophthalmic applications, BBHs are used to ensure that no harmful by-products are introduced to the body during degradation. This reduces the risk of adverse side effects and ensures patient safety [73, 74].

Therapeutic Advances in BBHs

BBHs which are made from biomaterials as key players in modern medicine, offering promising therapeutic possibilities. These flexible materials, consisting of water-absorbing polymer networks, are particularly well-suited for drug delivery, tissue engineering, regenerative medicine, and diagnostic applications [75, 76].

Drug Delivery

New progress in BBHs has facilitated the development of complex drug delivery systems. For targeted action and controlled release, scientists are working day to night. However, injectable hydrogels with temperature sensitivity ensure precise drug delivery, enhancing therapeutic effectiveness while minimizing side effects. A good example of this is a heat-sensitive gel with curcumin particles that are used to treat cancer as it helps to release drugs slowly and steadily over time [77, 78]. To further illustrate, the researcher's Xu, Qi et al. (2021) and Deng, Yang et al. (2023), have mentioned that bio-based hydrogel which contains active 3D peptides has strong efficacy in curing long-term inflammation and cancer more accurately and precisely [79, 80].

This is the result of the hard work of the scientists. Even, Drug delivery is greatly improved by bioactive molecules and nanoparticles provide superior treatment options for chronic diseases and cancer [81].

Wound Healing and Tissue Regeneration

BBHs have seen remarkable progress, making notable contributions to wound management and tissue repair. The latest methods use hydrogels combined with growth factors, stem cells, or antimicrobial substances to promote faster healing and lower infection rates. Better mechanical and biological features in hydrogels support tissue repair in severe wounds and critical-sized bone defects.

For instance, Bai, Kyu-Cheol, et al. (2020) and Chen, Tong et al. (2021) demonstrated that hydrogel which contains mesenchymal stem cells (MSCs) can speed up healing in diabetic mice. Even it can assist in formatting blood vessels and producing collagen which also makes BBHs-(MSCs) stronger to give better performance for stubborn wound treatment [82, 83].

Despite this, the researcher's Wang, Pan, et al. (2020) and Fasiku, Omolo et al. (2021) have identified the synergistic effect of silver nanoparticles within a chitosan-based hydrogel that has the efficacy not only to boost antibacterial and fibroblast proliferation but also accelerating the process of wound closure and reducing inflammation. By developing the potentiality and utilization of bio-based hydrogel, intricate wound vulnerability to infections can be effectively managed [84, 85].

Moreover, new 3D bioprinting technologies have allowed the fabrication of hydrogel scaffolds that effectively replicate the natural extracellular matrix, promoting better integration and regeneration of damaged tissues [86, 87]

Hydrogels for Osteoarthritis and Cartilage Repair

In treating osteoarthritis and repairing cartilage, bio-based hydrogels show hopeful results. Current research is focusing on developing hydrogels with viscoelastic properties like cartilage to improve joint repair applications. To boost regenerative performance, these hydrogels usually contain chondrocyte cells or elements from cartilage matrices [88, 89].

Breakthroughs in injectable hydrogel technologies and in situ gelation methods are facilitating minimally invasive solutions for cartilage repair, presenting new hope for patients with joint conditions. For example, Bordbar, Li et al. (2024) mentioned in their research journal that a bioactive glass and collagen-based hydrogel can faster expression of cartilage genes and facilities for cartilage repair in osteoarthritis models which indicates probable future clinical therapy of collagen-based hydrogel for joint issues [90].

Cancer Therapy and Diagnostic

In cancer care and diagnosis, advances in BBHs are contributing to improvements. Recent developments in hydrogels include targeting ligands that enhance the precision of chemotherapy delivery, reducing collateral damage to healthy tissues [91–93]. Hydrogels designed for diagnostics allow for live monitoring of cancer biomarkers, facilitating both early detection and tailored treatment strategies. A notable instance of this is that Peng, Liang et al. (2024) engineered a hydrogel with ligands that can create chemotherapy drugs in tumors, having the capacity to minimize the possible side effects and enrich the therapeutic outcomes of doxorubicin in breast cancer treatment [94]. In parallel, the most advanced bio-based hydrogel biosensor is being demonstrated by Aranda Palomer, Relvas et al. and Nishat, Hossain et al. 2022 whose services can identify circulating tumor DNA (ctDNA) in real-time, permitting non-invasive malignant growth structure observation and enabling immediate action and individualized treatment plans in the management of lung cancer [95, 96].

Neural Tissue Engineering

BBHs are showing considerable advancements in neural tissue engineering, showing promise for the treatment of neurological injuries and disorders. Recent progress in hydrogels that aid in neuronal growth and repair by offering an environment that encourages neural cell attachment and proliferation. The use of electrically conductive hydrogels with growth factors to support nerve repair and functional recovery in neurodegenerative and spinal cord injury contexts [97, 98].

In another respect, Chen, Xia et al. (2023) investigated that promoting the repair of peripheral nerves, the bio-based hydrogel can be engineered by the effects of integrating graphene oxide, by boosting their electrical conductivity. According to the study's findings, modification leads to more effective neuron regeneration, a higher degree of function recovery, and less development of tissue scarring as compared to hydrogels missing conductivity [99].

Moreover, Li, Xu et al. (2024) formulated a novel hydrogel formulation that incorporates BDNF (brain-derived neurotrophic factor) and neurological growth factor (NGF), which stimulates the proliferation and development of neural cells at the wounded site and speed up nerve healing after spinal cord fractures. The formulation is relatively simple to implement [100].

The latest developments in BBHs are changing how we treat different medical problems from delivering medicine to fixing nerve damage. These advancements in BBHs indicate their potential to deliver innovative, non-invasive, and highly effective treatments, that can enhance outcomes for patients with challenging conditions. Table 2 summarizes the biomaterials utilized in BBHs and their therapeutic applications, from treating wounds to addressing cancer.

Table 2 Advance therapeutic application of BBHs

Therapeutic field	Biomaterials	Therapeutic activity	Ref
Wound care	Alginate, chitosan, collagen, hyaluronic acid	Create a moist environment, help cell migration, and repair wound healing	[101–105]
Drug delivery, pharmaceutical	Alginate, gelatin, dextran, pectin	Empowering drug efficacy and affinity, minimize side effects, encapsulate the drug, release them in control manner	[106–108]
Tissue engineering, implants	Collagen, gelatin, hyaluronic acid, fibrin	Assisting cell growth and tissue for genesis regenerative medicine	[109–112]
Ophthalmic	Hyaluronic Acid, chitosan, collagen	used to treat a variety of ocular disorders and are also utilized for drug administration to the eye	[113, 114]
Orthopedic	Hydroxyapatite, collagen, chitosan	Enhances the integration of newly formed bone tissue and is used in bone regeneration and repair	[114–118]
Cardiovascular	Alginate, collagen, hyaluronic Acid, Fibrin	Heart tissue engineering scaffolds that are utilized for cardiac tissue repair	[119–122]
Dermatological	Hyaluronic acid, collagen	To enhance skin moisture and attractiveness, hydrogels are utilized in fillers and skin care products	[123, 124]
Nerve Regeneration	Collagen, chitosan, hyaluronic acid	In nerve growth and regeneration, hydrogels offer a favorable environment	[125, 126]
Gastrointestinal	Pectin, chitosan, alginate	The gastrointestinal system can be specifically targeted for medication delivery with hydrogels	[127–129]
Cancer	Alginate, chitosan, gelatin	Anticancer medications can be delivered by hydrogels straight to the tumor site, enhancing targeted and lowering systemic toxicity	[130–132]

Sustainability and Environmental Impact

Current biomedical research highly values the sustainability and environmentally friendly biomaterials in BBHs is a top priority [133]. Polysaccharides (such as alginate, and chitosan) and proteins (such as gelatin, and collagen) from renewable resources, offer distinct advantages over synthetic materials [134]. Being biodegradable, these materials decompose over time, which reduces environmental harm and waste disposal worries [135].

One notable environmental advantage of BBHs is their lower carbon emissions [136]. Compared to synthetic polymers, these biomaterials are produced with reduced energy consumption and lower greenhouse gas emissions [137]. By using agricultural by-products and waste materials as raw materials, can enhance sustainability by transforming waste into beneficial biomedical applications, promoting circular economy principles. In addition, these hydrogels decompose into harmless, eco-friendly substances, minimizing environmental impact [138, 139]. This approach would also enhance the reuse and recycling of lignocellulosic biomass, supporting the circular bioeconomy as illustrated in Fig. 3 [15]. In the medical realm, where materials are generally discarded after a single use, this issue is particularly pertinent. The natural degradation capability without harmful releases is in line with green chemistry standards and furthers sustainable development [140, 141].

Ultimately, the use of biomaterials in bio-based hydrogels advances therapeutic solutions while fostering environmental sustainability. By emphasizing the use of renewable resources and biodegradability, these materials offer a promising route to environmentally friendly biomedical solutions.

Challenges of BBHs Formulation

BBHs, while offering great promise, they face a range of specific obstacles that affect their growth and practical application. The challenges in formulating and performing with natural raw materials arise from their variability and the

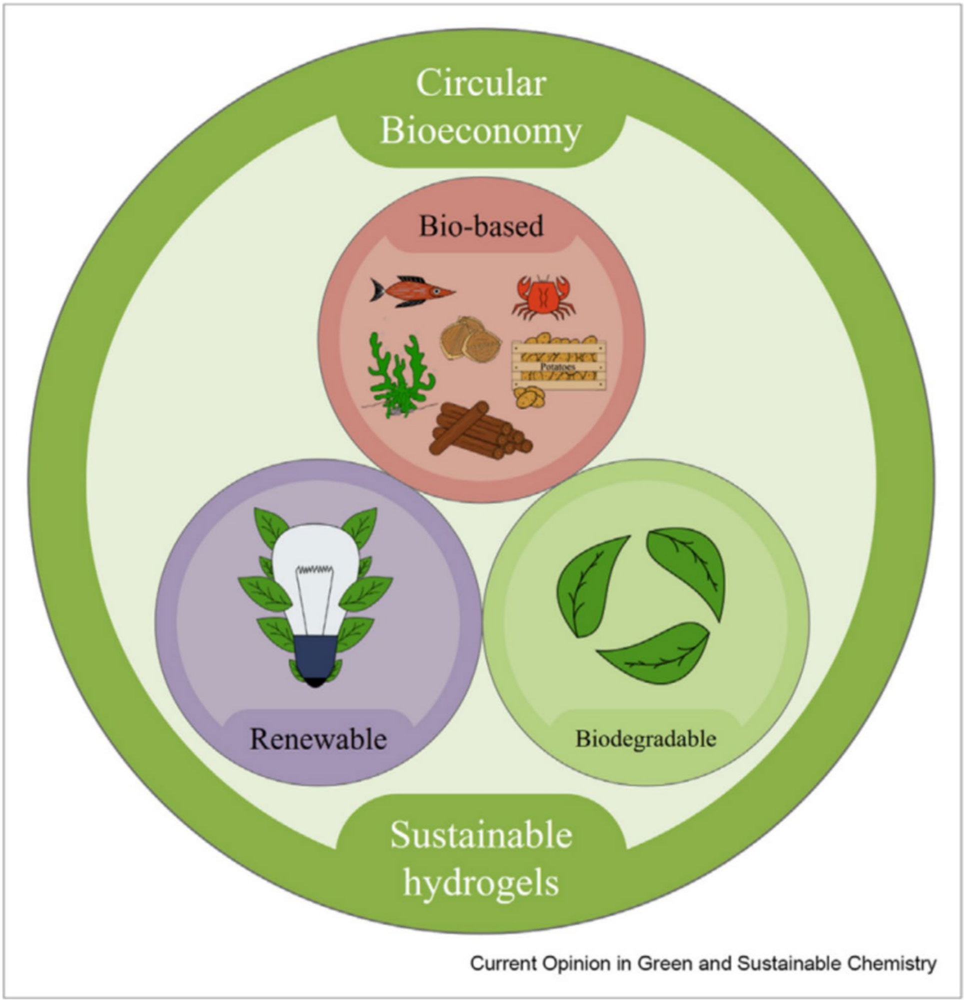

Fig. 3 The reuse and recycling of lignocellulosic biomass, supporting the circular bioeconomy [15]

complex requirements for crosslinking and functionalization. Besides, the constraints on functionalization and scalability issues add complexity to move these lab innovations into practical, widespread use. The challenges are mechanical inability, biocompatibility and immunogenicity, controlled drug release, long-term stability, environmental, cost, and ethical concerns.

Mechanical Inability

Compared to synthetic materials, biomaterials are less robust and stable. Alginate and chitosan have experienced mechanical inferiority because of brittleness, weak hydrogen bonds and affected on the environment. Due to this limitation, their structural integration is vulnerable, and they are unfit for advanced therapeutic application [142, 143]. Another example is gelatin which is relatively fragile and affected by temperature [144]. Moreover, not only physical factor but also chemical factors weak crosslinking networks makes them unfit to give the best performance in the medical field [145]. Addressing mechanical issues generally involves refining the hydrogel formulation or including supplementary materials to tackle mechanical problems [146].

However, Gao, Peng et al. (2021) and Ma, Liu, et al. (2022) have explored that by synthesizing synthetic polymers, such as poly (ethylene glycol) (PEG) or poly (vinyl alcohol) (PVA), with natural ones, or by using crosslinking agents, the mechanical appearance of bio-based hydrogels can be dramatically developed. For example, With the interfacing of alginate and PEG, the stronger stretcher hydrogel can be formulated. That capacity assists them more effectively in situations where the load requires physical support [146, 147].

Additionally, bio-based hydrogels containing cellulose nanocrystals (CNC) can maintain their mechanical durability, confirming the creation of stability and sturdiness. In this way, the hydrogel is synthesized and able to maintain more resistance to mechanical stress [148]. Furthermore, to improve mechanical integrity, Cross-linkers like calcium ions (for alginate) and genipin (for chitosan) have been used to reinforce hydrogels [149, 150] However, it is observed that modern advancements in hydrogel have been explored to meet the needs of more complex medical applications, like tissue repair and drug transport [151].

Biocompatibility and Immunogenicity

Bio-based hydrogels are typically biocompatible, yet they might still cause immunogenic reactions or other adverse biological outcomes [152]. Even with cutting-edge biomaterials, unpredictable interactions between advanced biomaterials and biological systems can sometimes lead to inflammation or immune reactions [153]. Recent research underscores that hydrogels made from naturally occurring polymers may still trigger immune responses, influenced by contaminants, degradation by-products, or structural changes in the material. Achieving precise control over the hydrogel's physical and chemical attributes is a major challenge, as these features can impact cellular and immune system responses [154, 155] To resolve these problems, the advancement of biomaterials, particularly through novel surface enhancements and immunomodulatory additions is needed. According to current findings by Song,Wang et al. 2024, a new double-network structure hydrogel can be achieved for tissue sealing and soft robotics by the combination of PVA (polyvinyl alcohol) with alginate, where adhesive and cohesive forces are sequentially utilized to create 3 times better potential hydrogel compared to before when the situation was unbalanced [156].

New approaches for in vitro and in vivo testing are being formulated to improve the assessment of hydrogel biocompatibility, aiming to lower the risk of adverse reactions and enhance safety for clinical applications. A formulation has been mentioned by Li, Zhang, et al. (2023), where the combination of immunosuppressive drugs, for example, dexamethasone contained in the hydrogel structure effectively controlled to the inflammatory reactivity in real-time studies [157]. Additionally, Canciani, Semeraro et al. (2023) demonstrated that finding out the immunogenicity in the hydrogel, a sophisticated in vitro testing technique has been followed as safe patient treatment is the main purpose [158].

Controlled Drug Release

The drug made from biomaterials is influenced by multiple factors, including the hydrogel composition, crosslinking density, and environmental conditions (e.g., pH, temperature). For instance, chitosan-based hydrogels are swell at low pH, which, in turn, can change the rate of drug release. Moreover, imbalanced degradation is another challenge of controlled-release drugs. Consequently, the degradation rate sometimes does not align with the expected drug release profile, resulting in either early release or inadequate dosage throughout the duration. Furthermore, biological interactions, enzymatic processes, and tissue responses are critical factors that play a key role in shaping drug release profiles from hydrogels post-implantation [159]. For instance, Mallakpour, Nikkhoo, et al. (2022) prepared a hydrogel that encompasses metal–organic frameworks (MOFs) within polyethylene glycol (PEG) gels, which works as carriers for chemotherapy medications and provides accurate drug release when enzymes in cancer tissues are reacted, thereby effective cancer therapy has been facilitated [160].

Furthermore, a special type of hydrogel which is used for the treatment of diabetes, has been demonstrated by the researcher Huang, Yu et al. (2021). This hydrogel contains a mixture of phenylboronic acid and chitosan which triggers swelling based on sugar concentration, it has great potential to generate insulin in response to blood sugar levels. Dynamic and customized diabetes counseling has been achieved from the phenylboronic acid and chitosan-based hydrogel [161]. Moreover, Singh, Tripathi, et al. (2023) developed a hydrogel system that is a mixture of silk fibroin and magnetic nanoparticles, which can enable distance drug release management via an outside magnetic field, that can work for non-invasive adjustments to drug delivery with precision, particularly needed for inflammation and cancer in the targeted zone [162].

In addition, Chen, Jiang et.al (2024) have presented a particular type of hydrogel which is made by betamethasone with hyaluronic acid (HA). It helps to relieve sciatica as it has sustained release capability over a period on the affected area of the human body [163].

Long-Term Stability

As bio-based hydrogels are mechanically weaker, excessive biodegradation rate, they also must face significant challenges in maintaining long-term stability and structural integrity compared to synthetic hydrogels. The interaction between the functional groups of carbon materials can potentially disrupt water transport. In a recent experiment, coating corn seeds with a potato-starch-based hydrogel showed only a slight increase in water absorption, and no substantial difference in plant growth compared to uncoated seeds [164, 165].

In the research study of Saberianpour, Melotto et al. (2024), it was claimed that interactions between functional groups in carbon materials can capacity to block water movement, and they explored that hydrogel dressings like Aquacel® can effectively capture moisture and be structurally sound for several days, in such way, healing and limiting degradation have acquired[166].

Likewise, Ghandforoushan, Golafshan et al. (2022) have pointed out that adding fibrin with injectable hydrogel can continue to execute lasting stability in physical conditions which can release the drug gradually over a longer period. This injectable hydrogel is significantly appreciated for cardiovascular disease, regenerative medicine, and neural tissue engineering [167].

Environmental, Cost, and Ethical Concerns

Obtaining natural polymers for bio-based hydrogels may raise environmental, financial, and ethical issues. Overharvesting and non-renewable energy usage in production can negate the eco-friendly benefits of bio-based hydrogels, highlighting the importance of sustainable sourcing. Due to the substantial costs of acquiring and processing natural polymers, bio-based hydrogels less cost-effective than synthetic options, hindering their broader use across industries [168, 169].

By way of example, Zhang, Zhou, et al. (2023) have emphasized the use of polymers that come from agricultural waste, that can be modified in the manufacturing of hydrogels. It lessens environmental issues by allowing ethical awareness which is associated with overharvesting [170]. Moreover, Kumar, Kumar, et al. (2023) have explained that hydrogel can be designed based on biowaste materials whose formulation costs are also much cheaper in comparison with synthetic and most importantly can be fruitfully used for industrial applications [171].

However, these hydrogels' formulation faces specific challenges, such as mechanical strength, degradation, and stability concerns. Addressing these challenges is critical for enhancing the therapeutic capabilities of bio-based hydrogels. Table 3 outlines the various biomaterials for BBHs, along with their types and formulation limitations.

The discussed challenges are pertinent and current, mirroring the continuous progress and focus on the field

Table 3 Formulation limitations for BBHs

Biomaterials	Formulation limitation	Ref
Alginate	Fast degradation, weak mechanical strength, sensitive gelation rate	[172, 173]
Chitosan	A high molecular weight substance can exhibit varying degrees of cytotoxicity, biodegradation, and Solubility Issues	[174, 175]
Hyaluronic Acid	Viscosity control, stability, cost issue	[176, 177]
Collagen	Mechanical strength, variability, ethical and cost concerns	[178, 179]
Gelatin	Thermal sensitivity, excessive crosslinking, degradation	[180, 181]
Fibrin	Varied due to a few factors, such as the presence of thrombin and fibrinogen, resulting in different gel characteristics, degradation	[182, 183]
Pectin	Source variability, crosslinking issues, degradation	[184, 185]
Dextran	Complex synthesis, limited mechanical Strength, biodegradability	[186, 187]
Hydroxyapatite	Poor solubility, brittleness, processing challenges	[188, 189]

of bio-based hydrogel research. Mirroring the continuous progress and focus on the field of bio-based hydrogel research. Long-standing challenges such as biocompatibility and mechanical strength are now joined by newer research focuses on advanced production techniques, economic considerations, and detailed evaluations of environmental impacts.

Conclusion and Future Prospects

In summary, bio-based hydrogels have shown possibilities as viable options for several therapeutic uses, including drug delivery, tissue engineering, and wound healing. They have been extremely desirable for clinical use due to their characteristics, especially their integration with host tissue, adjustable physical characteristics, controlled dosing capabilities, and biocompatibility. Bio-based hydrogels can have their properties tailored to specific applications through a combination of chemical and physical crosslinking techniques used in their synthesis. Even with these noteworthy developments, there are still a lot of obstacles to be solved, including sterilization problems, restricted drug loading, and uncertainty about long-term performance.

In the future, overcoming the obstacles related to bio-based hydrogels will facilitate their broader implementation in medical environments. The development of innovative sterilization methods, the improvement of pharmaceutical loading capacities, and the prediction of long-term performance should be the main goals of research. Additionally, investigating new synthesis techniques and material compatibility will make it possible to create bio-based hydrogels with improved characteristics and functions. To speed up the advancement of bio-based hydrogel technological advances from bench to bedside and ultimately improve patient outcomes and healthcare advancements, a collaborative effort among researchers, medical professionals, and industry stakeholders is imperative.

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Data Availability The data that support the findings of this study are not available as no datasets were analyzed during the current study.

Declarations

Conflicts of interest The authors declare that there is no conflict of interest.

Research Involving Human & Animal Participants On behalf of authors, corresponding author confirmed that there is no human participants and/or animals were conducted in this study.

Informed Consent This review paper did not include any new studies involving human participants; therefore, informed consent was not required. The analysis and summary presented are based on findings from previously published research.

References

1. A. Awasthi, K.K. Saxena, R.K. Dwivedi, An investigation on classification and characterization of bio materials and additive manufacturing techniques for bioimplants. Mater. Today Proc. **44**, 2061–2068 (2021)
2. S. Varghese et al., Biomaterials in medical applications. Curr. Mater. Sci. **17**(3), 212–239 (2024)
3. K.M. Agarwal et al., Comprehensive study related to advancement in biomaterials for medical applications. Sens. Int. **1**, 100055 (2020)
4. A.D. Štiglic, Preparation of three dimensional structures of polysaccharide derivatives for application in regenerative medicine. (Univerza v Mariboru (Slovenia), 2022)
5. S.J. Buwalda, Bio-based composite hydrogels for biomedical applications. Multifunct. Mater. **3**(2), 022001 (2020)
6. M. Zhu et al., Research progress in bio-based self-healing materials. Eur. Polymer J. **129**, 109651 (2020)
7. C. Dou et al., Bio-based poly (γ-glutamic acid)-gelatin double-network hydrogel with high strength for wound healing. Int. J. Biol. Macromol. **202**, 438–452 (2022)
8. M.D. Markovic et al., Biobased thermo/pH sensitive poly (N-isopropylacrylamide-co-crotonic acid) hydrogels for targeted drug delivery. Micropor. Mesopor. Mater. **335**, 111817 (2022)
9. M. Prasathkumar, S. Sadhasivam, Chitosan/Hyaluronic acid/Alginate and an assorted polymers loaded with honey, plant, and marine compounds for progressive wound healing—Know-how. Int. J. Biol. Macromol. **186**, 656–685 (2021)
10. S. Homaeigohar, A.R. Boccaccini, Antibacterial biohybrid nanofibers for wound dressings. Acta Biomater. **107**, 25–49 (2020)
11. V. Hegde et al., Alginate based polymeric systems for drug delivery, antibacterial/microbial, and wound dressing applications. Mater. Today Commun. **33**, 104813 (2022)
12. H. Nosrati et al., Delivery of antibacterial agents for wound healing applications using polysaccharide-based scaffolds. J. Drug Deliv. Sci. Technol. **84**, 104516 (2023)
13. S.M. Marques, L. Kumar, Improving the sustainability of biobased products using nanotechnology, in *Sustainable nanotechnology: strategies, products, and applications*. (Wiley, Hoboken, 2022), pp.51–70
14. R.K. Manivannan et al., A comprehensive review on natural macromolecular biopolymers for biomedical applications: Recent advancements, current challenges, and future outlooks. Carbohydr. Polym. Tech. Appl. **8**, 100536 (2024)
15. A. Morales et al., Synthesis of advanced biobased green materials from renewable biopolymers. Curr. Opin. Green Sustain. Chem. **29**, 100436 (2021)
16. A.A.H. AL-dabbagh, J.A.S. Salman, H.A. Ajah, Characterization of purified dextran from Lactobacillus fermentum
17. D.E. EL-Ghwas, Bacterial Cellulose, Fermentative Production and its Pharmaceutical Application (2022)
18. A. Bharadwaj, An overview on biomaterials and its applications in medical science. in IOP conference series: materials science and engineering. (IOP Publishing, 2021)
19. H. Seddiqi et al., Cellulose and its derivatives: towards biomedical applications. Cellulose **28**(4), 1893–1931 (2021)

20. B. Zhao et al., Antibacterial activity of bifunctional bacterial cellulose composite grafted with glucose oxidase and l-arginine. Cellulose **30**(14), 8973–8984 (2023)
21. X. Yu et al., Double network microcrystalline cellulose hydrogels with high mechanical strength and biocompatibility for cartilage tissue engineering scaffold. Int. J. Biol. Macromol. **238**, 124113 (2023)
22. N.H. Syed, H. Rajaratinam, A.A. Nurul, Chitosan from marine biowaste: current and future applications in tissue engineering, in *Sustainable material for biomedical engineering application*. (Springer, New York, 2023), pp.87–106
23. V. Kumar et al., Synthesis and characterization of chitosan nanofibers for wound healing and drug delivery application. J. Drug Deliv. Sci. Tech. **87**, 104858 (2023)
24. S. Baruah, A brief overview on potential biomedical and pharmaceutical application of naturally synthesized chitosan
25. D. Pacheco et al., Brown seaweed polysaccharides: a roadmap as biomolecules, in Seaweed biotechnology. (Apple Academic Press, 2022), pp. 97–152
26. D.R. Sahoo, T. Biswal, Alginate and its application to tissue engineering. SN Appl. Sci. **3**(1), 30 (2021)
27. M. Moscovici, C. Balas, Bacterial polysaccharides versatile medical uses, in *Polysaccharides of microbial origin: biomedical applications*. (Springer, New York, 2022), pp.859–891
28. Y. Wang et al., Production and characterization of insoluble α-1, 3-linked glucan and soluble α-1, 6-linked dextran from Leuconostoc pseudomesenteroides G29. Chin. J. Chem. Eng. **39**, 211–218 (2021)
29. R. Ciriminna, A. Scurria, M. Pagliaro, Microbial production of hyaluronic acid: the case of an emergent technology in the bioeconomy. Biofuels Bioprod. Biorefin. **15**(6), 1604–1610 (2021)
30. P. Shukla et al., Tapping on the potential of hyaluronic acid: from production to application. Appl. Biochem. Biotechnol. **195**(11), 7132–7157 (2023)
31. K.N.B. Azimi, Evaluation of the function of connective tissue fibers in the human body. Arch. Int. J. Multidiscip. Trends **2**, 15–19 (2020)
32. F. Musayeva, S. Özcan, M.S. Kaynak, A review on collagen as a food supplement. J. Pharm. Tech. **3**(1), 7–29 (2022)
33. S. Sharma et al., Collagen-based formulations for wound healing: a literature review. Life Sci. **290**, 120096 (2022)
34. M. Dille, I. Haug, K. Draget, Gelatin and collagen, in *Handbook of hydrocolloids*. (Elsevier, Amsterdam, 2021), pp.1073–1097
35. H. Singh et al., Dual cross-linked gellan gum/gelatin-based multifunctional nanocomposite hydrogel scaffold for full-thickness wound healing. Int. J. Biol. Macromol. **251**, 126349 (2023)
36. Y. Wang et al., A janus gelatin sponge with a procoagulant nanoparticle-embedded surface for coagulopathic hemostasis. ACS Appl. Mater. Interfaces **16**(1), 353–363 (2023)
37. K.J. Kearney, R.A. Ariëns, F.L. Macrae, The role of fibrin (ogen) in wound healing and infection control, in *Seminars in Thrombosis and Hemostasis*. (Thieme Medical Publishers, Inc, New York, 2022)
38. C.P. Jara et al., Novel fibrin-fibronectin matrix accelerates mice skin wound healing. Bioact. Mater. **5**(4), 949–962 (2020)
39. J.M. Davidson, Elastin: structure and biology, in *Connective tissue disease*. (CRC Press, Boca Raton, 2021), pp.29–54
40. M.M. Kucherenko et al., Elastin stabilization prevents impaired biomechanics in human pulmonary arteries and pulmonary hypertension in rats with left heart disease. Nat. Commun. **14**(1), 4416 (2023)
41. L. Baumann et al., Clinical relevance of elastin in the structure and function of skin, in *Aesthetic surgery journal open forum*. (Oxford University Press US, Oxford, 2021)
42. K. Wang et al., Review on fabrication and application of regenerated Bombyx mori silk fibroin materials. AUTEX Res. J. **23**(2), 164–183 (2023)
43. M. Kostag, K. Jedvert, O.A. El Seoud, Engineering of sustainable biomaterial composites from cellulose and silk fibroin: fundamentals and applications. Int. J. Biol. Macromol. **167**, 687–718 (2021)
44. R. Ziadlou et al., Optimization of hyaluronic acid-tyramine/silk-fibroin composite hydrogels for cartilage tissue engineering and delivery of anti-inflammatory and anabolic drugs. Mater. Sci. Eng. C **120**, 111701 (2021)
45. M. Li et al., Novel insights into whey protein differences between donkey and bovine milk. Food Chem. **365**, 130397 (2021)
46. R. Mehra et al., Whey proteins processing and emergent derivatives: An insight perspective from constituents, bioactivities, functionalities to therapeutic applications. J. Funct. Foods **87**, 104760 (2021)
47. C. Zhao et al., Untargeted metabolomic reveals the changes in muscle metabolites of mice during exercise recovery and the mechanisms of whey protein and whey protein hydrolysate in promoting muscle repair. Food Res. Int. **184**, 114261 (2024)
48. S. Tahmouzi et al., Application of guar (*Cyamopsis tetragonoloba L.*) gum in food technologies: a review of properties and mechanisms of action. Food Sci. Nutr. **11**(9), 4869–4897 (2023)
49. N. Wang et al., Effects of guar gum on blood lipid levels: a systematic review and meta-analysis on randomized clinical trials. J. Funct. Foods **85**, 104605 (2021)
50. M.J. Dev et al., Advances in fermentative production, purification, characterization and applications of gellan gum. Biores. Technol. **359**, 127498 (2022)
51. F.S. Palumbo et al., Gellan gum-based delivery systems of therapeutic agents and cells. Carbohyd. Polym. **229**, 115430 (2020)
52. Wafari, U. and K. Ta'awu, Biotechnological application and the importance of plant gum exudates acacia senegal and acacia seyal to the food industry. 2021.
53. J. Guan, S. Mao, Pharmaceutical Applications of Gum Arabic, in Natural Polymers for Pharmaceutical Applications. (Apple Academic Press, 2019), pp. 21–48
54. A.C.R. da Silva et al., Potential utilization of a lambda carrageenan polysaccharide, derived from a cultivated, clonal strain of the red seaweed Chondrus crispus (Irish moss) against toxic actions of venom of Bothrops jararaca and B. jararacussu snakes. J. Appl. Phycol. **32**, 4309–4320 (2020)
55. O. Olatunji, O. Olatunji, *Carrageenans.* Aquatic biopolymers: understanding their industrial significance and environmental implications (2020), pp. 121–144
56. A. Frediansyah, The antiviral activity of iota-, kappa-, and lambda-carrageenan against COVID-19: a critical review. Clin. Epidemiol. Glob. Health **12**, 100826 (2021)
57. M. Nejadmansouri et al., Production of xanthan gum using immobilized Xanthomonas campestris cells: effects of support type. Biochem. Eng. J. **157**, 107554 (2020)
58. T. Virmani et al., Xanthan gum-based drug delivery systems for respiratory diseases, in *Natural polymeric materials based drug delivery systems in lung diseases*. (Springer, New York, 2023), pp.279–295
59. C. Zhang et al., Process and applications of alginate oligosaccharides with emphasis on health beneficial perspectives. Crit. Rev. Food Sci. Nutr. **63**(3), 303–329 (2023)
60. L. Li et al., Recent advances in the production, properties and applications of alginate oligosaccharides-a mini review. World J. Microbiol. Biotechnol. **39**(8), 207 (2023)
61. M.A. Khalil et al., Exploring the therapeutic potentials of exopolysaccharides derived from lactic acid bacteria and bifidobacteria: antioxidant, antitumor, and periodontal regeneration. Front. Microbiol. **13**, 803688 (2022)

62. F. Salimi, P. Farrokh, Recent advances in the biological activities of microbial exopolysaccharides. World J. Microbiol. Biotechnol. **39**(8), 213 (2023)
63. L.K. Hakim et al., Biocompatible and biomaterials application in drug delivery system in oral cavity. Evid. Based Complementary Altern. Med. **2021**(1), 9011226 (2021)
64. H. Li et al., Recent progress and clinical applications of advanced biomaterials in cosmetic surgery. Regen. Biomater. **10**, rbad005 (2023)
65. Y. Li et al., *Synthesis of novel hydrogels with unique mechanical properties* (Frontiers Media SA, Lausanne, 2020), p.595392
66. X. Lin et al., Progress in the mechanical enhancement of hydrogels: Fabrication strategies and underlying mechanisms. J. Polym. Sci. **60**(17), 2525–2542 (2022)
67. H. Mndlovu et al., A review of bio material degradation assessment approaches employed in the biomedical field. NPJ Mater. Degrad. **8**(1), 66 (2024)
68. D. Umuhoza et al., Strategies for tuning the biodegradation of silk fibroin-based materials for tissue engineering applications. ACS Biomater. Sci. Eng. **6**(3), 1290–1310 (2020)
69. K. Joyce et al., Bioactive potential of natural biomaterials: Identification, retention and assessment of biological properties. Signal Transduct. Target. Ther. **6**(1), 122 (2021)
70. N. Goonoo, Tunable biomaterials for myocardial tissue regeneration: promising new strategies for advanced biointerface control and improved therapeutic outcomes. Biomater. Sci. **10**(7), 1626–1646 (2022)
71. I. Pepelanova, Tunable hydrogels: introduction to the world of smart materials for biomedical applications, in *Tunable Hydrogels*. (Springer, New York, 2021), pp.1–35
72. M.J. Austin, A.M. Rosales, Tunable biomaterials from synthetic, sequence-controlled polymers. Biomater. Sci. **7**(2), 490–505 (2019)
73. M. Chelu, A.M. Musuc, Biomaterials-based hydrogels for therapeutic applications (2024)
74. R. Hama et al., Recent developments in biopolymer-based hydrogels for tissue engineering applications. Biomolecules **13**(2), 280 (2023)
75. N.H. Thang, T.B. Chien, D.X. Cuong, Polymer-based hydrogels applied in drug delivery: an overview. Gels **9**(7), 523 (2023)
76. M. Chelu, A.M. Musuc, Advanced biomedical applications of multifunctional natural and synthetic biomaterials. Processes **11**(9), 2696 (2023)
77. M. Mahdian et al., Dual stimuli-responsive gelatin-based hydrogel for pH and temperature-sensitive delivery of curcumin anticancer drug. J. Drug Deliv. Sci. Tech. **84**, 104537 (2023)
78. R. Salehi et al., In situ forming thermosensitive vaginal hydrogels containing curcumin-loaded polymeric nanoparticles with their sustained release: rheological measurements and cytotoxicity effect on cervix cancer cell. Iran. Polym. J. **31**(12), 1495–1510 (2022)
79. Z. Deng, Z. Yang, J. Peng, Role of bioactive peptides derived from food proteins in programmed cell death to treat inflammatory diseases and cancer. Crit. Rev. Food Sci. Nutr. **63**(19), 3664–3682 (2023)
80. J. Xu et al., Advances in 3D peptide hydrogel models in cancer research. NPJ Sci. Food **5**(1), 14 (2021)
81. B. Liu, K. Chen, Advances in hydrogel-based drug delivery systems. Gels **10**(4), 262 (2024)
82. H. Bai et al., Regulation of inflammatory microenvironment using a self-healing hydrogel loaded with BM-MSCs for advanced wound healing in rat diabetic foot ulcers. J. Tiss. Eng. **11**, 2041731420947242 (2020)
83. K. Chen et al., Injectable melatonin-loaded carboxymethyl chitosan (CMCS)-based hydrogel accelerates wound healing by reducing inflammation and promoting angiogenesis and collagen deposition. J. Mater. Sci. Technol. **63**, 236–245 (2021)
84. K. Wang et al., Recent advances in chitosan-based metal nanocomposites for wound healing applications. Adv. Mater. Sci. Eng. **2020**(1), 3827912 (2020)
85. V.O. Fasiku et al., Chitosan-based hydrogel for the dual delivery of antimicrobial agents against bacterial methicillin-resistant Staphylococcus aureus biofilm-infected wounds. ACS Omega **6**(34), 21994–22010 (2021)
86. S.-M. Tatarusanu et al., New smart bioactive and biomimetic chitosan-based hydrogels for wounds care management. Pharmaceutics **15**(3), 975 (2023)
87. Y. Zhao et al., Recent advances of natural-polymer-based hydrogels for wound antibacterial therapeutics. Polymers **15**(15), 3305 (2023)
88. S. Wang et al., Hydrogels for treatment of different degrees of osteoarthritis. Front. Bioeng. Biotechnol. **10**, 858656 (2022)
89. Y. Yang et al., Ultra-durable cell-free bioactive hydrogel with fast shape memory and on-demand drug release for cartilage regeneration. Nat. Commun. **14**(1), 7771 (2023)
90. S. Bordbar et al., Cartilage tissue engineering using decellularized biomatrix hydrogel containing TGF-β-loaded alginate microspheres in mechanically loaded bioreactor. Sci. Rep. **14**(1), 11991 (2024)
91. X. Li et al., Hydrogel systems for targeted cancer therapy. Front. Bioeng. Biotechnol. **11**, 1140436 (2023)
92. Q.-Q. Wang et al., Promising clinical applications of hydrogels associated with precise cancer treatment: a review. Technol. Cancer Res. Treat. **22**, 15330338221150322 (2023)
93. R. Solanki, D. Bhatia, Stimulus-responsive hydrogels for targeted cancer therapy. Gels **10**(7), 440 (2024)
94. Y. Peng et al., Engineered bio-based hydrogels for cancer immunotherapy. Adv. Mater. **36**, 2313188 (2024)
95. Z.S. Nishat et al., Hydrogel nanoarchitectonics: an evolving paradigm for ultrasensitive biosensing. Small **18**(26), 2107571 (2022)
96. M. Aranda Palomer et al., Continuous remote monitoring of prostate cancer metabolites through an implanted biosensor. 28th and 29th July, 2022
97. G.A. Politrón-Zepeda, G. Fletes-Vargas, R. Rodríguez-Rodríguez, Injectable hydrogels for nervous tissue repair—a brief review. Gels **10**(3), 190 (2024)
98. S. Han et al., Recent progresses in neural tissue engineering using topographic scaffolds. Am. J. Stem Cells **13**(1), 1 (2024)
99. T. Chen et al., Loading neural stem cells on hydrogel scaffold improves cell retention rate and promotes functional recovery in traumatic brain injury. Mater. Today Bio **19**, 100606 (2023)
100. X. Li et al., Biological characteristics of tissue engineered-nerve grafts enhancing peripheral nerve regeneration. Stem Cell Res. Ther. **15**(1), 215 (2024)
101. B. Sheokand et al., Natural polymers used in the dressing materials for wound healing: past, present and future. J. Polym. Sci. **61**(14), 1389–1414 (2023)
102. H. Zhang et al., Developing natural polymers for skin wound healing. Bioact. Mater. **33**, 355–376 (2024)
103. Arunim et al., Natural biopolymer-based hydrogels: an advanced material for diabetic wound healing. Diabetol. Int. (2024). https://doi.org/10.1007/s13340-024-00737-2
104. K. Valachová, M.A. El Meligy, L. Šoltés, Hyaluronic acid and chitosan-based electrospun wound dressings: problems and solutions. Int. J. Biol. Macromol. **206**, 74–91 (2022)
105. N. Khandan-Nasab et al., Design and characterization of adipose-derived mesenchymal stem cell loaded alginate/pullulan/hyaluronic acid hydrogel scaffold for wound healing applications. Int. J. Biol. Macromol. **241**, 124556 (2023)
106. R.M. Hassan, Methods of polysaccharides crosslinking: future-promising crosslinking techniques of alginate hydrogels for 3D

printing in biomedical applications. 3D printable Gel-inks for Tissue Engineering: Chemistry, Processing, and Applications (2021), pp. 355–382

107. S.K. Moinuddin et al., A review on micro beads: formulation, technological aspects, and extraction. GSC Biol. Pharm. Sci. **26**(2), 059–066 (2024)
108. S. Das, Pectin based multi-particulate carriers for colon-specific delivery of therapeutic agents. Int. J. Pharm. **605**, 120814 (2021)
109. K.M. Sahu, S. Patra, S.K. Swain, Host-guest drug delivery by β-cyclodextrin assisted polysaccharide vehicles: a review. Int. J. Biol. Macromol. **240**, 124338 (2023)
110. V.K. Nandagiri et al., Biomaterials of natural origin in regenerative medicine, in *Polymeric biomaterials*. (CRC Press, Boca Raton, 2020), pp.281–326
111. N. Kohli et al., Pro-angiogenic and osteogenic composite scaffolds of fibrin, alginate and calcium phosphate for bone tissue engineering. J. Tiss. Eng. **12**, 20417314211005610 (2021)
112. L. Edgar et al., Regenerative medicine, organ bioengineering and transplantation. J. Br. Surg. **107**(7), 793–800 (2020)
113. G.H. Ángeles, K. Nešporová, Hyaluronan and its derivatives for ophthalmology: recent advances and future perspectives. Carbohyd. Polym. **259**, 117697 (2021)
114. M. Mofidfar et al., Drug delivery to the anterior segment of the eye: a review of current and future treatment strategies. Int. J. Pharm. **607**, 120924 (2021)
115. A.K. Sri et al., Nano-hydroxyapatite/collagen composite as scaffold material for bone regeneration. Biomed. Mater. **18**(3), 032002 (2023)
116. S.-K. Kim et al., Biomimetic chitosan with biocomposite nanomaterials for bone tissue repair and regeneration. Beilstein J. Nanotechnol. **13**(1), 1051–1067 (2022)
117. Y. Tian et al., Chitosan-based biomaterial scaffolds for the repair of infected bone defects. Front. Bioeng. Biotechnol. **10**, 899760 (2022)
118. L. Guo et al., The role of natural polymers in bone tissue engineering. J. Control. Release **338**, 571–582 (2021)
119. P. Chandika et al., Recent advances in biological macromolecule based tissue-engineered composite scaffolds for cardiac tissue regeneration applications. Int. J. Biol. Macromol. **164**, 2329–2357 (2020)
120. P. Pushp, M.K. Gupta, Cardiac tissue engineering: A role for natural biomaterials. Bioactive natural products for pharmaceutical applications (2021), pp. 617–641
121. S. Saghebasl et al., Biodegradable functional macromolecules as promising scaffolds for cardiac tissue engineering. Polym. Adv. Technol. **33**(7), 2044–2068 (2022)
122. M. Ghovvati et al., Recent advances in designing electroconductive biomaterials for cardiac tissue engineering. Adv. Healthcare Mater. **11**(13), 2200055 (2022)
123. B. Jadach, Z. Mielcarek, T. Osmałek, Use of collagen in cosmetic products. Curr. Issues Mol. Biol. **46**(3), 2043–2070 (2024)
124. J. Li et al., The development of hyaluronic acids used for skin tissue regeneration. Curr. Drug Deliv. **18**(7), 836–846 (2021)
125. M. El Soury et al., Chitosan conduits enriched with fibrin-collagen hydrogel with or without adipose-derived mesenchymal stem cells for the repair of 15-mm-long sciatic nerve defect. Neural Regen. Res. **18**(6), 1378–1385 (2023)
126. X.-Y. Liu et al., Integrated printed BDNF/collagen/chitosan scaffolds with low temperature extrusion 3D printer accelerated neural regeneration after spinal cord injury. Regen. Biomater. **8**(6), rbab047 (2021)
127. Z. Yang et al., Targeted delivery of hydrogels in human gastrointestinal tract: a review. Food Hydrocoll. **134**, 108013 (2023)
128. H. Azehaf et al., Microbiota-sensitive drug delivery systems based on natural polysaccharides for colon targeting. Drug Discov. Today **28**(7), 103606 (2023)
129. S. Li et al., Application of chitosan/alginate nanoparticle in oral drug delivery systems: prospects and challenges. Drug Deliv. **29**(1), 1142–1149 (2022)
130. M.A.J. Shaikh et al., Sodium alginate based drug delivery in management of breast cancer. Carbohyd. Polym. **292**, 119689 (2022)
131. A. Erfani, A.E. Diaz, P.S. Doyle, Hydrogel-enabled, local administration and combinatorial delivery of immunotherapies for cancer treatment. Mater. Today **65**, 227–243 (2023)
132. M. Saeedi et al., Customizing nano-chitosan for sustainable drug delivery. J. Control. Release **350**, 175–192 (2022)
133. R. Kundu et al., Cellulose hydrogels: green and sustainable soft biomaterials. Curr. Res. Green Sustain. Chem. **5**, 100252 (2022)
134. M. Gericke et al., The European polysaccharide network of excellence (EPNOE) research roadmap 2040: Advanced strategies for exploiting the vast potential of polysaccharides as renewable bioresources. Carbohyd. Polym. **326**, 121633 (2024)
135. T. Biswal, S.K. BadJena, D. Pradhan, Sustainable biomaterials and their applications: a short review. Mater. Today Proc. **30**, 274–282 (2020)
136. S.A. Edrisi et al., Carbon sequestration and harnessing biomaterials from terrestrial plantations for mitigating climate change impacts, in *Biomass, biofuels, biochemicals*. (Elsevier, Amsterdam, 2022), pp.299–313
137. K. Ghosal, S. Ghosh, Biodegradable polymers from lignocellulosic biomass and synthetic plastic waste: an emerging alternative for biomedical applications. Mater. Sci. Eng. R. Rep. **156**, 100761 (2023)
138. B. Koul, M. Yakoob, M.P. Shah, Agricultural waste management strategies for environmental sustainability. Environ. Res. **206**, 112285 (2022)
139. M.M. Ansari et al., Nanocellulose derived from agricultural biowaste by-products–sustainable synthesis, biocompatibility, biomedical applications, and future perspectives: a review. Carbohydr. Polym. Technol. Appl. **8**, 100529 (2024)
140. M.K. Sah et al., Advancement in "Garbage In Biomaterials Out (GIBO)" concept to develop biomaterials from agricultural waste for tissue engineering and biomedical applications. J. Environ. Health Sci. Eng. **20**(2), 1015–1033 (2022)
141. J. Cao, E. Su, Hydrophobic deep eutectic solvents: the new generation of green solvents for diversified and colorful applications in green chemistry. J. Clean. Prod. **314**, 127965 (2021)
142. A. Kumar et al., Polysaccharides, proteins, and synthetic polymers based multimodal hydrogels for various biomedical applications: a review. Int. J. Biol. Macromol. **247**, 125606 (2023)
143. A.B. Ribeiro et al., Bio-based superabsorbent hydrogels for nutrient release. J. Environ. Chem. Eng. **12**(2), 112031 (2024)
144. T. Baydin et al., Long-term storage stability of type A and type B gelatin gels: the effect of Bloom strength and co-solutes. Food Hydrocoll. **127**, 107535 (2022)
145. J.J. Andrew, H. Dhakal, Sustainable biobased composites for advanced applications: recent trends and future opportunities–a critical review. Composites Part C **7**, 100220 (2022)
146. C. Ma et al., Dynamic chemical cross-linking and mechanical training of bio-based polyamides fabricate strong and recyclable elastomers. ACS Sustain. Chem. Eng. **10**(20), 6775–6783 (2022)
147. Y. Gao, K. Peng, S. Mitragotri, Covalently crosslinked hydrogels via step-growth reactions: crosslinking chemistries, polymers, and clinical impact. Adv. Mater. **33**(25), 2006362 (2021)
148. L. Tie, W.-X. Zhang, Z. Deng, Ferrous ion-induced cellulose nanocrystals/alginate bio-based hydrogel for high efficiency tetracycline removal. Sep. Purif. Technol. **328**, 125024 (2024)
149. Y. Ma et al., Calcium spraying for fabricating collagen-alginate composite films with excellent wet mechanical properties. Food Hydrocoll. **124**, 107340 (2022)

150. K.Y. Ching et al., Genipin crosslinked chitosan/PEO nanofibrous scaffolds exhibiting an improved microenvironment for the regeneration of articular cartilage. J. Biomater. Appl. **36**(3), 503–516 (2021)
151. L. Qi et al., Progress in hydrogels for skin wound repair. Macromol. Biosci. **22**(7), 2100475 (2022)
152. A.A. Moud, Are mechanically adjusted cellulose nanocrystal (CNC)-based bio-targeted hydrogels satisfying the requirements of biologically based applications? (2022)
153. M.A. Naniz et al., 4D printing: a cutting-edge platform for biomedical applications. Biomed. Mater. **17**(6), 062001 (2022)
154. S. Wu et al., Recent advances on sustainable bio-based materials for water treatment: fabrication, modification and application. J. Environ. Chem. Eng. **10**(6), 108921 (2022)
155. S.S. Siwal et al., Additive manufacturing of bio-based hydrogel composites: recent advances. J. Polym. Environ. **30**(11), 4501–4516 (2022)
156. R. Song et al., Enhanced strength for double network hydrogel adhesive through cohesion-adhesion balance. Adv. Funct. Mater. **34**, 2313322 (2024)
157. J. Li et al., Weak acid-initiated slow release of Dexamethasone from hydrogel to treat orbital inflammation. Theranostics **13**(12), 4030 (2023)
158. B. Canciani et al., In vitro and in vivo biocompatibility assessment of a thermosensitive injectable chitosan-based hydrogel for musculoskeletal tissue engineering. Int. J. Mol. Sci. **24**(13), 10446 (2023)
159. B. Farasati Far et al., Multi-responsive chitosan-based hydrogels for controlled release of vincristine. Commun. Chem. **6**(1), 28 (2023)
160. S. Mallakpour, E. Nikkhoo, C.M. Hussain, Application of MOF materials as drug delivery systems for cancer therapy and dermal treatment. Coord. Chem. Rev. **451**, 214262 (2022)
161. Q. Huang et al., Preparation of dendritic mesoporous silica/phenylboronic acid-modified hydroxypropyl chitosan and its glucose-responsive performance. Polym. Sci., Ser. A **63**, 757–768 (2021)
162. V. Singh et al., Silk fibroin hydrogel: a novel biopolymer for sustained release of vancomycin drug for diabetic wound healing. J. Mol. Struct. **1286**, 135548 (2023)
163. L. Chen et al., Biphasic release of betamethasone from an injectable HA hydrogel implant for alleviating lumbar disc herniation induced sciatica. Acta Biomater. **176**, 173–189 (2024)
164. B. Farasati Far et al., A review on biomedical application of polysaccharide-based hydrogels with a focus on drug delivery systems. Polymers **14**(24), 5432 (2022)
165. T.A. Adjuik, S.E. Nokes, M.D. Montross, Biodegradability of bio-based and synthetic hydrogels as sustainable soil amendments: a review. J. Appl. Polym. Sci. **140**(12), e53655 (2023)
166. S. Saberianpour et al., Harnessing the interactions of wound exudate cells with dressings biomaterials for the control and prognosis of healing pathways. Pharmaceuticals **17**(9), 1111 (2024)
167. P. Ghandforoushan et al., Injectable and adhesive hydrogels for dealing with wounds. Expert Opin. Biol. Ther. **22**(4), 519–533 (2022)
168. H. Chenani et al., Challenges and advances of hydrogel-based wearable electrochemical biosensors for real-time monitoring of biofluids: from lab to market. A review. Anal. Chem. **96**(20), 8160–8183 (2024)
169. P. Kaur et al., Waste to high-value products: the performance and potential of carboxymethylcellulose hydrogels via the circular economy. Cellulose **30**(5), 2713–2730 (2023)
170. M. Zhang et al., Preparation of esterified biomass waste hydrogels and their removal of Pb2+, Cu2+ and Cd2+ from aqueous solution. Environ. Sci. Pollut. Res. **30**(19), 56580–56593 (2023)
171. K. Kumar et al., Biomass waste-derived carbon materials for sustainable remediation of polluted environments: a comprehensive review. Chemosphere **345**, 140419 (2023)
172. I.N. Besiri, T.B. Goudoulas, N. Germann, Custom-made rheological setup for in situ real-time fast alginate-Ca2+ gelation. Carbohyd. Polym. **246**, 116615 (2020)
173. T. Jeoh et al., How alginate properties influence in situ internal gelation in crosslinked alginate microcapsules (CLAMs) formed by spray drying. PLoS ONE **16**(2), e0247171 (2021)
174. M. Azmana et al., A review on chitosan and chitosan-based bionanocomposites: promising material for combatting global issues and its applications. Int. J. Biol. Macromol. **185**, 832–848 (2021)
175. P.S. Bakshi et al., Chitosan as an environment friendly biomaterial–a review on recent modifications and applications. Int. J. Biol. Macromol. **150**, 1072–1083 (2020)
176. A. Rossatto et al., Hyaluronic acid production and purification techniques: a review. Prep. Biochem. Biotechnol. **53**(1), 1–11 (2023)
177. K.C. Castro, M.G.N. Campos, L.H.I. Mei, Hyaluronic acid electrospinning: Challenges, applications in wound dressings and new perspectives. Int. J. Biol. Macromol. **173**, 251–266 (2021)
178. E. Gachon, P. Mesquida, Mechanical properties of collagen fibrils determined by buckling analysis. Acta Biomater. **149**, 60–68 (2022)
179. J. Duasa et al., An alternative source of collagen for Muslim consumers: halal and environmental concerns. J. Islam. Mark. **13**(11), 2232–2253 (2022)
180. Y. Liu et al., Tunable physical and mechanical properties of gelatin hydrogel after transglutaminase crosslinking on two gelatin types. Int. J. Biol. Macromol. **162**, 405–413 (2020)
181. L. Mao et al., Transglutaminase modified type a gelatin gel: the influence of intra-molecular and inter-molecular cross-linking on structure-properties. Food Chem. **395**, 133578 (2022)
182. I.V. Roberts et al., Fibrin matrices as (injectable) biomaterials: formation, clinical use, and molecular engineering. Macromol. Biosci. **20**(1), 1900283 (2020)
183. J. Du et al., The effect of fibrin on rheological behavior, gelling properties and microstructure of myofibrillar proteins. Lwt **153**, 112457 (2022)
184. F. Li, L. Foucat, E. Bonnin, Effect of solid loading on the behaviour of pectin-degrading enzymes. Biotechnol. Biofuels **14**(1), 107 (2021)
185. S. Basak, U.S. Annapure, Trends in “green” and novel methods of pectin modification-a review. Carbohyd. Polym. **278**, 118967 (2022)
186. Q. Hu, Y. Lu, Y. Luo, Recent advances in dextran-based drug delivery systems: from fabrication strategies to applications. Carbohyd. Polym. **264**, 117999 (2021)
187. W. Hyon, S.-H. Hyon, K. Matsumura, Evaluation of the optimal dose for maximizing the anti-adhesion performance of a self-degradable dextran-based material. Carbohydr. Polym. Technol. Appl. **4**, 100255 (2022)
188. M. Du et al., Recent advances in biomedical engineering of nano-hydroxyapatite including dentistry, cancer treatment and bone repair. Compos. B Eng. **215**, 108790 (2021)
189. J.A. Lett et al., Recent advances in natural polymer-based hydroxyapatite scaffolds: properties and applications. Eur. Polymer J. **148**, 110360 (2021)