

Review

Status and future scope of plant-based green hydrogels in biomedical engineering

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ABSTRACT

Hydrogels are the most iconic class of soft materials, and since their first report in the literature, they have attracted the attention of uncountable researchers. Over the past two decades, hydrogels have become smart and sophisticated materials with numerous applications. This class of soft materials have been playing a significant role in biomedicine due to their tunable and often programmable properties. Hydrogels from renewable polymers have been popularized in biomedical applications as they are often biocompatible, easily accessible, and inexpensive. The challenge however has been to find an ideal plant-based hydrogel for biomedicine that can mimic critical properties of human tissues in terms of structure, function, and performance. In addition, natural polymers can readily be functionalized to engineer their chemical and physical uproperties pertinent to drug delivery and tissue engineering. Here, the most recent advances in the synthesis, fabrication, and applications of plant-based hydrogels in biomedical engineering are reviewed. We cover essential and updated information about plants as green sources of biopolymers for hydrogel synthesis, general aspects of hydrogels and plant-based hydrogels, and

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thorough discussion regarding the use of such hydrogels in the biomedical engineering area. Furthermore, this review details the present status of the field and answers several important questions about the potential of plant-based hydrogels in advanced biomedical applications including therapeutics, tissue engineering, wound dressing, and diagnostics. , *etc.*

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1. Introduction

Disease, injury, and trauma are conditions that affect the normal function of tissues, which may consequently lead to tissue and organ failure. It is necessary to treat the damaged sites and facilitate the process of tissue regeneration. Conventional strategies for tissue repair, such as autografts and allografts are accompanied with several limitations including multiple surgeries, high infection risk, painful procedures, and lack of donors. In this regard, there is an increasing demand for alternative strategies to effectively regenerate the damaged tissues [1]. Tissue engineering using biomimetic 3D scaffolds seeded by cells is a promising strategy to promote tissue repair [2–13]. Hydrogels have gained attraction as tissue engineering scaffolds due to their structure similarity to the extracellular matrix (ECM). Hydrogels provide 3D microenvironments for cell function, proliferation, and survival [14,15]. For

inducing optimal tissue regeneration, it is necessary to use a proper scaffold with the ability to promote cell recruitment and control the release rate of bioactive molecules [16,17]. Delivery vehicles with a controlled release rate help preserve the bioactivity of biomolecule while sustaining their local concentrations [18].

To date, various techniques have been used for fabricating polymeric scaffolds with different structures and morphologies, including electrospinning, freeze-drying, gas-foaming, solvent casting particulate-leaching, and stereolithography [19–24]. The physico-chemical properties of polymers along with their surface characteristics define the choice of method for scaffold preparation [25]. Each method has its own benefits and drawbacks. For instance, solvent casting particulate-leaching is a simple and cost-effective method that is limited due to applying toxic solvents, poor interconnectivity of scaffold, and the formation of skin-like layers when evaporating the solvent. In contrast, freeze-drying is more suitable

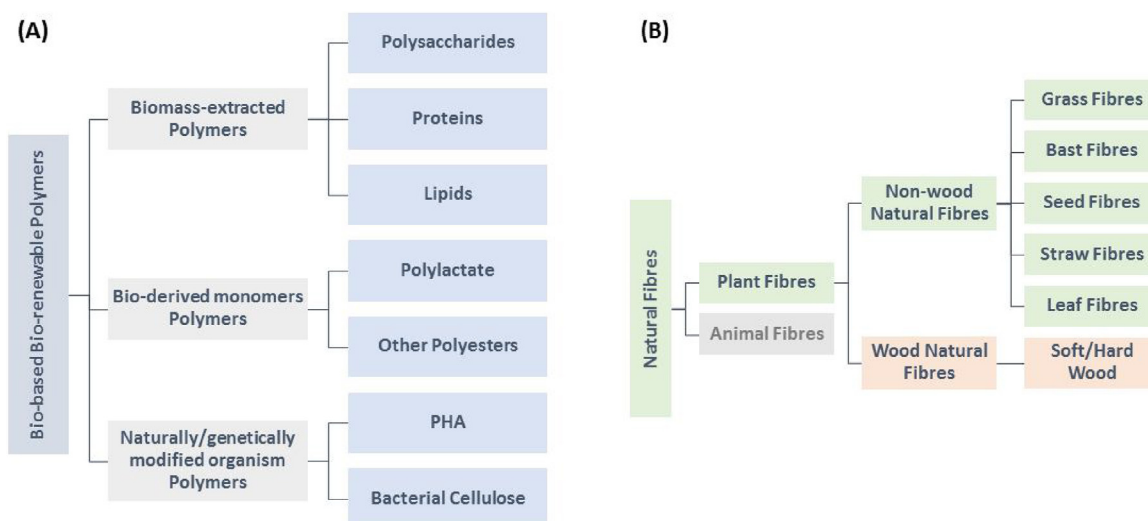


Fig. 1. (A) Classification of bio-based polymers (reproduced with permission from [427]); (B) classification of natural fibres (reproduced with permission from [427]).

because organic solvents are not used for scaffold fabrication and the size of interconnected pores and the porosity of scaffolds can be controlled by optimizing different parameters. Scaffolds with high interconnected pores can also be produced by gas-foaming; however, the formation of skin layers on the outer layer of scaffolds reduces mechanical strength, limiting the application of this method for fabricating tissue constructs [8].

Different natural (Fig. 1) and synthetic polymers have been used for scaffold fabrication. Natural polymers are excellent candidates for tissue engineering applications due to their biocompatibility, while synthetic polymers can exhibit outstanding mechanical properties [26–28]. Currently, numerous investigating have focused on the structure–function relationship of plant-based-biopolymers. Plant-polysaccharide based polymers (e.g., cellulose, hemicellulose, lignin, starch, and pectin) and plant protein-based hydrogels (e.g., soy and zein) are promising materials for tissue engineering and drug delivery purposes. These natural polymers are biocompatible [29,30], which have some similarity to mammalian ECM components, such as glycosaminoglycan molecules. Furthermore, polymers with plant sources such as flavonoid or biflavonoid polyphenolic agents have gained attentions for biomedical applications as antimicrobial agents and antioxidants [31–33]. As an example, *Stevia rebaudiana* leaf-extracts are sources of bioactive compounds such as carotenoids, polyphenols, ascorbic acid, and chlorophylls, which are antioxidants and have antimicrobial characteristics [34,35]. Recently, Bajpai et al. reported that a (+)-syringaresinol (SGRS), a lignan isolated from *Rubia philippinensis* had anti-inflammatory properties. SGRS down-regulated the nuclear factor-kappa B (NF- κ B), which consequently activated p38 and c-Jun NH2-terminal kinase (JNK) proteins in RAW 264.7 cells [36]. There are many original articles using plant based-polymers for tissue engineering. In this paper, we provide an extensive review of recent progress in the biomedical applications of plant-based hydrogels.

2. Plants as green sources for advanced biomedical applications

Throughout the centuries, the human civilizations have mainly relied on plants for their basic needs, such as foodstuffs, fuel, and therapeutics, etc. and all everything was obtained directly or indirectly from plant-based materials (bark, leaf, wood, fibre, etc.) and storage tissues (seed, fruit, bulb, tuber, root, rhizome, etc.) [37–40]. These demands have rapidly increased over time

due to the growing world population, and urbanization, and hence increased basic needs. There exist approximately 300,000 known plant species worldwide, while only ~5000 have been studied so far towards medicinal applications until now; therefore, a huge source of plant-derived materials is available for medical applications [41–43]. Plant-based chemical compounds can be classified as primary and secondary (or specialized) metabolites (phytopharmaceuticals), depending on whether they are directly involved in the development, normal growth, or reproduction [44–46].

Bulk materials such as carbohydrates, proteins, fats, fibres, and nucleic acids are generally obtained from various plants through primary metabolism including photosynthesis, glycolysis, Krebs cycle, transamination, synthesis of amino acids, proteins, enzymes and coenzymes, duplication of genetic materials, reproduction of cells and absorption of nutrients, etc. These materials are involved in the primary metabolites, which generally occur in relatively high levels in the plant cells which then gets converted into the food-stuffs of other organisms [47–49]. Apart from being a source of food or food additive, many terrestrial vascular plants do produce a large variety of pharmaceutically significant secondary metabolites such as terpenoids (plant volatiles, monoterpenes, sesquiterpenes, diterpenes, triterpenes, cardiac glycosides, carotenoids, steroids, and saponins), phenolics (phenolic acids, polyacetylenes, polyketides, phenylpropanoids, flavonoids, coumarins, lignans, stilbenes, tannins and lignin), and nitrogen-containing compounds (alkaloids, cyanogenic glycosides, amines, non-protein amino acids, and glucosinolates), etc. [50–55].

Water soluble compounds, alkaloids, cyanogenic glucosides, glucosinolates, saponins, anthocyanins, flavonoids, cardenolides are usually stored in the vacuole of the plant cell, however, the lipophilic substances are sequestered in glandular hairs, resin ducts, laticifers, trichomes, in/on the cuticle [56–60]. Plants of commercial importance (mostly from families of apiaceae, apocyanaceae, araliaceae, araceae, asphodelaceae, asteraceae, ginkgoaceae, hypericaceae, lamiaceae, papaveraceae, piperaceae, rhamnaceae, rubiaceae, rutaceae, solanaceae, and zingiberaceae) serve as potential sources of advanced materials such as industrial oils, tannins, resins, gums, saponins, natural rubber, flavours and fragrances, waxes, cosmetics, dyes and colourants, plant protection and production products, pesticides, colchicines and phorbol esters, and so on [61–64] and therefore, they are of very high interest.

Botanical excipients are the organic substances originated from different parts of a plant, such as cell walls, trunk exudates, and

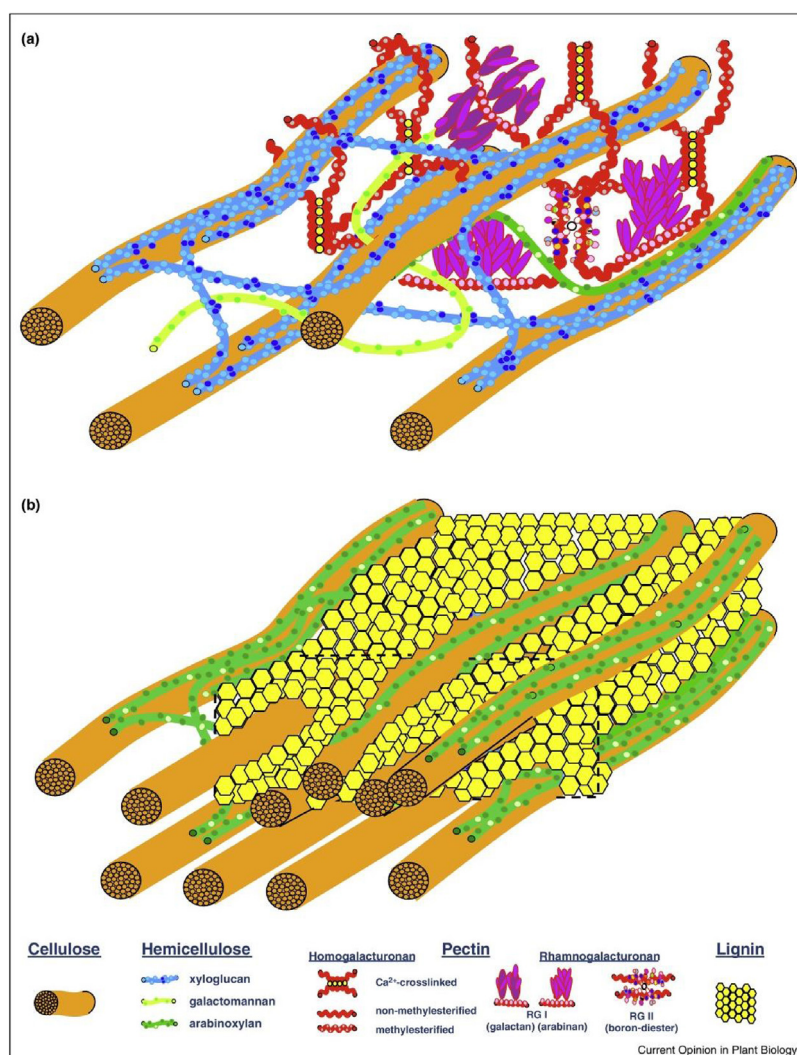


Fig. 2. (a) Pectinaceous cell walls in dicots. (b) Lignified cell walls.

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seaweeds [65]. The primary cell wall of terrestrial higher plants is mainly composed of the polysaccharides cellulose (the most plentiful renewable resource on the Earth), hemicelluloses, and pectin (in several cases), other biopolymers including lignin, cutin, and suberin are chained down to the cell walls as shown below (Fig. 2).

Recently there has been growing interest in complementary and alternative medicine and therapeutic applications of plant-based products [66]. Some of the major plant-derived therapeutic agents with no synthetic counterpart include vinblastine (anticancer, from *Catharanthus roseus*), rescinamine (tranquilizer, from *Rauvolfia serpentina*), quinine (antimalarial, from *Cinchona* spp.), pilocarpine (antiglaucoma, from *Pilocarpus jaborandi*), cocaine (topical anaesthetic, from *Erythroxylum coca*), morphine and codeine (painkiller and anticough, from *Papaver somniferum*), atropine (spasmolytic, from *Hyoscyamus niger*), taxol (antitumor, from *Taxus baccata*), plumbagin (antibacterial, antifungal, from *Plumbago indica*), gossypol (antispermatogetic, from *Gossypium* spp.), emetine (amoebiasis, from *Cephaelis ipecacuanha*), catechin (antiulcer, from *Accacia catechu*), digitoxin (cardio tonic, from *Digitalis* spp.) [67,68]. There is an increasing economical demand for industrial materials and products from renewable resources due to relatively low price, high stability, worldwide availability, non-toxicity, and their excellent potentials for biomedical applications.

3. Hydrogels: preparation, characterization, and properties

Hydrogels can be well defined as water-swollen and crosslinked hydrophilic polymeric networks. They exhibit the capacity to retain the large amounts of water within their structure without dissolving in water. They are of high interest for biomedical applications because of their high water content, tunable stiffness, etc. and their structural resemblance with living tissues, make them ideal candidates as biocompatible materials for *in vivo* applications [69,70]. Within the denomination “hydrogel”, one can find a large diversity based on different criteria, leading to various classifications which has already been summarized by Ahmed and co-workers in a comprehensive review [71]. Most commonly, the hydrogels are classified according to the type of crosslinking strategy governing the polymer chain interactions. Understanding and having control over the extent and nature of the crosslinking points is of high importance, because it mainly defines the network structure and the hydrogel properties. The crosslinking points maintain the integrity of the three-dimensional network, and are related to the mechanical strength of the hydrogel. As for as their structural identification is concerned, there are essentially three key parameters used to describe the bulk structure of a hydrogel [69–72]: (i) the polymer chain molecular weight between the two crosslinking

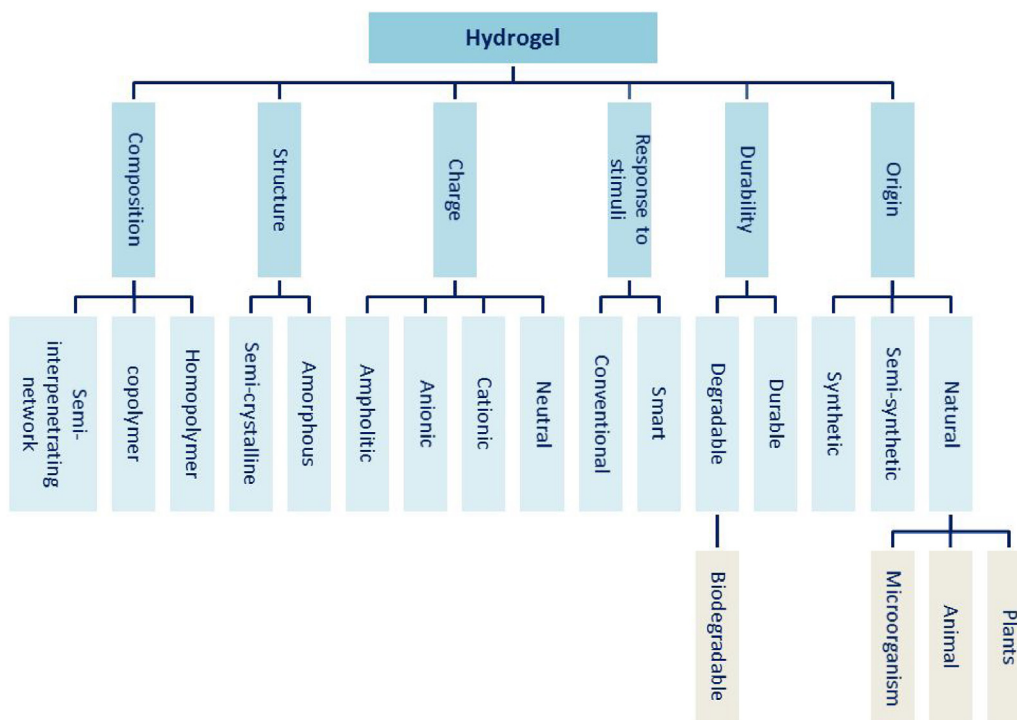


Fig. 3. Classification of hydrogels based on physical and mechanical properties.

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points (actually a measure of the crosslinking density); (ii) the volume fraction of polymer in the swollen state (is a measure of the amount of water retained by the hydrogel); and (iii) the mesh size (is a structural parameter “ ξ ” correlated to the linear length between two neighbouring crosslinks). There are several crosslinking possibilities between the polymeric chains, essentially depending on the nature of the involved polymer. They may be chosen in order to finely tune the bulk structure of the hydrogel, considering the envisaged biomedical application. For the better overview about the family of the hydrogels, the Fig. 3 illustrates the classification of hydrogels based on physical and mechanical properties which are briefly described in following subsequent sections..

3.1. Physical hydrogels

The physical which are reversible hydrogels, are defined as hydrophilic polymer networks held together by either physical entanglement of the polymer chains, or other non-covalent interactions, including self-assembly through hydrogen bonds, van der Waals interactions, and hydrophobic interactions, ionic forces, etc. There are several examples of physical gelation in biopolymers, for example, , calcium alginate gels can be prepared via the ionic interactions between negatively charged carboxylic acids and calcium ions (Ca^{2+}), and the self-assembly of various animal-derived gel-forming proteins is driven by hydrophobic interactions and hydrogen bonding [73]. The main advantages of physical crosslinking are mainly due to their ease of processability. The reversibility of the crosslinking points (through the disruption of bonds using external cues such as pH, temperature, ionic strength, and/or the addition of solutes competing for the crosslinking sites between polymer chains) allows their very simple synthesis, fo example, even thermal or solvent casting processes do the task. Additionally, the chemical modifications (often using toxic crosslinking agents) could be easily avoided, which is indeed an advantage for hydrogels being utilized in biomedical or food related applications. However, relatively weak mechanical properties of physical hydrogels

with respoet to chemical hydrogels is a major disadvantage which hinders their utilizations in certain applications where a level of mechanical stiffness is simultansouly desired.

3.2. Chemical hydrogels

Chemical or irreversible hydrogels are mainly obtained through covalent cross-linking. The covalent bonds between polymer chains are made up with the use of multifunctional molecules during the polymerization step, or *via* the reaction of the pendant groups or side chains in a post-polymerization approach. It is interesting to note here that the strategies to cross-link synthetic and bio-polymers may significantly differ. For example, in the case of biopolymers, the limitation arises from the imposed functional groups. Detailed comprehensive reports on the cross-linking strategies for biopolymers have been briefed by Reddy et al. [74] and Shen et al. [75]. In comparison to physical gels (can be dissolved or degraded easily), the chemical hydrogels are more stable and usually exhibit better mechanical properties. The high durability might also be seen as a disadvantage as easily utilization of such gels is indeed limited, since they cannot be reshaped easily. In addition, the gelation kinetics are usually slow which causes solubility issues too in early gel production. Last but not least, the chemical gelation is often accompanied by a certain levele of cytotoxicity due to residual chemicals used for cross-linking and they are difficult to be eliminated through purification.

3.3. Composite hydrogels

In many cases, both physical and chemical crosslinking impart higher mechanical stability to hydrogels at the expense of compromised degradationu, the reduced availability of functional groups and the significant changes in hydrogel rheology can significantly affect the processability. An alternative approach is to design the hybrid or composite hydrogels *via* the incorporation of nanomaterials, such as inorganic fillers or nanofibers in the matrix, or by

combining polymers using different crosslinking mechanisms (e.g., double-network hydrogels), etc. [76]. The combination of different materials provides the synergistic advantages of both components while ideally cancelling or limiting their intrinsic disadvantages which is briefly covered in a detailed reprot by Utech et al. on inorganic-polymer composite hydrogels [77], and by Zhang et al. on polymer-polymer composite hydrogels [78].

4. Plant-based green hydrogels

4.1. Plant lignocellulose materials-based hydrogels

4.1.1. Cellulose-based hydrogels

Cellulose is the most abundant biorenewable materials available on earth, which is expected to remain one of the main material resources in the future [79–81]. This biopolymer is formed by glucose molecules and can be found in plants (in their cells as a structural polymer) and in natural fibres [82]. Besides that, it can be produced by bacteria [81,82] with an identical chemical composition compared to plant-based cellulose, but different macromolecular structure and physical properties [83]. The structure of cellulose can be seen in Fig. 4. This biopolymer is formed by glucose molecules linked together by 1,4- β -glucosidic bonds. These linkages are responsible for the high crystallinity (typically in the range of 40–60% for plant cellulose), low water solubility, hydrophilicity, and biodegradability [82,84]. However, due to the lack of cellulase enzymes in humans, cellulose may be considered as non- or slow biodegradable *in vivo* [85]. Nevertheless, the biocompatibility of cellulose has been extensively reported [86–89]. Accordingly, cellulose can be used for biomedical applications; however, it may not be biodegraded in the body. The main source of cellulose is wood [81]. Considering that wood is a composite material containing cellulose and lignin, it requires various treatments to yield cellulose [81]. Similarly, one of the challenges for the widespread use of plant cellulose is its association with other

biopolymers, such as lignin and pectin [82,89]. Cellulose properties depend on the source and extraction/purification methods [84]. To leverage the properties of cellulose and yield an easily-processable material, it is chemically modified [82]. A common chemical modification of cellulose is the esterification of hydroxyl groups to improve water solubility. Typical cellulose derivatives are shown in Fig. 4 [79].

A newly emerged class of nanoscale cellulose-based particles is referred as hairy nanocelluloses [90,91], which has overcome the structural limitations of conventional nanocelluloses. While cellulose nanocrystals (CNC) and cellulose nanofibrils (CNF), two major types of nanocelluloses [92–96], are produced through strong acid hydrolysis and mechanical disintegration of fibrils, respectively, hairy nanocelluloses are yielded through controlled oxidation [97]. Strong acid-mediated hydrolysis of fibrils completely eliminates the amorphous regions by targeting $\beta(1 \rightarrow 4)$ glycosidic linkage. This process yields nanocrystals of cellulose with a crystalline structure that depends on the cellulose source; typically, cellulose I as the main constituent of native cellulose [92], which consists of I α or I β structures [98,99]. Assuming a 10 nm by 10 nm crystal packing of glucose units, complete carboxylic acid substitution may result in a maximum theoretical charge content of 0.8 mmol g⁻¹ [100]. Inaccessible inner layers of cellulose crystals prevent further functionalization of nanocrystals, therefore, leaving these nanoparticles with limited functionally and colloidal stability [101,102]. Controlled oxidation of cellulose fibrils through reaction with periodate decorates the fibrils with dialdehyde cellulose, a highly reactive intermediate with an intact structure, ready for a wide range of chemical reactions [103].

Heating dialdehyde functionalized fibrils increases the solubility of amorphous regions, which already exhibited a higher dialdehyde content than crystalline regions due to better accessibility during periodate oxidation, break the fibrils from the amorphous regions. The products of this process are: (i) cellulose nanocrystals sandwiched between protruding dialdehyde-modified amorphous

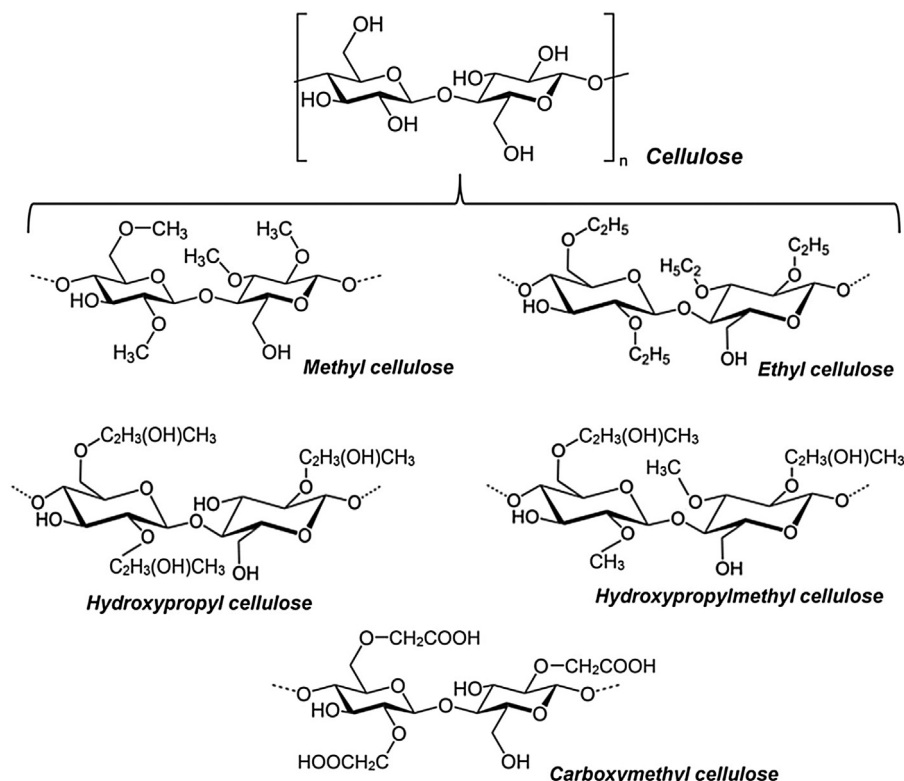


Fig. 4. Chemical structure of cellulose and common cellulose derivatives.

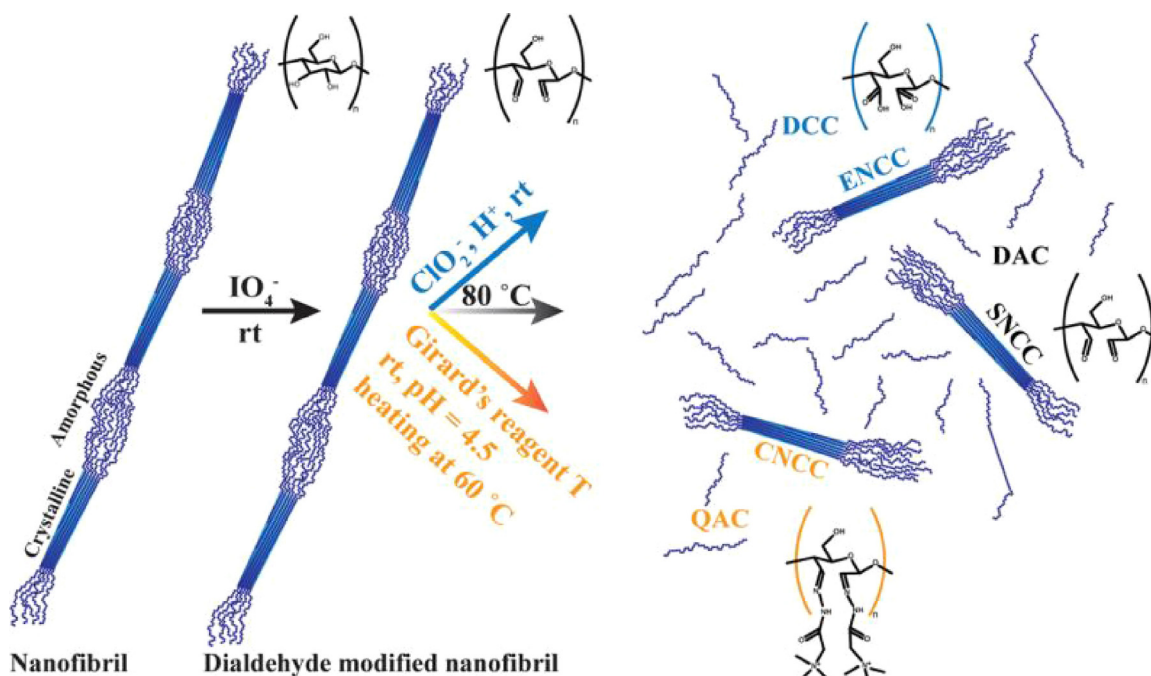


Fig. 5. Schematic of hairy nanocellulose synthesis. Cellulose nanofibrils are oxidized using periodate to yield dialdehyde modified fibrils (DAFs). (i) Heating DAFs, (ii) reacting DAFs with chlorite, or (iii) reacting DAFs with Girard's reagent T results in neutral (SNCC: sterically stabilized nanocrystalline cellulose), negatively charged (ENCC, electrosterically stabilized nanocrystalline cellulose), and positively charged (CNCC: cationic nanocrystalline cellulose) hairy cellulose nanocrystals and their counterpart functionalized biopolymers (DAC, dialdehyde modified cellulose, DCC, dicarboxylated cellulose, and QAC, quaternary amine (ammonium) modified cellulose). Reproduced with permission from [90].

cellulose chains, a neutral hairy cellulose nanocrystal known as sterically stabilized nanocrystalline cellulose (SNCC), and (ii) free dialdehyde modified cellulose chains (DAMC) [103]. Dialdehyde-modified cellulose fibrils may be further oxidized using chlorite to convert the aldehyde to carboxylic acid. This results in negatively-charged hairy cellulose nanocrystals known as electrosterically-stabilized nanocrystalline cellulose (ENCC) and its counterpart free polymer chains, dicarboxylated cellulose (DCC) [104]. Similarly, the dialdehyde-modified cellulose fibrils may be functionalized with a quaternary amine to yield positively-charged hairy nanoparticles (quaternary amine-modified nanocrystalline cellulose, QNCC) and biopolymers [105]. Hairy cellulose nanocrystals, with amorphous cellulose chains, can easily accommodate one order of magnitude higher charged groups than conventional nanocelluloses [100]. As an example, four-day periodate oxidation of fibrils followed by one-day chlorite oxidation yields ENCC with more than 5.5 mmol g^{-1} carboxylic acid groups per gram of nanoparticles.

Dialdehyde functionalized cellulose fibrils may be partially oxidized by chlorite to yield bifunctional fibrils bearing both aldehyde and carboxylic acid groups, which fall apart upon mild heating, producing bifunctional hairy cellulose nanocrystals (BHCNC) [105]. These cellulose nanocrystals are highly reactive with amine-functionalized polymers, such as chitosan, through the Schiff base reaction. This reaction results in an immediate formation of bifunctional hydrogels and thus eliminates the post-purification complexities. The one-pot synthesis of bifunctional hydrogels using hairy cellulose nanocrystals therefore provides a robust infrastructure for preparing soft materials with a broad range of applications. When BHCNC is mixed with chitosan, a negatively-charged hydrogel is obtained that may be used as a superabsorbent, heavy metal ion removal agent, tissue scaffold, and catalytic reaction medium. This gel may be lyophilized to produce bifunctional aerogels with a density as low as $\sim 10 \text{ kg m}^{-3}$, being able to adsorb positively-charged species, such as methylene blue, a model dye, in aqueous

media, providing a green, reusable material for environmental remediation [105] (Fig. 5).

Aerogels synthesized from BHCNC [105] with $\sim 3 \text{ mmol COOH g}^{-1}$, and carboxymethylated chitosan ($\sim 3 \text{ mmol COOH g}^{-1}$) has been able to remove up to $\sim 785 \text{ mg}$ of methylene blue, a cationic dye, per gram of adsorbent through a time-dependent diffusion-adsorption process at $\text{pH} \sim 7.5$. This aerogel performed as one of the most efficient bio-based adsorbents considering its high adsorption capacity, reusability (only 10% decrease in the adsorption capacity was observed after 6 cycles of dye adsorption-desorption), and applicability in a wide range of pH. Interestingly, the limiting step in the dye removal process was the dye diffusion to the aerogel-medium interface followed by almost-immediate dye adsorption, attesting to a fast removal process [105]. The BHCNC may readily be functionalized with a wide range of molecular moieties and polymers, such as aldehyde, amine, carboxylic acid, ionic liquids, surfactants, epoxides, silanes, polycaprolactone, and polyethylene glycol, and thus paving the way towards the facile synthesis of multifunctional hydrogels and aerogels.

4.1.1.1. Physical cellulose hydrogels. Cellulose hydrogels made from native cellulose can be prepared through physical crosslinking. Due to a large number of hydroxyl groups present in cellulose molecules they can form hydrogen bond-mediated networks easily [79]. The main limitation is to find a proper solvent for cellulose as it is insoluble in the majority of common solvents [75,79]. Currently, there are a few solvents that can dissolve native cellulose: N-methyl morpholine N-oxide (NMMO) [106,107], LiCl/dimethylacetamide (DMAc) [108–111], some ionic liquids (ILs) [112–115], and thiourea aqueous systems (also known as alkali/urea) [116–118].

When dissolved, the native cellulose behaves as random coils, semi-flexible/rigid chains, or entangled chains [75]. The degree of entanglement is proportional to the polymer concentration. When the cellulose concentration increases, the solution starts to form a

liquid crystalline gel followed by phase transition to a solid gel with an anisotropic structure [75]. When the cellulose concentration increases, the number of hydrogen-bonding interactions increases too. In order to enhance the physicochemical interactions between the polymer chains and subsequently the hydrogel stability, two processes can be done: curing or coagulation. The former involves keeping the solution at various temperatures between 5 and 60 °C for a defined period of time (the time scale ranges from minutes to weeks) [75,119], while the latter is achieved through contacting the cellulose solution with an anti-solvent such as water, ethanol, methanol, and sulfuric acid/sodium sulfate [75,120]. The physical association between the chains could be reversible too [75].

Nevertheless, there are two scenarios for the hydrogels: either the reversible gel is coagulated in an anti-solvent, or the thiourea is used as a solvent at high curing temperatures (higher than 60 °C). These irreversible gels present a reduction in the degrees of crystallinity (between 9 and 22%) compared to native cellulose [75]. The main parameters evaluated in these gels are the transparency and the strength. The transparency depends on the parameters, such as the curing temperatures or the coagulation bath [75]. For example, Cai et al. studied the gelation of native cellulose in sodium hydroxide/urea and showed that an increase in curing temperature led to a decrease in transparency [116]. However, the higher temperatures caused a increased degree of phase separation leading to hydrogels with more heterogeneity. The other key parameter affecting the transparency is the composition of the coagulant [111]. Also, the transparency strongly depends on the internal structure of hydrogel which is directly related to the coagulant and the coagulation condition.

In addition to transparency, strength is another parameter to characterize native cellulose hydrogels. Generally, strength is associated with transparency (the higher, the stronger) and the degree of phase separation during the preparation of hydrogels [75]. Tensile strength is a function of the biopolymer concentration, particle size, pH, and curing condition [75]. The mechanical strength of native cellulose-based physical hydrogels can be improved by using a pre-gelation process before performing the coagulation [119]. In this case, using a relatively low pre-gelation temperature (~5 °C), the resulted strain and stress at break were 192% and 1.97 MPa, respectively. These values were significantly higher than the hydrogels prepared through a general solution casting method (the strain 50 and 60%, and the stress at break was between 0.8 and 1 MPa).

An alternative to native cellulose is the cellulose nanowhiskers which is actually a product of cellulose acid hydrolysis with lateral dimensions ranging from 3 to 30 nm [121]. Such cellulose behaves in a similar way as native cellulose and are able to self-organize into solid gels above certain concentrations [122]. Cellulose nanowhiskey hydrogels can be obtained through treatment of aqueous nanowhiskey suspension with one of the following procedures: ultrasonication [123] or solvent exchange [124]. The ultrasonication provides enough energy to rearrange the hydrogen bonding leading to the formation of a 3D-percolated network [75]. On the other hand solvent exchange method results in chain rearrangements [124]. The transparency of these gels is decided by the thickness of the hydrogel and the density of the whiskers [75]. Furthermore, the cellulose nanocrystals may be used to prepare the bionanocomposite hydrogels, including injectable systems, which are able to encapsulate cells with improved mechanical properties [125].

Cellulose derivatives can be prepared as physical gels. The cellulose derivatives demonstrate higher water solubility and consequently easier preparation [75]. For example, the MC can form physical gels when heated above a critical temperature (depending on MC concentration) [75]. The proposed mechanism for this phenomenon is mainly the reorganization of the solvent. The interactions between the solvent and the cellulose chains change

at higher temperatures leading to the formation of hydrophobic aggregates [126]. The HPMC present similar behaviour, but the gelation temperatures are higher [75,127]. Another interesting approach to prepare cellulose gels is mixing with another biopolymer to form a physical gel [75]. For example, sodium alginate and pectin with carboxylic groups can be crosslinked through electrostatic interactions with divalent and trivalent cations (mainly Ca^{2+} and Al^{3+}) in the presence of cellulose [128,129]. Finally, the physical hydrogels can be easily obtained by combining cellulose derivatives such as HPMC with PEG containing nanoparticles due to the interactions between the cellulose derivative and the surface of the nanoparticle [130].

4.1.1.2. Chemical cellulose hydrogels. The chemical cellulose hydrogels are prepared by the use of chemical crosslinkers [75]. A wide variety of molecules are used for this purpose, including 1,2,3,4-butanetetracarboxylic dianhydride (BTCA) [131], succinic anhydride (SA) [132], citric acid (CA), epichlorohydrin [133,134], ethylene glycol diglycidyl ether (EGDE) [135], and divinyl sulfone (DVS) [136]. Depending on the type of crosslinking reaction, all these molecules can be classified as esterifying agents or etherifying agents [75]. The esterifying agents result in the formation of $-\text{COOR}$ bonds while the etherifying agents result in the formation of $\text{R}-\text{O}-\text{R}$ bonds [75]. The majority of esterification-type cross-linking reactions of biopolymers with carboxylic anhydrides require nucleophilic catalysis [75]. The typical example of this type of catalyst is the 4-dimethylaminopyridine (DMAP) [131,137,138]. On the other hand, when carboxylic acids are used as crosslinkers, carbodiimide is a mediation agent [75]. An alternative for carboxylic acid derivatives as crosslinkers is cellulose derivatives that contain carboxylic acid groups such as CMC and a composite hydrogel of CMC with other biopolymers can be achieved [139] however, the etherification reactions generally require alkaline environment [75]. To address this issue, the hydroxyl groups of the cellulose are deprotonated to make nucleophiles and consequently they become more reactive with the crosslinker (organochlorines, epoxides, and vinyl compounds) [134,135].

The irradiative cross-linking can easily form chemically crosslinked hydrogels and this process offers several advantages over the previously described methods, including non-toxic and high purity cross-linkers hydrogels [75]. This is a critical point for certain applications such as the development of pharmaceutical products which can be easily achieved by using γ -radiation [140]. Hydrogels are formed due to the generation of hydroxyl radicals [140] however, only a small fraction of gel aggregates can be obtained by using this type of radiation [75]. It is also possible to use other types of radiation to improve the hydrogel formation such as electron beam irradiation (requires vacuum) [141] and UV irradiation [142]. But the latter approaches requires a photoinitiator (4-benzoylbenzyl)trimethylammonium chloride [142] and this could result in the partial destruction of the cellulose structure due to irradiation with high-energy radiation doses [75].

The combination of cellulose molecules with synthetic or natural polymers is among realistic approaches to prepare hybrid hydrogels and the involved chemical reactions are similar to those described before [75]. The Fig. 6 illustrates SEM images of cellulose hydrogels obtained after crosslinking the cellulose and sodium alginate with epichlorohydrin [133]. The main characteristic parameters of chemically crosslinked cellulose hydrogels exhibit high transparent with large pore dimensions and hence and hence significant water absorption capabilities [75]. The transparency of chemical hydrogels mainly depends on the crosslinking degree. Also the higher crosslinking degrees contribute to the formation of a highly hydrophilic and homogeneous three dimensional (3D) network like structures from hydrogels. The use of some crosslinkers can affect transparency as well because they incorporate hydrogel

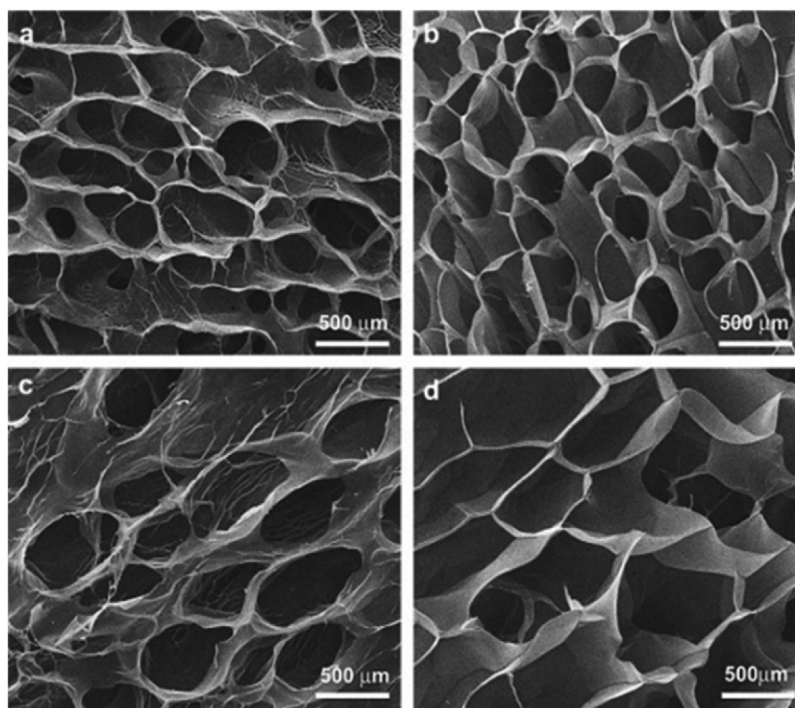


Fig. 6. (a–d) SEM images of different cellulose/SA hydrogels.

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with a certain colour. Finally, the transparency of the hydrogels also depends on the swelling degree [75]. The pore size is a very important parameter that affects several properties such as the swelling kinetics and/or the ability to uptake and release a drug molecule [143,144] which is normally determined by scanning electron microscopy (SEM) investigations. Based on the preparation process, the hydrogel pore size can vary. For example, the HPC hydrogels prepared at temperatures higher than the LCST showed microporosity, while those synthesized (cross-linked in the single-phase regime) below LCST were non-porous [145]. Additionally, the pore size is strongly affected by the drying process, for example, when the hydrogels were freeze-dried, the average pore size ranged from 3 to and 8 μm [134]. However, by controlling the freezing conditions, this range can be easily changed [146]. On the other hand, when supercritical drying is conducted, the pores normally exhibited a narrower size distributions [147].

Another critical parameter is the strength of the hydrogels [148,149], which strongly depends upon the type of cellulose, the concentration of the biopolymer, and the crosslinking density [75]. It is necessary to mention that the elastic modulus of chemical cellulose hydrogels changes over the water uptake process. At low swelling degrees, it showed a minimum modulus value which was rising steadily with swelling mainly because of the high intrinsic chain stiffness of the cellulose backbone. Finally, the last governing parameter in cellulose hydrogels is their ability to absorb water [75] which is a key factor for the chemical hydrogels. Due to the weak interactions between chains in physical hydrogels, their capacity for water absorption is quite much limited. The water uptake is significantly influenced by several factors such as the drying process, the molecular weight of the cellulose, the crosslinking degree and the cellulose concentration, etc. [75].

4.1.2. Hemicellulose-based hydrogels

After cellulose, the hemicellulose is the second most abundant biomass which has strengthened the plant cell wall with lignin and cellulose. The hemicellulose has a heterogeneous structure

composed of branched polysaccharides groups such as pyranoses and furanoses units and constitutes more than 20% of wood cell walls [150]. Xylans, xyloglucans, glucomannans and mannans are various types of hemicellulose that consist of the terrestrial plant cell walls mainly. Given that hemicelluloses are biocompatible, not toxic, and biodegradable, the hemicellulose are the subject of several studies for biomedical applications.

Depending on the source of biomass, the synthesized hemicellulose hydrogels exhibit different physical properties because of changed structure, composition and amounts of the hemicellulose in different biomass. In case of hardwood, xylose is the most important hemicellulosic monomer which occurs as O-acetyl-4-O-methylglucuronoxylan with a degree of polymerization between 100 and 400. In soft wood, however, the Mannose is the predominant hemicellulosic monomer which occurs as O-acetyl-galactoglucomannan. Hemicellulose from various sources such as aspen wood, birch wood spruce, straw, etc. have used for the development of hydrogels. Weak hydrogel with low shear modulus and low swelling ratio was produced from the hemicellulose derived from spruce chips after thermomechanical pulping process, nevertheless it showed a high swelling rate. In another report, the hydrogel produced from acetylated galactoglucomannan-rich wood hydrolysate (WH) showed a high swelling ratio of up to 270 g/g [151,152].

Hemicelluloses with high content of hydroxyl group, unique structure, solubility and susceptibility to hydrolysis have immense potential for diverse applications. Modification of the hydroxyl groups with various reactions including ester, ether, and cross linking make it possible to develop different products such as films, coating, hydrogels, etc. A number of monomers such as acrylic acid (AA) and maleic acid (MA) have been evaluated for the development hemicellulose hydrogels. The reaction of hemicellulose with AA is particularly facile leading to the formation of biodegradable hydrogel. The bamboo derived hemicellulose in one study copolymerised with AA resulting in a pH sensitive hydrogels with adsorption capacity of up to 822 times of its weight. Esterification

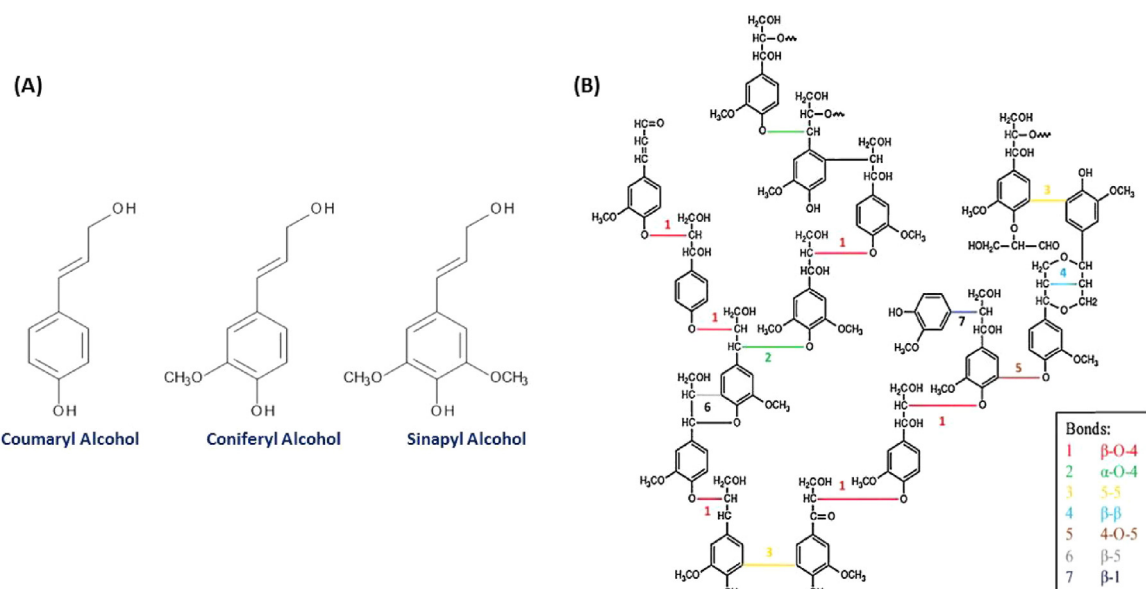


Fig. 7. (A) Basic units of lignin; (B) the structure of lignin.

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of hemicellulose derived from spruce pulp was achieved with MA which resulted in ionic hydrogel matrix for drug release applications. The grafting of monomer on the hemicellulose backbone was initiated by the generation of sulphate anion radicals from the oxidizing agent such as ammonium persulfate which formed alkoxy radicals with the hydroxyl group of hemicellulose which initiate the polymerization process [153].

4.1.3. Lignin-based hydrogels

Lignin is one of the main constituents of the natural lignocellulosic polymers, along with cellulose and hemicellulose [154–156]. Lignin is present in the cell walls of the cellulosic materials and provides strength and protection to the cell wall from biochemical stresses [157]. It has been reported that lignin induces higher resistance to most of the biological attacks compared to other similar materials such as cellulose, hemicellulose or other polysaccharides [158]. Lignin also provides other interesting advantages such as biodegradability, antioxidant/antimicrobial activity, and availability as a by-product of industrial activities [159–161]. Lignin is composed of phenylpropane units: p-coumaryl, coniferyl, and sinapyl alcohols (Fig. 7, A) [162] and its structure is mainly defined by different types of carbon-carbon and carbon-oxygen bonds that link monomer units (Fig. 7, B) [163]. The amount and type of lignin depend on the cultivation of the parent cellulosic material and the types of the species (soft wood/hard wood) [164]. One of the advantages of lignin over other biopolymers is its high global availability. This type of polymers is produced as one of the waste products of the paper and bio-refinery industries [159,160]. However, the efforts are being made to reuse these waste materials. It is well established that lignin is an imperative aromatic renewable source due to the high presence of aromatic rings in its structure [157,161]. Consequently, the lignin is hydrophobic by nature and prevents the permeation of water into the cell wall [161]. The presence of a wide variety of chemical groups in these biomolecules makes them susceptible to chemical modification. Accordingly, recently several research groups are developing new types of materials based on lignin [161,162,165,166].

The potential applications of lignin are limited by some considerations such as unclearly defined structure and the variability of its properties depending on the source [157]. The molecular weight of lignin lies in the range of 1000–20,000 g/mol [161]. The

Table 1

Molecular weight and percentage of functional groups of lignins.

Lignin type	Mn (g/mol)	COOH (%)	OH phenolic (%)	Methoxy (%)
Soda (bagasse)	2160	13.6	5.1	10.0
Soda (wheat straw)	1700	7.2	2.6	16.0
Kraft (softwood)	3000	4.1	2.6	14.0
Organosolv (hardwood)	800	3.6	3.7	19.0
Organosolv (bagasse)	2000	7.7	3.4	15.1

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degree of polymerization of this type of materials is challenging to measure since during the extraction process molecules are regularly fragmented [158]. Commonly, to treat lignin three main process can be done: the sulfite process, the kraft process, and the soda lignin process [161]. The extraction process of lignin involves different chemical techniques along with acid/base catalyzed processes. During these processes, lignin is broken down to fragments with lower molecular weight. Researchers are working currently on more efficient extraction strategies like the use of ionic liquids as solvents. The physicochemical properties of the resulting material are affected by the presence of these smaller fragments. The glass transition temperature (T_g) of lignin is a good example of these variable properties. Lignin has been found to act as a thermoplastic material showing a defined T_g [157]. However, due to the variability of the material T_g is dependent on several factors such as the molecular weight. Researchers found that the T_g for lignin has a direct correlation with the molecular weight [157]. Some of the main characteristics, such as molecular weights and the functional group of different types of lignin have been reported in Table 1. There is a high demand for low cost and environment friendly materials and lignin seems to be a potential alternative [159,165,167]. Lignin is being used, after chemical modification, extensively to prepare polymer composites and hydrogels [161]. The majority of the lignin-based hydrogels have been developed for heavy metal and cationic compounds removal from aqueous solutions [86,89,168–170]. However, several studies investigated the application of these types of hydrogels for drug delivery and

tissue engineering. The following sections will describe the preparation, characterization and drug delivery and tissue applications of lignin-based hydrogels.

4.1.3.1. Preparation and characterization of lignin hydrogels. In order to prepare the lignin-based hydrogels, several procedures can be applied; however, most common lignin-hydrogel preparation involves the formation of covalently crosslinked hydrogels [171]. For this purpose, lignin is combined with other compounds such as acrylic polymers, polyvinyl alcohol, polyethylene glycol derivatives or cellulose [161]. El-Zawawy developed lignin hydrogels using extracted Kraft and alkaline lignin [161]. These types of lignin were characterized by UV and Fourier-transform infrared spectroscopy (FTIR) techniques. In order to obtain the hydrogels, a graft copolymerization reaction was applied. This chemical reaction was carried by combining lignin with acrylamide and polyvinyl alcohol. To characterize the resultant hydrogels, swelling and deswelling tests were performed in combination with UV/FTIR and SEM. Hydrogels prepared with alkaline lignin had significantly higher swelling ratios, slower water uptakes, and slower deswelling rates in comparison to the Kraft lignin hydrogels. This behaviour was attributed to the presence of a higher porosity in the structure for the hydrogels prepared through alkaline lignin [172]. Additionally, it was observed that the addition of NaCl reduced the absorption capacity of the hydrogels. A decrease of the osmotic pressure difference between the gel and the external solution is responsible for this phenomenon. Similarly, Shen et al. compared the Kraft lignin with lignin extracted by ionic liquids for hydrogel formation [87] and several crosslinking agents were used including epichlorohydrin, polyethylene glycol (PEG), and epoxide-terminated PEG. Additionally, the acrylamide was utilized by other groups to obtain lignin-based hydrogels [173].

El-Zawawy et al. also investigated hydrogels using black liquor as the backbone material [174]. The black liquors used to synthesize hydrogels were obtained from alkaline pulping of rice straw. In order to crosslink the compounds present in black liquors, two different chemical crosslinking techniques were developed: radical polymerization and cross-linking by an addition reaction. For the first type of crosslinking, ceric ammonium sulfate was an initiator in the presence of N,N'-methylenebisacrylamide to form the graft copolymers of poly vinyl alcohol (PVA) and (polyacrylamide) (PAAm). Subsequently, black liquor was added to this copolymer solution.

On the other hand, to form a crosslinked gel by an addition reaction, the same reaction was carried out without the initiator. The hydrogels were characterized by SEM and UV/FTIR spectroscopy. Hydrogels prepared using radical polymerization exhibited a higher swelling capacity compared to addition reaction hydrogels (60% vs. 27.27%). Besides, the resultant hydrogels showed a pH-dependent swelling behaviour [174]. Feng et al. developed a temperature-sensitive lignin hydrogel by using a graft copolymerization reaction [175]. The chemical crosslinking was carried out using acetic acid lignin, N-isopropyl acrylamide (NIPAAm) (as a thermo-responsive polymer), methylenebisacrylamide (MBA) (as a crosslinker) and H₂O₂ as radical initiator. The hydrogels were studied by their morphological, thermal and swelling behaviours. It was reported that the pore size in the hydrogel structure increased with the increase in the acetic acid lignin content. The differential scanning calorimetry (DSC) study showed that the material presented a lower critical solution temperature (LCST) at 31 °C [175]. Consequently, the resulting hydrogels were thermo-responsive. The use of acetic acid lignin to produce hydrogels was evaluated by another research group. Peng et al. developed acetic acid lignin hydrogels crosslinked with NCO-terminated polyurethane ionomers [176]. The hydrogels showed a pH-dependent swelling ratio.

A different approach was developed by Grishechko et al. for preparation of lignin hydrogels with applications as aerogels and cryogels [177]. To synthesize the hydrogels, lignin was chemically combined with phenol and formaldehyde under alkaline condition. The initial hydrogels were freeze-dried to obtain cryogels or dried using supercritical CO₂ to obtain aerogels. After characterization by FTIR, SEM and BET surface area, aerogels showed higher porosity compared to cryogels [177]. Incorporation of lignin led to higher macroporosity. This group also developed aerogels based on tannin, lignin, and formaldehyde hydrogels group [177]. They showed that higher amount of lignin significantly modified the pore size distribution of the aerogels. Quraishi et al. developed lignin hybrid aerogels as tissue engineering scaffolds by exposing alginate and lignin alkaline solutions containing calcium carbonate to CO₂ at 4.5 MPa [178]. Passauer et al. proposed hydrogels and xerogels from water swellable oligo (oxyethylene) lignin derivatives [179]. Organosolv lignin is a type of lignin extracted using organic solvents [180]. During fabrication process, lignin was pre-activated through an oxidative process and combined with poly (ethylene) glycol diglycidyl ether (PEGDGE) [179]; crosslinking reaction occurred via esterification between PEGDGE and OH groups of lignin [161]. The swelling tests showed that the water content of the hydrogels decreased significantly with the increasing the cross-linking density. Consequently, hydrogels with higher degrees of chemical modification with PEGDGE had lower swelling capacity [179]. Using the same technique, Nishida et al. developed hydrogels made of acetic acid lignin and PEGDGE [181].

Lignin hydrogels also can also be produced by combining with other biopolymers such as cellulose-lignin hydrogels [182]. Cellulose and lignin were mixed under alkaline condition and crosslinked by adding epichlorohydrin. FTIR was used to confirm the crosslinking reaction. As mentioned earlier, lignin played a role in increasing the pore size. These hydrogels were used to deliver different types of polyphenols [182]. Lignin significantly alters the properties of the hydrogels. It increases the hydrogel porosity and leads to coloured products [183]. Wang et al. produced cellulose-lignin hydrogels by the use of ultrasonic irradiation [170]. The prepared hydrogels showed promising properties for the detection and removal of heavy metals in aqueous media [170].

Starch, acrylamide, and lignin have been used to fabricate hybrid gels [86]. The synthesized hydrogels showed maximum water absorption values after 100 h and followed a Fickian water transport mechanism [86]. The hybrid hydrogels based on xanthan gum and lignin were studied by Raschip et al. [184,185]. Xanthan gum and lignin were crosslinked by addition of epichlorohydrin under alkaline condition. These hydrogels showed promising ability as vanillin (active aroma ingredient) delivery systems [184]. Yamamoto et al. used a two-step process to produce lignin-based hydrogels containing phenol, resorcinol, and glutaraldehyde [186]. The first step was mixing lignin, phenol, and resorcinol under alkaline condition to form a resin and then crosslinking by glutaraldehyde. The crosslinking reaction was carried out at 25 °C for 72 h. This hydrogel was biodegradable [186]. Lignin derivatives such as lignosulphonate combined with acrylic acid and polyvinylpyrrolidone were studied as drug delivery hydrogels [187]. Kai et al. developed a lignin supramolecular hydrogel via combining poly(ethylene glycol) methyl ether methacrylate with lignin to create hyper branched copolymers [188]. The crosslinking happened by the formation of inclusion complexes between this hyper branched polymer and α -cyclodextrin, resulting in a hydrogel with self-healing properties [188].

Larrañeta et al. and Domínguez-Robles et al. developed a method to crosslink lignin by using poly(methyl vinyl ether-co-maleic acid) in solid state [168,189]. For this purpose films prepared by drying dissolutions containing lignin and poly(methyl vinyl ether-co-maleic acid) were heated at 80 °C in an oven for 24 h

to crosslink. The crosslinking of lignin molecules took place by an ester formation between the acid groups of poly(methyl vinyl ether-co-maleic acid) and the multiple alcohol groups present in lignin molecules [189]. Domínguez-Robles et al. showed that the resulting hydrogels showed different water uptake capabilities depending on the type of lignin used to prepare the hydrogel [168]. On the other hand, Larrañeta et al. used alternative crosslinkers such as poly(ethylene glycol) to improve the mechanical properties of the hydrogels while influencing the swelling capabilities of the materials [189]. Moreover, in the same work, Larrañeta et al. demonstrated that the use of microwave radiation could be used to crosslink the hydrogels using shorter periods of time (1 h) [189]. Due to the lack of toxic reagents and solvents, lignin-based hydrogels developed by Larrañeta et al. and Domínguez-Robles et al. can be considered green hydrogels [168,189].

4.2. Plant polysaccharide-based hydrogels

4.2.1. Starch-based hydrogels

Starch is an abundant polysaccharide found in the chloroplast and amyloplast of the plant (seeds, tubers, and granules). This polysaccharide composed of glucose molecules attached together via α -D(1-4) and α -D(1-6) bonds. Amylose and amylopectin are two main molecular arrangements and exist in different ratios in starch-rich plants such as potato and corn [190]. Linear attachment of molecules forms the amylose while amylopectin has a highly branched structure. Starch has mainly amorphous structure due to the presence of amylose, while amylopectin forms the crystalline regions [191]. Depending on the ratio of amorphous to crystalline sub-structures, starch can form a gel at different processing temperatures. The hydrophilic 3D structure of starch hydrogels has diverse applications such as food industry, water treatment, and agricultural usage for delivery of nutrients to plants, tissue engineering and drug delivery.

Starch-based hydrogels are prepared using chemical crosslinking [192]. For this purpose, acrylic acid is grafted into starch and Ce^{4+} or persulfates are used as initiators [193–195]. These types of hydrogels have not been extensively explored for biomedical applications. The main applications of these hydrogels have been explored in other disciplines such as agriculture or the removal of pollutants [192,196,197]. However, some authors have reported its use for drug delivery and tissue engineering [192].

Starch-based hydrogels containing methacrylic acid are pH responsible. Accordingly, these hydrogels are ideal for colon-targeting. These materials were able to swell in the slightly alkaline intestinal medium extensively while minimally swell under gastric acidic conditions [192,198]. Due to these properties, El-Hag Ali et al. used them for ketoprofen delivery [198]. Finally, Ngoenkam et al. reported the use of starch/chitosan thermosensitive injectable hydrogel for chondrocyte delivery for cartilage tissue engineering [199]. In this case it was reported that the presence of starch in the hydrogel improved water absorption while increasing pore size.

4.2.2. Pectin-based hydrogels

Pectin is an important biopolymer composed of D-galacturonic acid (GalA) units joined by chains of α -(1→4) glycosidic linkages [200]. Commercially, pectin is isolated from different sources (fruit peels and pulp, sugar beet, and sunflower heads), which causes variation in the composition, molecular weight, and polydispersity [201,202]. For example, part of the carboxyl groups of the GalA units occurs naturally as methyl esters. Such characteristic allows classifying pectin based on the degree of esterification (DE). High methoxyl (HM) pectins demonstrate DE of 60–75%, while low methoxyl (LM) pectins DE lies in the range of 20–40% [202,203]. HM-pectins have an apparent pK_a of 3.55 which negatively

correlates with DE [203]. One of the most important properties of pectin is its gelling capacity. Pectin forms ionically crosslinked hydrogels in the presence of metal ions (e.g., Ca^{2+} , Cu^{2+} , Al^{3+}) [204–206], sugar (e.g., sucrose and glucose) [207] and acid specimens [208]. Of note, the gelling properties of pectin are influenced by its DE. Overall, HM-pectins have gelation mechanisms distinct from those who worked in LM-pectins [202]. The more ionic gelation and the more hydroxyl, carboxylic, and methyl esters groups along the pectin backbone allow the application of crosslinking agents (e.g., epichlorohydrin and glutaraldehyde) [209,210], as well as the synthesis of cross-linkable pectin-derivatives [211]. All these possibilities associated with the unique properties offered by pectin have attracted enormous attention to the synthesis and application of pectin-based hydrogels in several promising research areas [202,212–214]. This section reports the main advances in pectin-based hydrogels, as well as the techniques for hydrogel formation and characterization. Furthermore, a rational discussion regarding the use of pectin-based hydrogels as biomaterial will be provided.

4.2.2.1. Preparation and characterization of pectin hydrogels. Pectin is a water-soluble polysaccharide, which allows preparing hydrogels under mild conditions. At pH higher than its pK_a , pectin's carboxylic groups are ionized ($-\text{COO}^-$) and contribute to chain-chain repulsion and facilitate the ionic crosslinking of pectin chains by divalent cations; in the case of LM-pectins, using this approach in the presence of cations (usually Ca^{2+}) form hydrogel networks (Fig. 8) [206,215]. The mechanism of LM-pectin crosslinking by divalent cations relies on the well-known “egg-box” model [216]. According to this model, junction zones are created by the ordered and side-by-side association of galacturonans, whereby specific sequences of GalA unit in parallel or adjacent chains are joined together by ionic and electrostatic bonding of carboxyl groups [216].

Generally, the complexation between Ca^{2+} ions and pectin chains occurs instantaneously, which allows the formation of *in situ* hydrogels. The gel formation, as well as its kinetics, can be monitored through rheological measurements using dynamic experiments [217]. On the other hand, the pectin- Ca^{2+} network can be characterized by spectroscopic techniques. For instance, FTIR identifies the interaction between the ionized carboxyl groups of pectin and the Ca^{2+} ions, as well as the formation of hydrogen bond among the pectin chains [215]. Changes in the pectin structure due to Ca^{2+} can be studied by X-ray diffraction (XRD) measurements [218]. Moreira et al. reported the preparation of injectable LM-pectin hydrogels by internal gelation with calcium carbonate (CaCO_3) [219]. These hydrogels were fabricated by the simple addition of CaCO_3 suspension to pectin solutions and can be tuned to support biological applications [219]. Another approach used to obtain ionically crosslinked pectin hydrogels is drop-wise addition of pectin solution into the Ca^{2+} solution to form beads [220]. This technique is frequently utilized to prepare delivery systems for bioactive compounds (usually drugs) [220,221]. The parameters including the concentration of pectin and Ca^{2+} solutions, the inner diameter of the needle (drop forming device), fall distance, drop-wise speed, and stirring rate should be controlled [221]. Overall, these parameters define the particle size and surface morphology. Other parameters such as surface area, surface charge, and zeta potential can affect the properties of final hydrogel [222,223]. Kim et al. reported the production of monodisperse pectin-based microspheres ionically by Ca^{2+} ions [224]. They developed a microfluidic approach that involved *in situ* gelations of pectin in continuous production of pectin-based microspheres with narrow size distribution. Compared to other methods (drop-wise, capillary flow system, and electrostatic generation system) this microfluidic approach enables precise control over droplet formation and the mechanical properties [224].

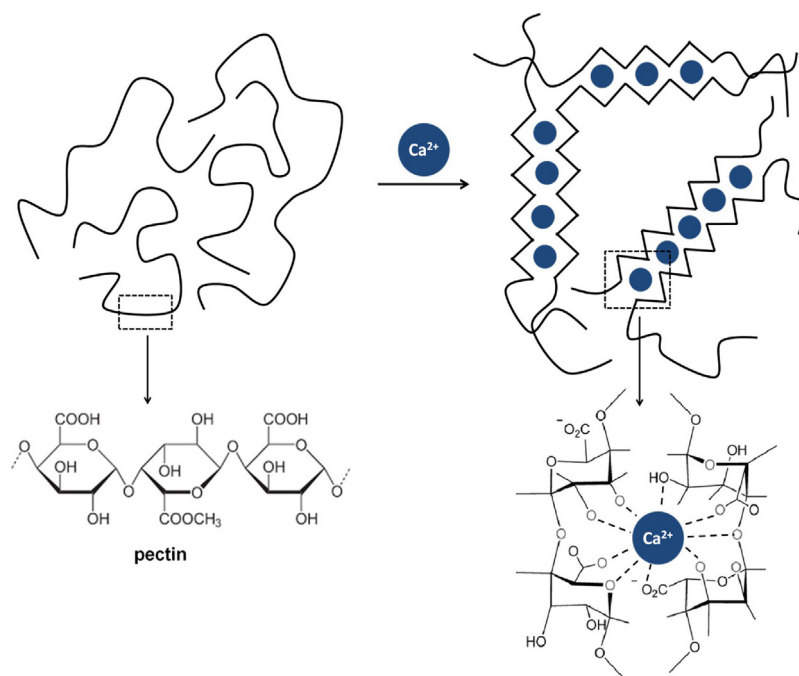


Fig. 8. A schematic representing the Ca^{2+} induced gelation of pectin (“egg-box” model).

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Amidation of LM-pectin improves its gelling ability by reducing the calcium level required for gel formation [220,225]. Indeed, amide groups along the pectin chains favour the hydrogen bonding which keeps the pectin chains joined together. Alternatively, physically crosslinked hydrogels can be prepared by mixing LM-pectin (polyanionic) with polycationic molecules under aqueous medium [226]. At pH sufficiently higher than pectin's pK_a (~ 3.5), LM-pectin exhibits anionic characteristic due to its ionized carboxyl groups. The electrostatic interaction between these ionized groups with oppositely charged groups (positively charged groups in this case) results in polyelectrolyte complexes (PEC). Pectin has been extensively complexed with chitosan, a polycationic polysaccharide, to form PECs [227–229]. Furthermore, aqueous mixtures of pectin/chitosan enable the procurement PEC with thermoreversible gelation properties. The properties of PECs are determined mainly by the degree of interaction between these two polyions.

On the other hand, their stability depends on charge density, polyanion/polycation ratio, solvent, ionic strength, pH, and temperature [230]. Therefore, a comprehensive investigation regarding the PEC stability on different experimental and application conditions has to be performed before their practical use. Thermal analyses (e.g., TGA/DSC) and liquid uptake experiments under different conditions (ionic strength, pH, and temperature) are required [231,232].

Unlike LM-pectin, HM-pectin does not have sufficient carboxyl groups to crosslink in the presence of Ca^{2+} ions, but it forms gels in the presence of other sugar and acid specimens [207]. Important forces in the aggregation of pectin chains include hydrogen bonding and hydrophobic interactions [200,233]. Hydrogel forms by hydrogen bonding between free carboxyl groups along the pectin chains and also between the hydroxyl groups of neighbour chains. Close to neutrality or only slightly acid dispersion of pectin, most of the unesterified carboxyl groups are present in their ionized form. The great number of carboxyl ions and hydroxyl groups on the pectin backbone induces considerable negative charge density that causes the attraction of water molecules and prevents the formation of a pectin network.

On the other hand, acid specimens present in the medium convert the carboxyl ions to carboxylic acid groups ($-\text{COOH}$) which decreases the negative charge density along the pectin molecule. As a result, the attraction between pectin and water molecules is reduced as well as the repulsive forces among the pectin chains. The hydration of pectin is also reduced when other sugars added to the medium due to the competition for water molecules. Therefore, under an acidic condition or the presence of other sugar molecules, the ability of pectin to stay in dispersed state decrease. This condition allows the formation of pectin hydrogel at low temperature due to the unstable dispersing of less hydrated pectin chains which leads to a continuous network [233].

Chemical crosslinking of pectin forms irreversible hydrogels due to covalent bonds which produce hydrogels with improved mechanical properties compared to ionically (or physically) crosslinked ones. The chemical crosslinking of pectin chains can be obtained by reaction of its functional groups (hydroxyl, carboxyl, and methoxyl) with bi-functional molecules such as epichlorohydrin, di-isocyanates, and glutaraldehyde [210,234]. Yoshimura et al. developed a series of pectin-based superabsorbent hydrogels using ethylene glycol diglycidyl ether (EGE) and glutaraldehyde (GA) as chemical crosslinkers [210]. The swelling ability for pectin-GA hydrogels was higher than pectin-EGE hydrogels. The reactivity and molecular weight of crosslinkers define the final contents of the gel [210]. The chemical characterization of the pectin-based hydrogel can be assessed by using FTIR and nuclear magnetic resonance (NMR) spectroscopy [235,236]. In addition, functional groups such as vinyl, acrylate, methacrylate, and epoxy can incorporate in the fabrication of pectin hydrogels through chemical crosslinking [237,238]. Pectin derivatives containing these reactive groups can form inter/intramolecular bonds by radical reaction through an initiator such as chemical/photochemical/thermal stimulation or ultrasonic radiation). The extent of pectin modification determines the crosslinking density, a vital parameter affecting the mechanical, morphological, degradation, and uptake properties [71]. High crosslinking density results in stiffer hydrogels with a low degradation rate [239]. Souto Maior et al. [240] studied the chemical

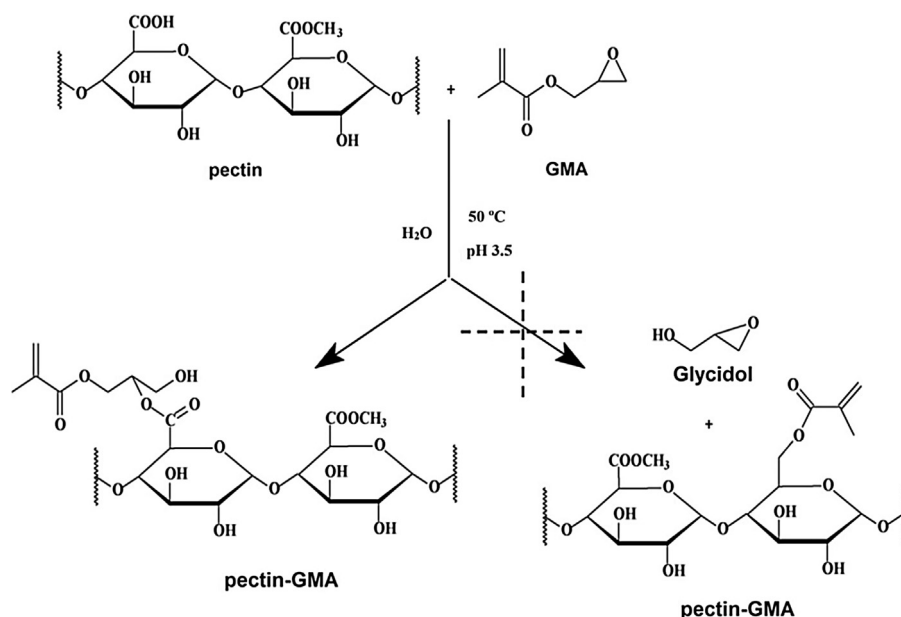


Fig. 9. Schematic representation of the reaction between pectin and GMA.

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modification of LM-pectin with glycidyl methacrylate (GMA) to insert vinylic groups into the polysaccharide backbone (Fig. 9) with potentials for a target and site-specific drug release [240].

Hydroxyl and carboxyl pendent groups along the pectin chains favour the grafting of various polymer monomers (such as acrylic monomers) into pectin [241–243]. The application of Vinyl graft copolymerization into pectin has been proposed as a reliable technique for the synthesis of natural-based superabsorbent hydrogels [244]. Superabsorbent hydrogel fabrication by grafting mixture of acrylic acid (AA) and acrylamide (AM) monomers into pectin backbone using ammonium persulfate as free radical initiator and N,N'-methylene bisacrylamide (MBA) as crosslinker agent produces pectin-g-poly(AA-co-AM) hydrogels with remarkable liquid uptake capacity, salt-sensitivity, and pH-reversibility properties, which are considered as potential carriers for bioactive molecules [244].

However, pectin-based hydrogels have demerits include unsatisfactory mechanical and liquid uptake properties. To overcome this issue, incorporating distinctive materials within the pectin hydrogel network and fabrication of hydrogel composite has been proposed. Pectin-based hydrogel composites have been prepared via incorporation of different materials including clays [245], cellulose-derivatives [215], metal/magnetic particles [246,247], and carbon-based species (graphene oxide and carbon nanotubes) [248]. Pectin-based hydrogel composites are prepared through conventional techniques (physical or chemical crosslinking procedures) followed by some modifications.

4.2.3. Plant gum-based hydrogels

Natural bioactive hydrophilic polysaccharides, made up of sugars such as xylose, rhamnose, dextrose, mannose, arabinose, galactose, and uronic acids (except glucose) which can produce viscous solutions/emulsions and gel-like media are termed as natural gums [249]. These water-soluble, inert, and biocompatible materials induce viscosity and rheological properties to solutions. Water solubility of natural gums (hydrocolloids) makes them ideal options for gelling agents, thickeners, and emulsifier. Plant-based gums are extracted from plants exudation (tragacanth), seed endosperm (locust bean and guar), and tree exudation (karaya, sterculia, and arabic gums) [249]. Interaction of hydroxyl functional groups, polar

groups, and hydrogen bonds between polymer chains, as well as molecular weight, length of linear chain, branches and moieties, define the gum structural properties [250]. Gum-based hydrogel preparation depends on polymerization (copolymerization), in which the gum (and other monomers), as well as initiator and cross-linker, are used to produce the polymer (copolymer) under continuous stirring and in some cases vacuum. Later on, the polymer (copolymer) is dried under vacuum to result in hydrogel network [251,252]. One of the convenient methods to prepare gum hydrogel film is application of irradiation to polymerize the polymeric solution, which is composed of gum and other monomers and using gamma ray to sterilize the hydrogels [53]. Members of this family provide excellent biocompatibility and biodegradability, as well as mimicking extracellular matrix, which are excellent properties for tissue engineering [253]. Furthermore, these hydrogels are low-cost, renewable, and in most cases edible which makes them great candidate for oral delivery platforms, like tragacanth gum hydrogels [253,254]. Of note, guar gum-graft-poly(acrylic acid) hydrogels indicated self-healing property due to the hydrogen binding of guar gum hydroxyl groups with poly(acrylic acid) carboxyl groups [255]. Guar gum-poly(acrylamide) demonstrated first-order swelling kinetics and non-Fickian drug release profile in acidic/basic milieu [256]. Karaya gum provides the hydrogel with branched structure and bonding sites; locust bean gum induces high elasticity and mechanical properties to the hydrogel; karaya gum-locust bean gum showed optimized swelling and consequently controlled drug release in gastrointestinal environment [257]. Karaya gum-poly(vinyl alcohol) cryogels have viscoelastic behaviour mimicking the mechanical properties of muscle tissues [258]. Oxidized cashew gum-gelatin hydrogels demonstrated high capacity to absorb the water, as well as maintaining the mechanical properties under cyclic compression, developed for tissue engineering scaffolds [259].

4.3. Plant protein-based hydrogels

Amongst natural polymers, proteins may be the most valuable and under-utilised polymeric starting materials for the development of novel materials for biomedical and biotechnological utilization [260–262]. In the last decade, many protein and

protein-based composite have been investigated for various purposes due to their high competency for utilization in the contemporary biomedical researches [263–265]. Recently the plant-based proteins such as soy, zein, gliadin, and lectins have drawn significant attention for biomedical and life science applications due to their renewability, availability, and their processability to the multiple neat forms like fibre, nanoparticles, hydrogels, films, etc. [266–269]. Also, plant-derived proteins are able to mitigate some drawbacks of animal-based proteins, e.g., collagen, regarding the immunogenicity, risk of viral transfer due to the batch to batch variability, and their relatively high extraction costs [270–273]. Plant-based proteins have a lower molecular weight and more hydrophobic than animal-based proteins which provide them with an opportunity of cell attachment without being undergone to the additional surface modifications. Furthermore, they usually, possess more functional groups when compared to the animal-based protein which conferring them with a potential of being adsorbed or covalently coupled to the various molecules to modify the target properties [274]. Among the various forms of plant-based protein, in this section, we will only focus on their hydrogel forms regarding the preparation and their biomedical and biotechnological applications.

Generally speaking, the protein-based hydrogel is a three-dimensional macromolecular protein network which is formed in the presence of a chemical or physical crosslinker. Thanks to the hydrogel unique structural characteristic, plant-based protein hydrogels have also been reported as promising biomaterials for various novel applications ranging from food formulation applications to drug delivery, tissue engineering and regenerative medicine [275]. Apart from their biocompatibility, bioreactivity, and biodegradability, the relevant properties of protein-based hydrogel that make them interesting for aforementioned applications are their water-holding capacities especially in drug delivery applications in which the swelling is a key parameter, as well as their compression strength which is very important for some specific applications [276]. Among the plant-derived proteins, the hydrogels prepared from the soy and zein were mostly studied for drug delivery and tissue engineering applications which will be elaborated in the following sections [274].

4.3.1. Soy protein-based hydrogels

Soybean contains 40% proteins and 20% oil in the dried weight. At the low temperatures, the oil is extracted to produce soy protein isolate (SPI) [277–280]. SPI contains a mixture of albumins and globulins, 90% of which is a storage protein containing two important components of glycinin and β -conglycinin with globular structure [281,282]. Glycinin comprises six subunits with basic and acidic polypeptides moieties which are bonded together by single disulfide bonds [283]. β -Conglycinin has a trimeric structure with three different subunits of α , α' and β with different molecular weights that bind together through hydrophobic interactions [284]. Overall, 20 different amino acids are responsible for building up the soy proteins structure which are mainly lysine, leucine, phenylalanine, tyrosine, aspartic, and glutamic acid [285]. In addition to their specific tissue engineering application for examples orthopaedic implants, soy protein hydrogels are ideal carriers for drug delivery systems and controlled release of drug thanks to their stable structure upon exposure to the ionic compounds or solution with varying pHs.

4.3.2. Zein-based hydrogels

Zein is a prolamin based protein with the molecular weight of ca. 40 kD [286]. This protein is a major storage protein in corn kernels. The unique solubility and good biocompatibility in this polymer render it promising for several biomedical applications such as food, drug delivery, and tissue engineering. Zein in

its primary structure comprises one-third hydrophilic glutamine and two-thirds hydrophobic amino acid moieties. Thus, it exhibits an amphiphilic character [287]. On the other hand, due to the dominant hydrophobic properties, zein indicates unique solubility profile with less solubility in water, but a better solubility in aqueous–alcohols, –glycols, and –acetone, or extreme alkali conditions with a sufficient concentration. This unique solubility in zein is attributed to the presence of nonpolar amino acids in its structure [288].

4.3.3. Preparation and characterization of plant protein-based hydrogel

The gelation in protein occurs as a consequence of physical (such as high temperature and pressure application), enzymatic crosslinking, and chemical treatment (such as a change in pH or addition of crosslinker or changing in the ionic strength by addition of salts). Mechanism of gelation in protein is accompanied by two steps: unfolding the native protein structure and subsequent aggregation of protein chains to form a 3D network with the ability to retain the water inside its structure [289]. Upon gelation, polymer network undergoes a crosslinking between its polymeric chains through establishing non-covalent bonds, e.g., hydrophobic interactions and hydrogen bonds or through more robust covalent disulfide bonds. The strength in the gels depends on the extent of crosslinking and physical gelation usually leads to the structure with poor mechanical strength and low stability in the physiological environments. Despite high mechanical strength obtained by the chemical gelation, these hydrogels are often associated with toxicity due to the presence of toxic chemical crosslinker components in the structure. The final physical and mechanical properties of protein hydrogel like strength and elasticity as well as water holding capacity, thermal stability are determined by the several factors like protein intrinsic properties and the processing conditions used to produce the gelation including temperature, time, and a heating rate of solution [290]. There is an optimal concentration for gelation of each protein which is affected by its structural characteristic and gelation conditions. Extremely depending on the pH and ionic strength of reaction, in the case of plant-based proteins, the minimum concentration for gelation are reported as 6.6%, 4–12% and 15–20% for soy [291], whey protein [292], and zein [293] respectively.

For protein-based biomaterials, particularly in a hydrogel form, increasing the thermal stability of proteins is a very important criterion. There are several ways to enhance thermal stability of protein-based hydrogel for biological applications which have recently been reviewed systematically by Yuan et al. [294]. Among them, the occurrence of stable hydrogel bonding, a great extent of hydrophobic interactions and increased helical content in the polypeptide polymer chains render the hydrogel to exhibit high-temperature resistance (80 °C) for extended times.

4.3.3.1. Preparation and characterization of soy protein hydrogels.

Soy protein hydrogel and gel composites can be prepared using protein isolate (SPI), as well as the gelation of soy individual subunits [295,296]. In the case of physical gelation of soy protein, Renkema investigated the heat-induced gelation of SPI under different conditions [297]. Dumoulin et al. studied the high-pressure-induced gelation of SPI by the pressurization up to 500 MPa for 30 min in the temperature range of –20 to 50 °C [298]. Puppo and Anon prepared the acidic SPI gels at different salt solutions [299]. Molina and Ledward explored the effects of combined high-pressure along with the heat treatment on the synthesis of the SPI gels [300]. Although physical gelation of SPI has successfully proceeded in an aqueous solution by application of physical driving forces like heating, pressure, cooling, acidification, and tuning the ionic strength of the

solution; in these cases, the gels usually have a delicate structure with low mechanical strength.

Chemical gelation using crosslinkers can promote the gelation process in SPI to mitigate the low mechanical strength and limited water holding capacity in physical hydrogel [301]. Proteins have several reactive groups ($-\text{NH}_2$, $-\text{OH}$, and $-\text{SH}$) which enable cross-linking reaction. Low molecular weight aldehydes such as formaldehyde, glutaraldehyde, and glyoxal, so-called “Maillard-type” crosslinking agents, bind to free amine groups of arginine, lysine and hydroxylysine residues in the proteins and forms intra- and intermolecular crosslinks [302]. In the case of SPI, the gel swelling ratio is influenced by the type of the crosslinker and its concentration, as well as the addition of salts. However, most of the chemical crosslinkers have high cytotoxicity due to the release of crosslinker from the hydrogel network which limits the biomedical applications of chemical hydrogels. Natural crosslinkers like genipin are less cytotoxic (compared to glutaraldehyde) and are recommended for the SPI gelation [289]. The enzymatic technique has been studied to promote the gelation of the proteins. Transglutaminase (EC 2.3.2.13, protein-glutamine γ -glutamyltransferase, TGase) is an enzyme with the ability to catalyze the crosslinking reaction between protein molecules, peptides, and primary amines through an acyl transfer reaction to create inter- or intramolecular ϵ -(γ -glutamyl)lysine isopeptide bonds [303–306].

Due to the SPI emulsifying ability, emulsion-based soy protein hydrogels have also been produced by forming SPI-based oil-in-water (O/W) emulsions which can be later on converted to the soft-solid-like materials by destabilization of oil droplet through several processes including heating, acidifications and enzymatic reaction [307,308]. The emulsion preparation of protein-based hydrogels is a useful technique, especially for drug and food delivery, production, and storage [309]. In addition, the compositing SPI with other components have been proposed to enhance the performance of the hydrogel through improving the structural properties like pore size and pore interconnectivity, as well as reinforcing the mechanical strength and endowing the hydrogel with stimuli responsivity, particularly when blended with intelligent polymers [295,305,310,311]. Nishinari et al. have comprehensively reviewed the gelation conditions for soy protein [308].

4.3.3.2. Preparation and characterization of zein hydrogels. Zein exhibits high potential to form hydrogels with or without linking to the other polymers to form 3D brick-like structures with sufficient space to host biomolecules [288]. Most of the zein-based hydrogels have been used for drug delivery applications in which the gelation and entrapment of biomolecules are carried out in a single stage resulting in a so-called ‘*in situ* gels’ [312,313]. For chemotherapy and site-specific delivery, zein-based smart *in situ* hydrogels have been developed with the capability of protecting the therapeutic agents from the harsh and unfavourable environment with the potential to respond to the external stimuli like heating, ionic strength, and pH [314]. Vries et al. found that zein as an amphiphilic triblock can form a thermos-responsive 3D hydrogel network in the presence of a hydrophobic nucleation site like oil droplets or hydrophobic silica and a proper solvent like glycerol [315]. In this case, several factors like temperature variation, nuclei hydrophobicity, or solvent polarity can govern the gel formation, mechanical strength, and its stimuli-responsivity accordingly. With respect to applications of plant protein-based hydrogel systems in bioactive cargo delivery, the utilization of cold set gels are preferable over the heat-induced gel, because the bioactive elements are temperature sensitive. On the other hand, particularly in the case of food and nutraceutical delivery, bioactive elements can be entrapped and protected inside the plant protein hydrogels and be adsorbed inside the intestine tract without being affected by a gastric environment like pH and temperature [316]. In general, a facile modulation of

release rate of molecules from food or plant-based gels is due to the presence of acidic (e.g., carboxylic) and basic (e.g., ammonium) groups in the polypeptide chains, which either accept or release protons in response to the pH changes of the gastric environment (acidic in the stomach and neutral in the intestine) [317].

4.3.4. Characterization of plant-based proteins

Physicochemical and microstructural characteristics of protein-based hydrogels have also been addressed with several known techniques that are used to study in general for other protein-based materials. Chemical characterization based on FTIR or Raman spectroscopy are employed on dried samples to monitor the chemical structure of extracted proteins from their initial resources, as well as monitoring the incorporation of crosslinker to the gel structure and type of crosslinking reactions, especially when the chemical crosslinking or enzymatic reactions are involved in the hydrogel preparation. Thermo gravimetric analysis (TGA) can also be useful to assess the thermal stability and the weight percentages of different fractions in the gel structures. Among the solution based characterization techniques, circular dichroism techniques can be used to study the secondary structure of the protein to define the average α -helical contents in the protein [318]. The small-angle X-ray scattering (SAXS) can investigate the size, the shape of particles and/or aggregates in the protein hydrogel structures [319]. Microscopy techniques such as scanning electron microscopy (SEM) and in some cases transmission electron microscopy (TEM) are promising to visualize the microstructure of hydrogels and tracking the network morphology, size of porosity and pore interconnectivity upon different processing on hydrogel [320].

To measure the mechanical properties of hydrogels such as strength and elasticity, the dynamic rheological tests are generally conducted which determine the development of storage modulus and loss modulus through exposing and holding the gel to the subsequent heating and cooling conditions at well defined rates [310]. It is believed that storage modulus is strongly influenced by both the number of bonds between particles, which means the extent of cross-linking in the case of cross-linked hydrogels and morpho-structural properties including compactness, effective particle and pore sizes [321]. Furthermore, the toughness of hydrogel can be evaluated by its compressive properties through extracting its stress-strain curve while the consolidated gel is being compressed at a constant rate [320]. Similar to the other natural and synthetic hydrogels, the swelling behaviour and swelling kinetics in plant-based hydrogels are also one of the most important characteristics for their applications. This characteristic can be analyzed by exposing or immersing the known weight of as-prepared hydrogel or dried gel into the simulated physiological environments or to the media where the hydrogel to be utilized. After getting to the equilibrium in swelling, the uptake water percentage is calculated from the difference in weight before and after hydrogel swelling [301]. Therefore, ease of synthesis and deliberately tailored properties of soy and zein hydrogels render them a promising and novel biomaterial for biomedical applications including tissue engineering and drug delivery.

5. Biomedical applications of green hydrogels

5.1. Green hydrogels for drug delivery

5.1.1. Cellulose-based hydrogels for drug delivery

The use of cellulose for drug delivery has been extensively investigated [322]. Hydrogels made from cellulose offer interesting properties as drug delivery systems thanks to their high biocompatibility and availability as the most abundant naturally occurring

polymer [82]. These systems can be used mainly for conventional drug delivery or stimuli-responsive systems [323]. In order to modify the release profile from cellulose based-hydrogels, a second component can be added to the system [75]. Therefore, the diffusion properties of drug molecules loaded inside the hydrogel structure can be controlled [75]. Chang et al. showed that the use of carboxymethyl cellulose (CMC) in cellulose hydrogels contributes to increasing pore size, the swelling rate, and consequently the drug release rate [324]. Ciolacu et al. proposed cellulose/lignin hydrogels [182]. The incorporation of lignin into the hydrogel produced less dense hydrogel structures leading to a higher drug release rate. The influence of the addition of cellulose nanowhiskers to cellulose physical gels was evaluated by Wang et al. [325]. The incorporation of cellulose nanowhiskers to a cellulose hydrogel resulted in the more steady release of the protein [325]. Nizam El-Din et al. developed a CMC/acrylamide hydrogel crosslinked by gamma radiation for drug release [326].

Stimuli-responsive cellulose hydrogels have been developed [327,328], and among all these types of hydrogels, the most common types are temperature-sensitive and pH-sensitive. The combination of temperature-sensitive polymers such as NIPAAm with cellulose has studied to produce thermoresponsive green materials [328]. Wang et al. developed NIPAAm hydrogels containing nanocrystalline cellulose [329]. The release of a model molecule (dimethyl methylene blue) showed that these systems are promising smart materials for drug delivery [329]. In addition, to being thermoresponsive, NIPAAm/cellulose showed pH-responsiveness as these hydrogels showed higher water uptake capacities at alkaline pHs than at acidic pHs [330]. Bajpai et al. developed a polyacrylic acid, and carboxymethyl cellulose semi interpenetrated polymer network for the controlled release of ciprofloxacin [331]. The release of the drug from these hydrogels was pH-dependent. In addition to temperature-sensitive and pH-sensitive, magnetic-induced release hydrogel systems can be developed by using cellulose. Luo et al. developed Fe_3O_4 /cellulose microspheres with potential for magnetically targeted drug-protein delivery [332]. This type of particles in a hydrogel can be targeted to a specific location by applying a magnetic field. In this case, Fe_3O_4 nanoparticles were incorporated in the pores of microspheres made of regenerated cellulose. The regenerated cellulose microspheres were prepared by using a sol-gel transition method from cellulose drops in NaOH/urea aqueous solution precooled to -12°C . The resultant particles showed magnetic-responsive properties and the ability to the controlled delivery of a model protein (bovine serum albumin).

Injectable drug delivery systems have developed by use of cellulose-based hydrogels. Injectable hydrogels present interesting properties as drug delivery systems; they can be implanted in the body without surgery through a conventional needle/syringe procedure [333]. Baumann et al. developed an injectable drug delivery platform for drug delivery into the spinal cord [334]. The system was a physical hydrogel made of MC and hyaluronan. The released molecules were the neuroprotective molecules NBQX and FGF-2, the neurodegenerative molecules dbcAMP and EGF, and proteins α -chymotrypsin and IgG. The hydrogel was able to sustain the delivery up to 4 days for neuroprotective molecules and up to 28 days for neuroregenerative molecules. The release rate was mainly controlled by the slow degradation rate of the system as MC and hyaluronan were not chemically crosslinked.

5.1.2. Hemicellulose-based hydrogels for drug delivery

Being partially digestible in the colon, xylan has been investigating for the development of pH-sensitive hydrogels for drug delivery [335,336]. Hemicellulose based hydrogels have widely synthesized with the introduction of alkenyl functional groups on to the hemicellulose structure followed by covalent cross-linking for the

formation of hydrogel [337,338]. Sun et al. synthesized a series of acrylic acid monomer/hemicellulose hydrogels with varying ratios of hemicellulose to monomer and evaluated the parameters affecting on the swelling behaviour and pH sensitivity of the hydrogels [339]. An increase in the swelling of the hydrogel observed from 33 to 79% when the monomer/hemicellulose ratio increased from 6:1 to 8:1. A higher ratio of the monomer increases the ionizable carboxyl groups of the hydrogel and the content of carboxyl group effect on the pH sensitivity of the hydrogel. The optimum ratio of 8:1 for the acrylic acid monomer to hemicellulose was recommended [339].

Electrical conductive hydrogels can induce cell proliferation, adhesion, and differentiation [340]. Given the potential of biomaterials with electrical conductivity properties, in a series of studies Zhao et al. developed hemicellulose-based hydrogel with electroconductivity and magnetic field sensitivity properties [341,342]. The electroconductive hydrogel synthesized using aniline tetramer (AT) as the conductive polymer that covalently attached to carboxylated O-acetyl galactoglucomannan of the hemicellulose structure. The hydrogel properties such as swelling and release properties were controlled by varying the AT content. Increasing the AT from 10 to 40% (w/w), the swelling ratio reduced from 548% to 228% while the conductivity increased by two magnitude orders [341].

5.1.3. Lignin-based hydrogels for drug delivery

Lignin hydrogels have been used previously for controlled release of several substances such as food ingredients, fertilizers or pesticides [176,185,343]. Due to the capability of these hydrogels to control and sustain the release of molecules, they have potential to be used as drug delivery systems. Ciolacu et al. developed lignin-cellulose hydrogels crosslinked with epichlorohydrin for the delivery of polyphenols [182]. The results suggested that an increase in lignin content led to an elevated release of polyphenols. Besides, the swelling process and the drug release from these matrices can be controlled by the composition of the hydrogels. Recently, Wang et al. studied a sodium lignosulphonate-grafted poly(acrylic acid-co-poly(vinyl pyrrolidone)) hydrogel for drug delivery [187]. Amoxicillin was used as a model drug to study the release properties of these hydrogels. The release of amoxicillin was pH dependent showing higher drug release rates in simulated intestinal fluid (pH 7.4) than in simulated gastric fluid (pH 1.2). Consequently, these hydrogels showed potential to deliver therapeutic agents into the intestine with small amounts of drug losing in the stomach [187]. Lignin nanoparticles, either pure or combined with iron(III) or Fe_3O_4 were developed for the delivery of drugs with low aqueous solubility and high toxicity, namely sorafenib and benzazulene (shown in Fig. 10). These nanoparticles demonstrated low cytotoxicity and high capacity for loading the therapeutic reagents [344].

Larraneta et al. developed hydrogels containing lignin and poly(ethylene glycol) crosslinked via an esterification reaction using poly(methyl vinyl ether-co-maleic acid) [189]. The synthesis was carried out in the solid state so no solvent was required and as lignin was included in the hydrogel, these materials can be classified as green materials. The resulting materials were able to be loaded with a model hydrophobic compound (curcumin). Moreover, these lignin-based hydrogels showed sustained curcumin release profiles. Some formulations were capable of sustaining the release of this molecule in one week. Finally, the hydrogels showed a reduction in adherence of *Proteus mirabilis* and *Staphylococcus aureus* relative to poly(vinyl chloride) that is the most commonly employed medical material. Accordingly, these hydrogels are ideal candidates to be used as medical materials as they show resistance to bacterial adhesion preventing biofilm formation while providing sustained release of hydrophobic drugs.

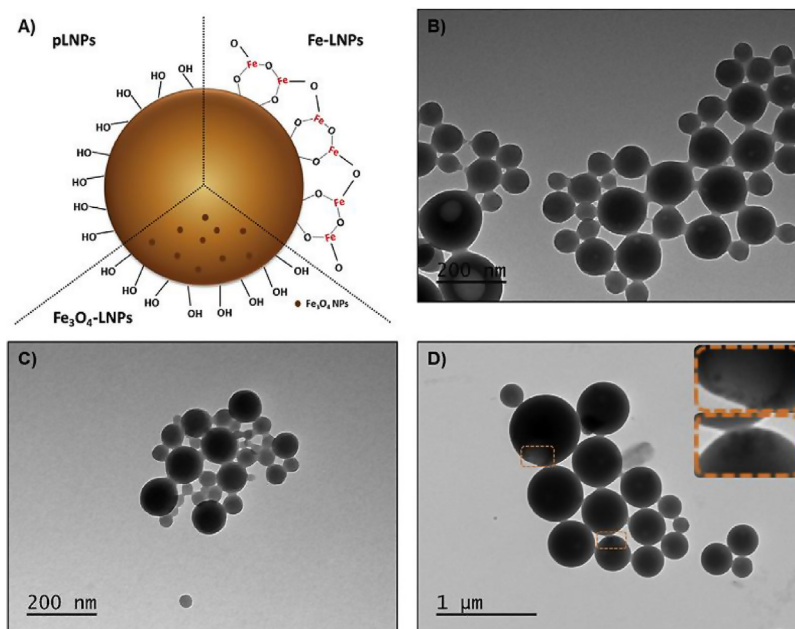


Fig. 10. (A) Schematic of three pure, iron(III)-complexed, and infused Fe₃O₄; TEM images of (B) pure; (C) iron(III)-complexed; and (D) infused Fe₃O₄ lignin nanoparticles. Reproduced with permission from [344].

5.1.4. Starch-based hydrogels for drug delivery

The starch hydrogel is a polymeric network of the hydrophilic structure with high adsorption capacity with the increasing trend for biomedical applications. Given the flexibility of the hydrogel structure, the physical properties of the hydrogel can be fine-tuned by changing the cross-linking intensity. Additionally, it is feasible to change the hydrophilicity of the hydrogel in a liquid environment. Starch hydrogels have been widely used to deliver and release selected drugs to the target tissue without affecting other organs. A hydrogel with desirable properties should be biocompatible, biodegradable with adjustable mechanical properties, loading capacity, controlled release properties, adjustable swelling kinetics and specific sensitivity to the physiological solution. It would not be normally possible to achieve all these properties using a single material such as starch. Therefore, studies have been using starch gel network as the backbone and copolymerization or grafting of a different natural or synthetic monomers into the structure. Examples are bis-acrylamide, poly glycolic acid (PGA) and poly lactic acid (PLA) [345].

The synthesized hydrogels have various properties with a range of biomedical applications. Delivery of drugs to the colon is one of the complicated examples where the hydrogel structure needs to withstand various basic and acidic conditions of the intestinal tract. The pH-sensitive starch/poly aspartic acid hydrogels were designed and successfully tested for delivery of 5-fluorouracil as a colon anticancer drug in the pH range of 2.2–7.4 [346]. Cross-linking, monomer grafting, and degree of polymerization are used to control and adjust the release behaviour of the hydrogels. The copolymer of starch and methacrylic acid hydrogel were loaded with ketoprofen as a model drug which showed a wide working pH range of 1–7 [347]. Apart from the pH stability of the hydrogel, other important factors such as drug loading capacity, concentration, composition gelation/crosslinking process, and swelling kinetics have an important effect on the clinical applications of the hydrogel. Just not enough, the *in vivo* studies are also available to support the pH-sensitive hydrogel applications. Successful *in vivo* and pharmaceutical applications of the starch hydrogels are not well studied. In addition, in some severe diseases, the gastrointestinal tract of the patients is affected in a way that there is variant in the

physiological pH which hampers the success of pH-sensitive hydrogels. Magnetic field sensitive hydrogels are advancing as the biological environment does not normally affect them. Magnetic sensitive vinyl modified starch hydrogel (doped with Fe₃O₄) were evaluated for albumin delivery by Guilherme et al. [348]. By applying the magnetic field, the albumin release was governed by anomalous transport where magnetic field increased the tortuosity effect. The presence and formation of the starch network in the hydrogel were visualized using the iodine test. In another study, the presence of iron oxide (Fe₃O₄) nanoparticles had a negative impact on the drug loading and also drug release capacity of the starch hydrogel composite [349]. The presence of iron oxide particles might occupy some regions in the hydrogel network and therefore limits the drug loading of the hydrogel. Therefore, starch-based hydrogels need to be designed and developed in a case by case basis, and it is not possible to have a hydrogel structure that can be used for loading and release of different drugs. Parameters such as drug concentration, drug loading, and release kinetic need to be considered in designing of starch hydrogels for drug delivery.

In addition to drug loading and release behaviour of the hydrogel, the texture and rheological properties are also critical factors in designing a hydrogel. Retrogradation is a useful tool to adjust the rheological properties of the starch hydrogels. The structural and functional properties of the starch hydrogels can be improved and optimized via the retrogradation process. Using the starch retrograded at 4 °C for 8 days and gellan gum, Cardoso et al. synthesized a stable and cohesive hydrogel with high stiffness, suitable for a wide range of biomedical applications. When the retrogradation carried out at thermal cycles of 4–30 °C for sixteen, a more adhesive hydrogel with looser network structure and higher polymer chain flexibility obtained. The mechanical and rheological properties of the hydrogels can be fine-tuned according to the required applications by changing the polymer concentration and degree of cross-linking [350].

5.1.5. Pectin-based hydrogels for drug delivery

The use of pectin-based hydrogels as a drug delivery system is probably the most common application a soft material in the biomedical research field. Beyond interesting properties associated

Table 2
Colon-specific drug delivery using pectin-based hydrogels.

Hydrogel	Configuration	Loaded drug	Reference
Pectin/zein complex ionically crosslinked by Ca^{2+} ions	Beads	Indomethacin	[433]
Pectin-cysteine conjugate	Beads	Insulin	[434]
Pectin-g-poly(acrylamide)	Film	Salicylic acid	[243]
Pectin/chitosan	Microspheres	Vancomycin	[435]
polyelectrolyte complex			
Pectin-g-poly(vinylpyrrolidone)	Macro gels	Theophylline	[436]
Pectin crosslinked by glutaraldehyde	Microspheres	Resveratrol	[437]
Poly(ethyleneimine)-modified pectin ionically crosslinked by Ca^{2+} ions	Beads	Resveratrol	[438]
Pectin-g-poly(<i>N</i> -isopropylacrylamide)	Macro gels	Theophylline	[439]
Pectin/chitosan ionically crosslinked by Zn^{2+} ions	Microparticles	Resveratrol	[440]
Pectin	Beads	Indomethacin	[441]
methylesterase-modified pectin ionically crosslinked by Ca^{2+} ions			
Pectin/chitosan/gelation polyelectrolyte complex	Film	Bovine serum albumin	[442]
Pectin/carboxymethyl sago pulp dually-crosslinked by Ca^{2+} ions and electron beam irradiation	Beads	Diclofenac sodium	[443]
Amidated pectin/sodium carboxymethyl cellulose ionically crosslinked by $\text{Zn}^{2+}/\text{Al}^{3+}$ ions	Microspheres	Progesterone	[20]
Pectin/chitosan ionically crosslinked by Zn^{2+} ions	Microparticles	Progesterone	[444]

with pectin, it has considerable stability under acidic conditions which makes it a promising candidate for drug delivery systems [351]. Such properties are particularly desirable to target drugs or other compounds to the colon region *via* oral administration. To deliver bioactive compounds in a non-degraded form to the last part of the gastrointestinal tract, these compounds must pass through the stomach, a strong acidic region. The encapsulation of these bioactive compounds into the pectin-based hydrogels aiming colon targeted delivery is a reliable strategy to protect them against degradation in the stomach due to the strong acidic condition or degradation caused by gastric and intestinal enzymes. Moreover, such hydrogels are able to use the biological characteristics of the colon to specifically release the drugs in the digestive tract [352]. Overall, several studies have reported the development of pectin-based hydrogels and their use to target drugs to the colon for systemic action or topical treatment of diseases (colon carcinomas, Crohn's disease, and ulcerative colitis). Table 2 summarizes different pectin-based hydrogels utilized in colon-specific drug delivery.

The release of drug-loaded pectin-based hydrogels can be triggered by different mechanisms (pH, microflora, enzymes, reducing medium, transit time and temperature), which are related to the specific characteristics of the target site [353]. This characteristic can vary according to the site condition (healthy or pathologic). Pectin- Ca^{2+} networks can be easily degraded by colonic pectinolytic enzymes while pectin-g-poly(acrylamide) hydrogels show pH-dependent release behaviour [352]. In the colon, pH varies from 6.4 to 7.0 which lead to the ionization of the carboxyl groups of pectin [352]. The repulsion among the pectin chains due to the negatively charged groups expands the hydrogel network and favours the liquid uptake. Consequently, the drug is released by diffusion out of the hydrogel matrix. A similar strategy has been adopted to control and sustain the release of different drugs in various target

sites. Takei et al. developed an injectable hydrogel based on sugar beet pectin chemically cross-linked with gelatin [354]. The association with gelatin enhanced the *in vivo* biodegradability of such hydrogels as compared to the pure sugar beet pectin hydrogels. Furthermore, gelation time and mechanical properties of the hydrogels were tailored by adjusting the sugar beet pectin/gelatin ratio. The hydrogels were loaded with doxorubicin (Dox), an anticancer drug, and tested on the suppression of tumour growth (B16F1 mouse melanoma model). Dox-loaded hydrogels were more effective in suppression of tumour growth compared to Dox-free ones (as control) [354]. These results are attributed to the controlled release of Dox which can be explained by the disruption of the hydrogel network through hydrolysis of glycosidic linkages and/or peptide linkages of sugar beet pectin and gelatin. Hadebe et al. proposed insulin-loaded hydrogels patches based on amidated pectin [355]. The insulin loading was performed *in situ* during the patches preparation where the loading efficiency varied from 76 to 94%. *In vivo* studies on animal models of type 1 diabetes demonstrated that the animals transdermally treated with the insulin-loaded patches exhibited lower blood glucose levels, whilst short-term treatments restored hepatic and muscle glycogen concentrations. On the other hand, the untreated diabetic animals (control cohort) exhibited hyperglycemia and depleted hepatic and muscle glycogen concentrations. Furthermore, the results suggest that the pectin hydrogel patch enables the sustained and controlled insulin release up to 5-week post-treatment initiation. This delivery device sustains the levels of insulin in the bloodstream of diabetic animals with the concomitant alleviation of some undesirable diabetic symptoms [355]. Dutta et al. designed nanocarriers (~100–200 nm) based on pectin ionically crosslinked by Ca^{2+} ions filled with nanoparticulate magnetite (superparamagnetic iron oxide) and oxaliplatin, a third generation platinum based anti-cancer drug [356]. The magnetite was encapsulated within the pectin- Ca^{2+} network to induce magnetic targeting ability as well as to confine localized areas for sustained drug delivery. These pectin-based nanocarriers exhibited a sustained release of oxaliplatin in phosphate buffer solution maintained at pH 5.5 and 7.4. The drug release profile is driven by both diffusion and swelling mechanisms [356]. The cytotoxicity of these nanocarriers on pancreas cancer cell line (MIA-Pa-Ca-2) revealed that the oxaliplatin-loaded exhibited 10-folds higher cytotoxicity than the equivalent concentration of the free drug [356].

The use of delivery devices based on pectin hydrogels is also a practical strategy to transport hydrophobic drugs through an aqueous medium. The encapsulation of hydrophobic drugs in hydrophilic matrices improves important pharmacological aspects such as solubility, absorption, and bioavailability. Marraz-Marques et al. developed pectin and pectin/agarose hydrogels incorporated with surfactants (Pluronic, Tween and sodium lauryl sulfate) to produce the carriers for tolbutamide. The surfactants may facilitate the inclusion and ulterior control release of this drug. Tolbutamide, a first-generation sulfonylurea oral hypoglycemic agent, presents poor and pH-dependent water solubility and it may show dissolution-related low oral bioavailability [357]. A set of tolbutamide-loaded pectin hydrogels with different formulations was prepared through freeze-drying. This approach allowed to shape pure pectin and blend systems and also generates porous structures that affect the drug release behaviour. The structural modifications are induced by the surfactant agents [357]. Moreover, the surfactant nature and its content within the hydrogel networks allow tailoring the release profile of tolbutamide and reduce its pH-dependent solubility [357].

5.1.6. Plant gum-based hydrogels for drug delivery

Gum-based hydrogels require modification (co-polymerization or cross-linking) to optimize their properties for biomedical applications. Tragacanth gum-based hydrogels indicate high

biocompatibility and cell growth potential. Tragecanth gum-sodium alginate-polyvinyl alcohol hydrogels were able to release moxifloxacin antibiotic with a non-Fickian profile with no sudden release. This can induce initial release following by retained concentration of drug (Hixson-Crowell model for drug release) [53]. Tragcanth gum-poly(vinylpyrrolidone)-poly(acrylic acid) hydrogels have shown pH-dependency and mucoadhesiveness which are critical for localized drug delivery [252,358]. Furthermore, Tragecanth gum-polyvinyl alcohol-polyvinyl pyrrolidone hydrogel has been developed as drug-loaded wound dressing with enhanced mechanical properties and biocompatibility [358]. Sterculia gum-based hydrogels are applicable for drug delivery and wound healing [359]. However, modifiers of 2-hydroxyethylmethacrylate and acrylic acid can improve drug release and swelling kinetics of sterculia gum [360]. Guar gum with high molecular weight galactomannans, backbone of D-mannose residues and pendant of D-galactose residues, can control release of therapeutic molecules in drug delivery systems [360,361]. Guar gum can form bi-gels (high shear rate combining of two gels) with sorbitan monostearate to enhance drug release profile [360]. Furthermore, copolymerization of guar gum with succinate-sodium alginate can induce the pH-dependent swelling and drug release of guar gum have been modified via copolymerization with [362]. Aminated guar gum hydrogel (–OH groups substituted by –NH₂ groups) has been developed as injectable drug delivery platform to prevent side effects of chemotherapeutic agents. This platform, accompanied with imaging reagent in core-shell nanoparticles and doxorubicin hydrochloride, could release the drug in sustainable manner in long-term [363]. For protein-based drug delivery, guar gum hydrogel cross-linked with butanetetracarboxylic dianhydride has been developed and resulted in enhanced release profile [361]. Hydrogel based on guar gum oleate-graft-poly(methacrylic acid) can be considered as a pH-responsive drug delivery system with a mere cytotoxicity in *in vitro* [364]. Indian gum (ghatti gum), non-starch tree-derived polysaccharide, is composed of β-D-GlcA/D-mannose residues as a core with neutral sugar moieties and has demonstrated promising copolymerization potential [365]. Copolymerization of ghatti gum with poly(acrylic acid-aniline) has been developed as a hydrogel platform for drug carriers with the controlled release and pH-responsibility [251].

5.1.7. Plant protein-based hydrogels for drug delivery

The soy and zein based hydrogels are among the most used plant-based protein hydrogels for drug delivery applications [366]. However, soy protein due to the structural balance in their polar and nonpolar groups along with compositional balance in their amino acids and subsequent easily bonding with different drugs has drawn more attentions in drug delivery applications [367]. Additionally, soy protein due to the intrinsic cell attachment properties and network stability in different pHs are a more interesting candidate for targeted controlled drug delivery applications [368,369].

Several properties of hydrogel influence the release behaviour of hydrogels such as morpho-structural properties of hydrogel including pore size, surface area, network formation morphology (filamentous vs. particulate structure), and degree of crosslinking [370]. In the study by Subirade et al. two types of cold-set soy protein hydrogels, either filamentous or particulate were prepared using different concentrations of calcium chloride, and the obtained gels were investigated regarding the controlled release behaviour [371,372]. Per this study due to the lower extent of porosity in the filamentous hydrogels, a delayed release of riboflavin has been attained when compared to the particulate hydrogels. However, at pH of 1.2, both hydrogels had the ability to protect riboflavin for at least 6 h; the release of riboflavin were not influenced by time or concentration, while the gels were digested in the presence of pancreatin at pH 7.5 [371,372]. Hydrogels with micropores,

pore interconnectivity, as well as the high surface area have shown high swelling capacity and fast swelling kinetics more efficient nutraceutical delivery systems compared to conventional hydrogels. However, due to the intricate preparation procedure for porous edible hydrogels and the requirement for adding and leaching the porogen, their applications are limited [373].

The most important parameters for the success of the hydrogel in drug delivery applications are proper mechanical strength and a fast response time to release drugs upon alteration of the environmental pH. Soy proteins hydrogels, in particular, demonstrate pH-responsive characteristic, however, their stability, especially in the neutral and alkaline pHs should be improved [367]. Most of the soy protein hydrogels show the quick release rate at pH of 7, while the release rate at pH 1.2 is very low.

To improve the low mechanical strength and stability and to release profile of soy protein hydrogels, crosslinking of hydrogel have been recommended to achieve the desired stability and release rate of hydrogels [367]. Also, by varying the extent of crosslinking, the swelling of the hydrogels and subsequently the release rate of cargo from the gels could be controlled [374]. Glutaraldehyde crosslinked soy protein hydrogels were developed, and their potential for *in vitro* releasing of the ionic compounds (amaranth and methylene blue) was investigated [321,375]. It has been shown that increasing the extent of crosslinking and the salt concentration during gel preparation led to a decrease in the rate of swelling/release rates regardless of using a digestive enzyme. On the other hand, the release behaviour in this study was extremely dependent on the loaded drug. Amaranth as an anionic molecule had a slow release in gastric conditions, while methylene blue, a cationic drug, showed the higher rate [375]. Genipin crosslinked SPI hydrogel was also reported with the less cytotoxic property than commonly used glutaraldehyde crosslinked SPI hydrogel. In addition, the reported hydrogel has indicated a pH sensitive swelling property as well as sustained release profile of the bovine serum albumin (BSA) in simulated gastrointestinal tract conditions at 37 °C [289].

The composition of soy protein hydrogel with different synthetic polymer networks has also been studied. Polyacrylonitrile-blended soy protein hydrogel fibres with improved swelling/shrinkage properties and dynamic pH responsiveness depending on the soy protein concentrations have been developed [376]. Interpenetrating polymer network (IPN) hydrogels from composed of soy proteins with polyacrylic acid and crosslinked with N,N'-methylene bisacrylamide has also been fabricated with a potential of carrying the bovine serum albumin (BSA) [366]. The developed IPN hydrogels were suitable for colon-specific proteins and peptide delivery applications due to the enhanced release mechanism of the BSA in the low pH of the colon. Recently, Chien et al. developed a biocompatible and injectable soy hydrogel in various concentrations in aqueous solution without using a crosslinker and chemical modifier [290]. The fabricated hydrogels were biocompatible *in vitro* for L929 mouse fibroblasts for one week. The release profile of the model drug, fluorescein, from the hydrogels *in vivo* and *in vitro* indicated a complete, steady, and controlled release over 7 days concordant with the biodegradation of hydrogel.

Although soy proteins hydrogels have been comprehensively studied for their application in drug delivery; other plant-based proteins like zein carrying a different surface charge and various amino acids are recently being attracted for biomedical applications [287,288,315]. Thermo-responsive zein-based hydrogel has been fabricated by assembling amphiphilic triblock of zein molecules into a three-dimensional network in the presence of a hydrophobic nucleation site and a solvent like glycerol. Gel properties were finely tuned by controlling some parameters like temperatures, nuclei hydrophobicity, and solvent polarity. Although no data in regard to the drug release behaviour of

the prepared hydrogel is available, it was hypothesized that the thermo-responsive hydrogels could have a potential for delivery of hydrophobic bioactive elements like drug and nutrient [315]. Zein–sucrose acetate isobutyrate (SAIB) *in situ* gels for carrying a water-soluble glycopeptide drug, pingyangmycin hydrochloride (PYM), have been investigated. This hydrogel showed the capability for release the PYM in 7 days *in vitro* and 4 days *in vivo*. Also, the hydrogel has indicated a significant reduction in the initial burst of PYM. [313].

Furthermore, the complex hydrogels composed of zein and pectin have been fabricated. The obtained hydrogel indicated a less swelling capacity in physiological environments, but able to be hydrolyzed in the presence of pectinases [314]. It has been shown that these hydrogels have the capability to endure protease attack and residence time variation [314]. Therefore, these pH- and enzyme-specific responses promise to develop new innovative delivery systems based on zein–pectin hydrogels for the target delivery of bioactive food ingredients. An overview of type and drug release behaviour of hydrogels developed from different plant-based protein is summarized in Table 3.

5.2. Green hydrogels for tissue engineering

5.2.1. Cellulose-based hydrogels for tissue engineering

The use of cellulose-based hydrogels for tissue engineering has been explored by numerous authors. The main reason for this is the excellent bio- and cyto-compatibility of these materials [377]. Fibroblasts, the most common type of cell found in connective tissue, have been extensively used to test cytocompatibility of cellulose-based hydrogels [377]. It has been shown that cells grow ordered and aligned with cellulose fibres [377]. Moreover, cellulose and their derivatives (especially cellulose nanofibers and nanocrystals) have a highly hydrated three dimensional porous structure that is similar to biological tissue [378,379]. Accordingly, cellulose-based hydrogels are ideal candidates for tissue engineering.

To fabricate 3D scaffolds native cellulose physical gels have been used [75]. Cai et al. developed a cellulose nanofibrils aerogel crosslinked with Kymene (a polyamide-epichlorohydrin resin) and cultured 3T3 NIH cells on it. The aerogel microspheres were biocompatible and non-toxic. Moreover, they facilitated cell attachment, differentiation, and proliferation [380]. Similarly Yang et al. developed injectable carboxymethyl cellulose/dextran hydrogels reinforces with cellulose nanocrystals [381]. These hydrogels showed no cytotoxicity to 3T3 NIH fibroblast. A wide variety of researchers has included cellulose nanofibers and nanocrystals into hydrogels to provide extra mechanical resistance to the materials for tissue engineering [378].

An alternative way of obtaining hydrogels for tissue engineering is by combining cellulose with other molecules that can form gels through electrostatic interactions. The combination of pectin/carboxymethyl cellulose with cations such as Ca^{2+} yields physical hydrogels. This type of hydrogels can be easily lyophilized to obtain scaffolds. Ninan et al. developed and characterized these scaffolds [128]. These composite scaffolds displayed formidable mechanical properties low cytotoxicity.

The combination of inorganic materials with cellulose matrices has shown promising results for tissue engineering. Zadegan et al. developed a cellulose/hydroxyapatite nanocomposite scaffold for bone tissue engineering [382]. The composite presented high porosity ($\geq 85\%$) with pores size ranging from 350 to 500 μm . MTT and alkaline phosphatase activity (ALP) assays showed elevated both biocompatibility and ALP activity in the presence of hydroxyapatite. Furthermore, cellulose hydrogels have been used as injectable systems for tissue engineering applications. Tang et al. developed an injectable chitosan/MC/inorganic salts blend physical hydrogel. This hydrogel as the chondrocytes scaffold showed

improved cell viability and proliferation [383]. Similarly, Vinatiers et al. studied the injectable silanized HPMC physical gel for articular cartilage defect repair [384].

Recently, the development of 3D printing technologies for preparation of cellulose-based hydrogels for tissue engineering purposes has received significant attention [378]. This type of technique offers a high degree of versatility as the hydrogels can be prepared on-demand with different shapes. However, the majority of the obtained hydrogels are physical hydrogels. In order to prepare more resistant and durable cellulose-based hydrogels for tissue engineering the materials should be chemically crosslinked. Accordingly, Shin et al. developed hydrogels by combining cellulose nanofibers and gelatin methacrylamide that can be used for 3D printing applications and subsequently crosslinked to prepare structures with higher mechanical resistance [385]. On the other hand, Markstedt et al. developed hydrogels containing cellulose nanofibers and alginate [386]. This material can be printed directly containing living cells, human chondrocytes. Using a similar combination of biopolymers, Martinez Avila et al. were capable of printing auricular cartilage tissue [387]. Therefore, it can be seen that the uses of cellulose-based hydrogels in tissue engineering are gaining importance due to the recent advantages in 3D bio-printing techniques.

5.2.2. Hemicellulose-based hydrogels for tissue engineering

Reactive functional groups on the hemicellulose chain make it an ideal candidate for enzymatic and chemical modification and synthesis of different modules with a wide range of applications such as cell encapsulation [388–390], artificial skin and wound healing [391]. To improve the mechanical properties of the nano-fibrillated cellulose scaffold (NFC) for wound healing dressing, Liu et al. [392] applied different types of hemicellulose such as xylan and xyloglucan into the NFC structure. The charge density of nanocellulose was the key player in the incorporation of the hemicellulose [393]. The swelling, surface roughness, cell response, and mechanical properties of the films were affected by the nanocellulose charge density. Xyloglucan showed the highest adsorption on the NFC structure which provided the best mechanical properties and highest cell viability. A 90:10 ratio of NFC to xyloglucan, therefore, was suggested as the optimum formulation to develop films for healing applications. In a clinical trial, the application of hemicellulose and rayon dressing were compared for the healing of split-thickness skin graft in 28 patients. Pruritus, the level of the pain, colour, and texture of the graft and hyperemia were not significantly different between the groups treated with either rayon or hemicellulose. Nevertheless, hemicellulose dressing showed more adherence to the wound site [394].

Hemicellulose hydrogel can be designed into nano-fibrous matrices. Among various types of hemicellulose, xylan has ideal characteristics such as immunomodulatory activity and special gelling properties with diverse structure and complexity [395]. Vengopal et al. electrospun scaffolds using a mixture of xylan and polyvinyl alcohol for cardiac tissue engineering [396]. The scaffolds crosslinked with glutaraldehyde provided aligned interconnection between cardiac cells, mimicking the anisotropy, and stiffness of the native heart tissue. The xylan based nano-scaffolds eliminated the need of open heart surgery by directly delivering the nanofibers into the myocardium [396]. The scaffolds could also provide a low resistant structure for the propagation of the electrical signals and enhanced the cardiomyocytes electrical excitation [397,398]. A very recent study by Kundu et al. [399] on the synthesis of carboxymethyl cellulose (CMC) and xylan-based homopolymerized as well as copolymerized hydrogels using an ethylene glycol diglycidyl ether cross-linker in alkaline medium could effectively

Table 3

List of plant based protein hydrogels with their releasing properties.

Type of hydrogel	Properties	Cargo release	Remarks	Refs.
PEG-Soy protein	92–96% swelling, solubility <10%, pH 4; 48%, pH 9	Slower than pure PEG	Swelling and drug release dependent on pH	[423]
Cold set soyprotein hydrogel	7% swelling at pH 1.2, 25 °C, 24 h; 10–12% degraded in pH 1.2; 20–25% degraded in pH 7.5	10–15% in pH 1.2, 40–50% in pH 7.5, 37 °C, 24 h	Can protect riboflavin from gastric conditions and release in intestinal conditions	[371]
Tableted Cold set soyprotein hydrogel	8% swelling at 25 °C; 10% degraded at pH 1.2; 15% degraded at pH 7.5	20% in pH 1.2, 60% in pH 7.5, 37 °C, 24 h	Gels protect from pepsin but are digested by pancreatin at pH 7.5	[372]
Crosslinked soy protein hydrogels	54–74% degraded at pH 1.2; 33–57% degraded at pH 7.5	40–50% at pH 7.5 and <10% at pH 1.2 for methylene blue at 37 °C, 6 h	Suitable to release cationic compounds in stomach and anionic molecules in intestine	[375]
Pectin-zein protein hydrogel	Beads (1.98–2.22 nm) fabricated by changing ratio of pectin and zein, 60–70% encapsulated depending on the drug; no swelling irrespective of pH	4–15% depending on drug and presence of enzymes	Zein suppresses swelling of pectin and beads suitable for colon-specific drug delivery	[314]
Pea protein isolates (PPI) beads	Lower degradation ratio 80.24% ± 2.10 in simulated intestinal fluid (SIF) Swelling capacity in SIF: 29.17 g/g, 6 h, pH = 6.8	Prolonged releasing profile due to the polyelectrolyte complexation (PEC) coating of hydrogel	Hydrogels were less thermally stable than the native proteins; higher swelling and an increase in volume and partial degradation in SIF media	[445]
Canola protein isolates (CPI) beads	Lower degradation ratio 77.09% ± 2.06 in SIF Swelling capacity in SIF: 42.3 g/g, 6 h, pH = 6.8	Prolonged release profile due to the PEC of hydrogel	Hydrogels were less thermally stable than the native proteins; Higher swelling, an increase in volume and partial degradation in SIF	[445]
Guar gum oleate-graft-poly(methacrylic acid) hydrogel (GGO-g-PMAC)	Improved stability and swelling behaviour in the aqueous media Swelling degree of the hydrogel was 5000% (in the basic medium) and 800% (in the acidic medium)	pH-dependent release; 15%, pH = 1.2, 4 h 55%, pH = 7.4, 7 h 95%, pH = 6.8, 30 h	No cytotoxicity of GGO-g-PMAC hydrogel at 10–100 g/mL concentrations against the cultured C3H10T1/2 cell line. Gel was suitable for controlled release of colon-specific hydrophobic drug delivery	[446]
Cold-set whey protein nanofibrils hydrogels	Gelation induced by three types of cation Ca^{2+} , Zn^{2+} , Mn^{2+} In the absence of pepsin, Ca^{2+} and Mn^{2+} induced gels were relatively stable and their degradation value after 2 h, 7.5 and 10%, respectively. A pepsin-free gastric digestion degraded almost 35% of Zn^{2+} induced gel	Suitable for duodenal-targeted delivery	Chitosan coating decreased the simulated gastric degradability of all gel samples	[447]
Canola-poly acrylic acid hydrogel	Good thermal stability and super sorbent behaviour The maximum swelling behaviour in pH 7; minimum swelling behaviour in pH 7	The cargo release has not investigated	A good swelling behaviour confer them as smart materials for controlled and slow delivery of drugs and agricultural products	[448]
Soy lecithin self-assembled emulsion hydrogels	Emulsion hydrogel formed at lecithin conc. 40 w/w%; Amorphous network; Viscoelastic nature; Biocompatible towards HaCaT cells (human keratinocytes)	100% <i>in vitro</i> release of metronidazole at 24 h	The mechanism of drug release was predicted using Kor-smeyer–Peppas model; The drug loaded emulsion gels showed a good antimicrobial activity; Release behaviour of metronidazole from gels was dependent on the composition of gel.	[449]
Heat set whey protein hydrogels reinforced with gellan gum	Enrichment with gellan at 0.5 mg mL ⁻¹ increased 6.4-fold in the hydrogel hardness Swelling behaviour: gellan enriched, 6.45 ± 0.05, pH = 30, 30 h; 9.94 ± 0.09, pH = 7, 30 h Partial hydrogel disintegration Gellan/CaCl ₂ -enriched at pH 3 and 5	Gellan/CaCl ₂ -enriched, ~65% release in pH = 3, 270 min; Gellan (0.5 mg mL ⁻¹)-enriched, ~45% release in pH = 3, 270 min	Caffeine release at pH 3, 5, 7 was better in CaCl ₂ -enriched and gellan/CaCl ₂ -enriched hydrogels; Both gellan and CaCl ₂ enrichments decreased the β-sheet content	[450]

act not only for tissue engineering purposes but also for the localized delivery of small molecules to the defected sites.

5.2.3. Lignin-based hydrogels for tissue engineering

Some studies have reported that the lignin-based hydrogels have unique physic-chemical and biological properties to use for tissue engineering and wound healing applications [400–404]. The main concern about the application of lignin in tissue engineering is its phenolic nature. Organosol lignin has been reported to be cytotoxic for blood mononuclear cells. However, further

studies showed that lignin is not cytotoxic up to moderate concentrations [405]. Quraishi et al. developed alginate/lignin hybrid aerogels as scaffolds for tissue engineering [178]. The results showed that the synthesized alginate/lignin aerogels were non-cytotoxic. Besides, they presented enhanced cell adhesion which makes them proper candidates for an extensive range of applications in tissue engineering/regenerative medicine. Nakasone et al. studied the cytocompatibility of cellulose hydrogels containing a trace amount of lignin [406]. The results indicated that the presence of lignin in the hydrogels could reduce the water content. It can be

said that lignin traces in the hydrogels can potentially strengthen the hydrogels and subsequently increase the biological behaviour [407].

5.2.4. Starch-based hydrogels for tissue engineering

An ideal ECM structure for tissue engineering applications provides suitable physicochemical and mechanical properties which can harbour the cells and promote proliferation, adhesion, and differentiation [408]. The synthetic ECM can be a crosslinked hydrogel consisted of minerals, polysaccharide compounds (glycosaminoglycan), proteins, growth factors, water, and lipid [409]. In a recent study, Nieuwenhove et al. proposed a series of hydrogel films consist of methacrylamide modified gelatin and starch pentenoate for mimicking the ECM structure [410]. The hydrogel mechanical properties could be adjusted by varying the ratio of gelatin to starch. The gelatin/starch hydrogel showed the negative affect on the viability of the stem cells; the hydrogel with the highest degree of crosslinking showed the strongest osteogenic differentiation [411]. Elevated osteogenic differentiation may be associated with increased starch crosslinking and consequently the hydrogel stiffness; however, on compliant hydrogels with less starch crosslinking, the adipogenic differentiation increased. The hydrogel structure was tailored between adipogenic and osteogenic differentiation by changing the gelatin to starch ratio [411].

Starch hydrogels synthesized by free radical polymerization using different acrylic acid concentrations (starch: acrylic acid ratio of 1:15, 1:20, and 1:30), N,N'-methylenebisacrylamide (MBA), and sodium hydroxide showed eco-friendly behaviour and low cytotoxicity to small intestine cells. As shown in Fig. 11, the pore structure of the hydrogel depends on the ratios of starch, acrylic acid, and MBA. 48-h cell culture on 2 mg/L extract of the hydrogel demonstrated 100% viability [412].

5.2.5. Pectin-based hydrogels for tissue engineering

Physicochemical and biological properties of pectin (e.g., immunoregulatory, antibacterial, antitumor, and antioxidant activities and anti-inflammatory and hypoglycemic effects) [413] associated with the 3D structure of hydrogels, which mimics the ECM, results in interesting platforms (such as scaffolds) for tissue engineering applications. Overall, pectin hydrogels share biophysical similarity to soft tissues, while the presence of branched regions of pectin positively stimulates the cells immobilized on these hydrogels to grow and proliferate [414–416]. Despite this, the presence of negatively-charged carboxyl groups in pectin limits the cell adhesion because most cells are also negatively-charged on the surface causing electrostatic repulsion. Moreover, the hydrophilic nature of pectin also impairs cell adhesion by forming a hydration layer on the surface [417]. To overcome this limitation, several elegant strategies have been reported in the literature. Munarin et al. proposed to graft Arg-Gly-Asp (RGD)-containing oligopeptides on the pectin backbone to improve the adhesiveness of polysaccharide [416]. The amino acid sequence of Arg-Gly-Asp plays a key role in cell-cell adhesion/recognition and in cell-ECM interaction [416]. Partially oxidized-pectin hydrogels can be used as an accelerated degradation profile. Microspheres of RGD-pectin and oxidized-pectin were fabricated via ionic gelation with Ca^{2+} ions. Partial oxidation and RGD grafting modulated pectin microspheres degradation as well as biocompatibility [416]. In addition, the use of oxidized-pectin (i.e. with reduced molecular weight) resulted in the formation of a less entangled system improving diffusion of the culture medium, waste product removal, and oxygen exchange and therefore have a positive effect on the viability of the immobilized cells. As assessed, cell migration and growth were positively affected in this potential scaffold material [416]. Further, their attractive biological properties, the use of pectin in tissue engineering have gained attention also due to its useful

ability for homogenous immobilization of cells, genes, proteins, drugs, growth factors, and so on. Amirian et al. fabricated composite scaffolds composed of pectin/gelatin/biphasic calcium phosphate (BCP) by freeze-drying method. Generally, this method produces scaffolds with high porosity with interconnected pores of 100–300 μm . In addition, it was verified that composite scaffold has enhanced mechanical strength as compared to hydrogel formulated just by pectin. Generally, polysaccharide-based hydrogels exhibit weak mechanical properties. *In vitro* assays revealed that BCP entrapped into the pectin-matrix influenced on bone regeneration and the loaded growth factors such as morphogenetic protein-2 and vascular endothelial growth factor were used as model cargos. Both growth factors were released from the hydrogels in a controlled and sustained pattern. The growth factors-loaded hydrogels showed higher cell proliferation rate and enhanced spreading behaviour compared to the bare hydrogel (control) [418]. In a similar study, Nguyen et al. prepared a porous pectin/gelatin scaffolds embedded with BCP nanoparticles for bone tissue engineering. The scaffolds showed highly interconnected porous structures, which facilitated osteoconductivity and enhanced bone matrix formation. The presence of BCP nanoparticles within the pectin/gelatin network improved the mechanical properties and promoted cell adhesion, viability, and proliferation. According to the authors, the interfacial contact between the BCP nanocrystals and pectin/gelatin mixtures induced more rigid and stiffer scaffolds. *In vivo* studies confirmed new bone formation in rabbit models [419]. Indeed, calcium salts can stimulate bone regeneration [420]. In general, calcium salts applied as cement scaffolds show low compressive strength and poor osteogenesis, which restrict its clinical applications. Therefore, the stabilization of these salts into hydrogel matrixes seems to be a promising strategy to overcome such limitation. Zhao et al. proposed forming ionic complexes between pectin and calcium phosphate cement to improve the osteogenic activity and mechanical properties of the hydrogel [421]. Changes in the pectin concentration (2–6 w/w.%) allow tailoring the structure and morphology of the scaffold. According to the authors, this occurs due to the electrostatic interactions between the carboxylate groups of pectin and the Ca^{2+} ions of calcium phosphate. Further improvements attributed to the use of pectin were the enhancement of mechanical properties, high cellular attachment, proliferation, and high osteogenic efficiency. In addition, pre-clinical studies performed in New Zealand on white rabbits using the cavity defect model revealed that the pectin/calcium phosphate cement enables the defect regeneration within 8 weeks [421]. Probably, hydroxyl groups proceeding from pectin would increase the expression of osteogenic genes and matrix mineralization.

The incorporation of organic fillers into pectin hydrogels networks appears to be also a convenient strategy to obtain scaffolds with superior properties. Highly porous 3D scaffolds were developed by Ninan et al. using pectin, carboxymethyl cellulose (CMC), and microfibrillated cellulose [128]. Pectin/CMC/microfibrillated cellulose composite hydrogels with a small pore size (10–250 μm) and high total porosity (~88%) were prepared by the freeze-drying method. Herein, pectin chains were ionically crosslinked by Ca^{2+} ions, resulting in an “egg-box” like structure that enables the immobilization of the cellulosic materials. The presence of microfibrillated cellulose in the pectin hydrogel enables the control of water uptake as well as *in vitro* biodegradation in phosphate buffer solution (PBS, pH of 7.4). As assessed, the hydrophilic nature of pectin associated with its hydrogel and carboxyl groups allow its interaction with CMC and microfibrillated cellulose through hydrogen bonds. Furthermore, these composite scaffolds exhibited the highest cell viability for NIH3T3 fibroblasts cell line [128].

The synthesis of photo-crosslinked pectin hydrogels using cell-degradable peptide crosslinkers and integrin-specific adhesive

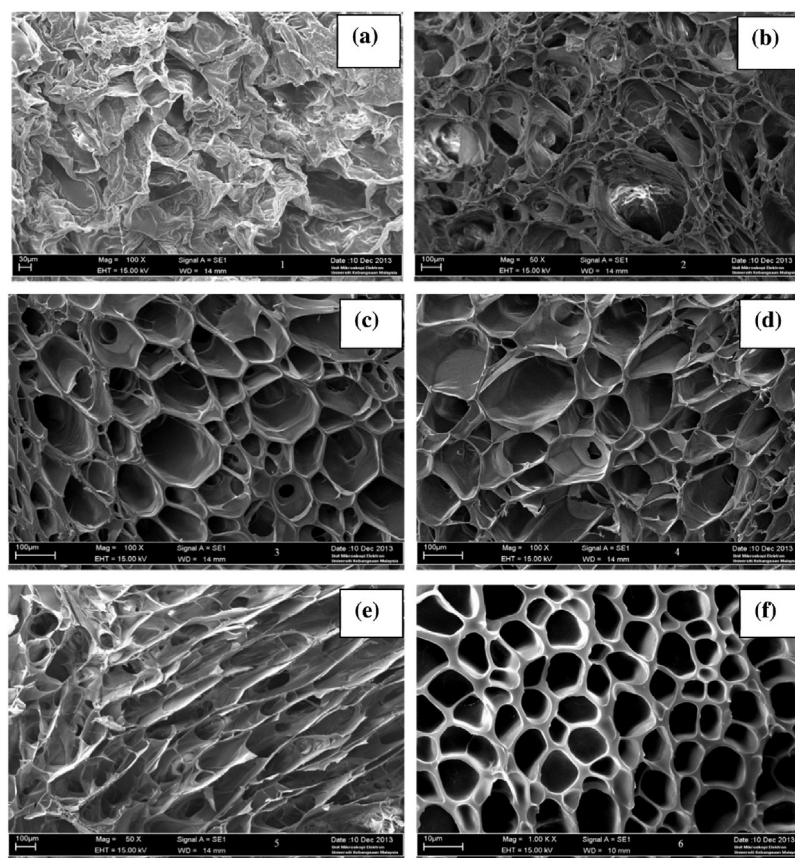


Fig. 11. Micrograph images of hydrogels with varying starch-acrylic acid ratio: (A) 1:15; (B) 1:20; (C) 1:30; (D) 0.02 M MBA; (E) 0.1 M MBA; and (F) 0.2 M MBA. Reproduced with permission from [412].

ligands was reported by Pereira et al. [422]. In summary, norbornene-functionalized pectin was crosslinked by exposure to UV light via thiol-ene click reaction. Hydrogels were rapidly formed in the presence of dermal fibroblasts exhibiting tunable properties and modulating the behaviour of embedded cells (e.g., cell spreading, hydrogel contraction, and secretion of matrix metalloproteases, MMP). By selecting suitable MMP-degradable peptide crosslinkers and pendant cell-adhesive peptides, the biofunctional hydrogels were engineered with varying levels of crosslinking density, resulting in distinct biological responses. Histological analyses revealed that cell-instructive pectin hydrogels supported the *in vitro* formation of full-thickness skin, with a morphological resemblance to the human skin. As clearly demonstrated in Fig. 12, histological analysis showed uniform and elongated dermal fibroblasts and a well-defined epidermal tissue within 14 days [422]. As mentioned by the authors, one relevant advantage of pectin over other bioactive natural polymers relies on the lack of endogenous cell-adhesive and cell-proteolytic sites. This feature allows for the precise introduction of specific biochemical moieties onto the otherwise bioinert pectin backbone in order to control cell fate and to decouple their effect on cell behaviour [422]. Such properties are paramount to design efficient tissue engineering scaffolds.

5.2.6. Plant protein-based hydrogels for tissue engineering

The biomimetic hybrid hydrogels that can mimic the cell adhesion and mechanical properties of tissues have been developed by compositing the soy protein with poly(ethylene glycol) (PEG) for moist wound dressing applications [423]. Soy proteins were contributed by providing tissue-like properties, and PEG was expected

to confer a hydrophilic characteristic to the hydrogels. Depending on the concentration of soy proteins in the composite, the elastic modulus and tensile strength of the hydrogels were modulated. The concentration of PEG influenced the water content of the hydrogels; the hydrogel with a high water content showed low mechanical strength. The hydrogel with better structural integrity, mechanical properties, and therefore with a high potential for wound dressing applications have been obtained by incorporation of ~12% soy protein to the PEG [423].

Chien et al. fabricated mechanically robust and injectable soy protein hydrogel for drug delivery and wound dressing applications [290]. The biocompatibility of these hydrogels was proved by both *in vivo* and *in vitro* studies and their releasing profile and swelling characteristics were controlled upon variation of soy protein contents. The developed hydrogels were injected into the subcutaneous pocket of mice, and histological staining indicated a minimal fibrous capsule formation for up to 20 days which revealed they are promising biomaterial for tissue engineering, particularly for wound healing applications. Also, the studies have shown that the physicochemical properties (injectability and composition) of soybean biomaterials make them interesting for several clinical applications. Namely, the isoflavone content of the soy protein can stimulate the osteoblast to differentiate and secrete collagen as well as calcified bone noduli with inhibiting the activity of monocytes/macrophages and osteoclasts [424]. The injectable soy protein hydrogels were fabricated, and their injectability was regulated by controlling the concentration of ionic and genipin crosslinkers, as well as isoflavone content in soy protein. It has been shown that the synthesized hydrogel could have a stimulatory effect on different soft and hard tissues, for example in the

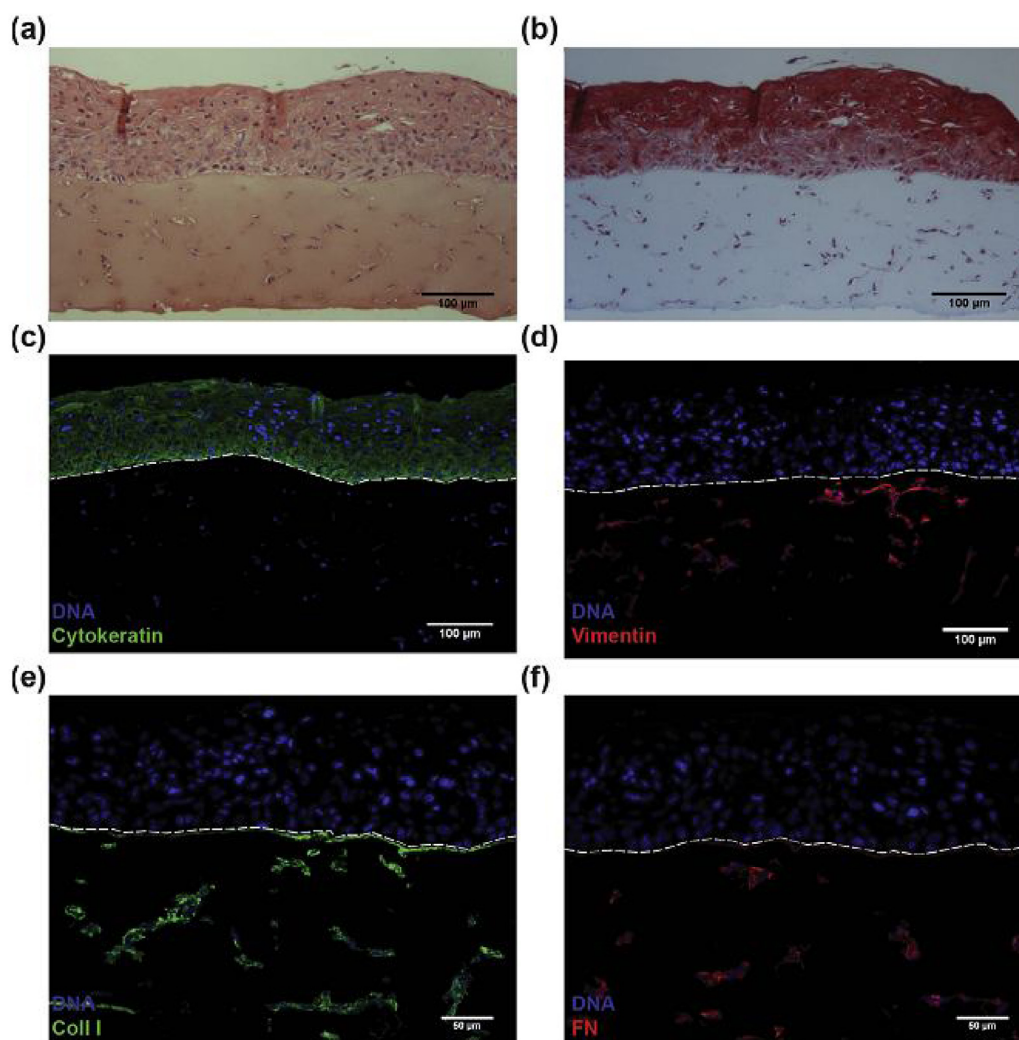


Fig. 12. Histological images of pectin hydrogels after 14 days: (A) haematoxylin & eosin; (B) Masson trichrome staining; immunostaining of tissues for (C) cytokeratin; (D) vimentin; (E) collagen I; and (F) fibronectin.

Reproduced with permission from [422].

synthesis of collagen by fibroblasts and the formation of mineralized bone noduli by osteoblasts through releasing of isoflavones [425].

Lin et al. developed customized scaffolds from thermoresponsive hydrogel bioink obtained by hybridization of polyurethane with soy protein isolate (PU/SPI) and blended by cells and subsequently subjected to 3D printing in a layer by layer deposition manner to form the 3D scaffolds [426]. The PU dispersion was previously prepared using diol (L-lactide diol/D,L-lactide diol and polycaprolactone (PCL) diol) as the soft segment. Such hybrid hydrogel was undergone rapid gelation at 37 °C with high structural integrity. Cell culture inside the hybrid hydrogel was studied for cell viability, metabolism, proliferation, and gene expression of neural-related markers. The improved fibroblast cell survival and growth profile in various time points (0–48 h) for a hybrid PU/SPI were achieved [426]. The rheological properties, structural integrity, and biocompatibility of hybrid hydrogel were adjusted with polymer and soy protein contents. It has been shown that the printability of hybrid hydrogel was enhanced due to the thermoplastic nature of soy protein. The unique properties of soy protein along with its liability to establish different intra- and inter-molecular covalent bonds like disulfide and hydrogen bonds and possible interactions

with PU make this hybrid hydrogel to print as biocompatible 2D, and 3D scaffolds [426].

6. Conclusions and future perspective

In this current review, we demonstrated that plant-based green hydrogels show tremendous potential to be used in the biomedical engineering field. Their attractive eco-friendly properties and ability to mimic the natural tissues are paramount to their wide range of biomedical uses. However, the careful revision of the literature revealed that there are still some challenges in the development and application of these soft-materials. The authors believe that future studies in this field must consider the following themes:

Hydrogel composites: the incorporation of filler materials (inorganic and metallic particles, cellulose nanofibrils and nanocrystals, graphene oxide, carbon nanotubes, and so on) into biopolymer hydrogel matrixes has demonstrated to be an interesting approach to mimic the native properties of load-bearing and electroactive tissues in the body. Considering the biomedical applications, specific properties provided by the fillers (e.g., electrical conductivity) not only increases the electrical conductivity, but also improves the elasticity and biological activity relative to the pure

plant-based green hydrogels. Therefore, we envision that nano-material incorporation within these hydrogels can aid in the design and development of more resilient tissues to generate multifunctional scaffolds with previously unattainable biological, mechanical, and electrical properties.

Optimization of the hydrogels fabrication process: it is consensual that to achieve desired bioactive functions the hydrogels have to mimic the biological system in terms of morphology and chemistry. The architecture of biological systems (e.g., ECM) is hardly reached by hydrogels fabricated by conventional methods (e.g., freeze-drying, bulk, solution, etc.), which requires new fabrication processes. More recently, novel fabrication methods based on 3D printing and electrospinning have help the researchers to achieve desired structures that mimic efficiently the biological systems. Up to now, limited information related to the use of biopolymers to fabricate hydrogels using those techniques. Problems related to stability, processability, and solubility of biopolymers in organic solvents are probably significant obstacles. Moreover, structural limitations remain a major challenge that warrants future research. For sure, further studies in this field should be developed over the next years.

Modification of plant-derived polymers: works focused on the chemical modification of biopolymers structures by including different modifier compounds are also important to promote sufficient cell spreading, proliferation, differentiation and physicochemical properties of the hydrogel. At a molecular level, biopolymers contain several reactive functional groups that can be modified by various molecules with biological potential. In other words, the possibilities related to a specific biopolymer in terms of properties can be amplified with the derivation process. The challenge, in this case, lies in the fact that the intrinsic properties of the neat biopolymer must be preserved after the modification process.

Multifunctionality: currently, plant-based hydrogels only have a single function during application. For example, a hydrogel applied as drug delivery system exhibits only one function; act as a reservoir up to release some encapsulated drug. Of course, the process is more complex than this, but the hydrogels could be designed to exhibit other useful functions (e.g., healing ability or multi-drug releasing ability). In this case, adequate chemical modifications or composite formation may be an alternative to converting the hydrogels in multifunctional biomedical devices.

One-step processes: in many fabrication methods utilized to obtain hydrogels from plant-based polymers the harsh experimental conditions limits or makes impossible the encapsulation of active compounds (drugs, gene or growth factors) or liver cells cannot be into the final device. From a practical and economic viewpoint, this is a relevant drawback since additional procedures are required decreasing the applicability of these devices due to contamination, inefficient cellularization, low loading efficiency, etc.

Degradability: this aspect is particularly important to devices designed to act in tissue engineering or drug delivery because the degradation rate of the hydrogels has straight relation with the tissue regeneration process or drug release rate. The most part of the plant-based polymers has complexes degradation mechanisms that should be elucidated in the future. Beyond the biopolymer structure, other experimental aspects related to the hydrogels such as crosslinking degree or network type can be investigated for controlling the degradation rate. Furthermore, other critical concerns associated with the degradation rate of this type of hydrogels should be addressed from *in vitro* and *in vivo* studies.

Multidisciplinary research interests: as demonstrated in this review, the use of plant-based hydrogels in biomedical and pharmaceutical applications is a pragmatic process since it involves multiple aspects that must be faced by the researchers who venture

into this field of research. We suggest a interdisciplinary dialogue by bringing together experts from different areas (chemistry, physics, materials and biomedical engineering, pharmaceuticals, etc.) in order to look after for the various aspects of these soft-materials as well as their application field. Multidisciplinary researchers with have more chances to notice and understand the entire process and predict the future of the plant-based hydrogels.

Conflicts of interest

Authors hereby confirm that this manuscript has not been published and is not under consideration elsewhere. Authors declare no conflicts of interest.

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References

- [1] B.W. Walker, R.P. Lara, E. Mogadam, C.H. Yu, W. Kimball, N. Annabi, Rational design of microfabricated electroconductive hydrogels for biomedical applications, *Prog. Polym. Sci.* 92 (2019) 135–157.
- [2] L. Bedian, A.M.V. Rodríguez, G.H. Vargas, R. Parra-Saldivar, H.M. Iqbal, Bio-based materials with novel characteristics for tissue engineering applications – a review, *Int. J. Biol. Macromol.* 98 (2017) 837–846.
- [3] M. Farokhi, F. Mottaghtalab, M.A. Shokrgozar, D.L. Kaplan, H.-W. Kim, S.C. Kundu, Prospects of peripheral nerve tissue engineering using nerve guide conduits based on silk fibroin protein and other biopolymers, *Int. Mater. Rev.* 62 (2016) 1–25.
- [4] S.B. Gutekunst, K. Siemsen, S. Huth, A. Möhring, B. Hessler, M. Timmermann, I. Paulowicz, Y.K. Mishra, L. Siebert, R. Adelung, C. Selhuber-Unkel, 3D hydrogels containing interconnected microchannels of subcellular size for capturing human pathogenic *acanthamoeba castellanii*, *ACS Biomater. Sci. Eng.* 5 (2019) 1784–1792.
- [5] R. Langer, J. Vacanti, Advances in tissue engineering, *J. Pediatr. Surg.* 51 (2016) 8–12.
- [6] M. Mecklenburg, A. Schuchardt, Y.K. Mishra, S. Kaps, R. Adelung, A. Lotnyk, L. Kienle, K. Schulte, Aerographite: ultra lightweight, flexible nanowall, carbon microtube material with outstanding mechanical performance, *Adv. Mater.* 24 (2012) 3486–3490.
- [7] Y.K. Mishra, R. Adelung, ZnO tetrapod materials for functional applications, *Mater. Today* 21 (2018) 631–651.
- [8] F. Mottaghtalab, H. Hosseinkhani, M.A. Shokrgozar, C. Mao, M. Yang, M. Farokhi, Silk as a potential candidate for bone tissue engineering, *J. Control. Release* 215 (2015) 112–128.
- [9] A. Nasajpour, S. Ansari, C. Rinoldi, A.S. Rad, T. Aghaloo, S.R. Shin, Y.K. Mishra, R. Adelung, W. Swieszkowski, N. Annabi, A. Khademhosseini, A. Moshaverinia, A. Tamayol, A multifunctional polymeric periodontal membrane with osteogenic and antibacterial characteristics, *Adv. Funct. Mater.* 28 (2018) 1703437.
- [10] A. Nasajpour, S. Mandla, S. Shree, E. Mostafavi, R. Sharifi, A. Khalilpour, S. Saghazadeh, S. Hassan, M.J. Mitchell, J. Leijten, X. Hou, A. Moshaverinia, N. Annabi, R. Adelung, Y.K. Mishra, S.R. Shin, A. Tamayol, A. Khademhosseini, Nanostructured fibrous membranes with rose spike-like architecture, *Nano Lett.* 17 (2017) 6235–6240.
- [11] F. Schütt, S. Signetti, H. Krüger, S. Röder, D. Smazna, S. Kaps, S.N. Gorb, Y.K. Mishra, N.M. Pugno, R. Adelung, Hierarchical self-entangled carbon nanotube networks, *Nat. Commun.* 8 (2017) 1215.
- [12] M. Taale, F. Schütt, T. Carey, J. Marx, Y.K. Mishra, N. Stock, B. Fiedler, F. Torrisi, R. Adelung, C. Selhuber-Unkel, Biomimetic carbon fiber systems engineering: a modular design strategy to generate biofunctional composites from graphene and carbon nanofibers, *ACS Appl. Mater. Interfaces* 11 (2019) 5325–5335.
- [13] M. Taale, F. Schütt, K. Zheng, Y.K. Mishra, A.R. Boccaccini, R. Adelung, C. Selhuber-Unkel, Bioactive carbon-based hybrid 3D scaffolds for osteoblast growth, *ACS Appl. Mater. Interfaces* 10 (2018) 43874–43886.
- [14] Y. Jiang, J. Chen, C. Deng, E.J. Suuronen, Z. Zhong, Click hydrogels, microgels and nanogels: emerging platforms for drug delivery and tissue engineering, *Biomaterials* 35 (2014) 4969–4985.
- [15] L.T. Saldin, M.C. Cramer, S.S. Velankar, L.J. White, S.F. Badylak, Extracellular matrix hydrogels from decellularized tissues: structure and function, *Acta Biomater.* 49 (2016) 1–15.
- [16] M. Farokhi, F. Mottaghtalab, J. Ai, M.A. Shokrgozar, Sustained release of platelet-derived growth factor and vascular endothelial growth factor from

- silk/calcium phosphate/PLGA based nanocomposite scaffold, *Int. J. Pharm.* 454 (2013) 216–225.
- [17] M. Farokhi, F. Mottaghtalab, M.A. Shokrgozar, K.-L. Ou, C. Mao, H. Hosseinkhani, Importance of dual delivery systems for bone tissue engineering, *J. Control. Release* 225 (2016) 152–169.
 - [18] N. Hassani Besheli, F. Mottaghtalab, M. Eslami, M. Gholami, S.C. Kundu, D.L. Kaplan, M. Farokhi, Sustainable release of vancomycin from silk fibroin nanoparticles for treating severe bone infection in rat tibia osteomyelitis model, *ACS Appl. Mater. Interfaces* 9 (2017) 5128–5138.
 - [19] S. Azizi, R. Mohamad, R.A. Rahim, R. Mohammadinejad, A.B. Ariff, Hydrogel beads bio-nanocomposite based on Kappa-Carrageenan and green synthesized silver nanoparticles for biomedical applications, *Int. J. Biol. Macromol.* 104 (2017) 423–431.
 - [20] H.H. Gadalla, I. El-Gibaly, G.M. Soliman, F.A. Mohamed, A.M. El-Sayed, Amidated pectin/sodium carboxymethylcellulose microspheres as a new carrier for colonic drug targeting: development and optimization by factorial design, *Carbohydr. Polym.* 153 (2016) 526–534.
 - [21] E. Poonia, P.K. Mishra, V.K. Poonia, J. Sangwan, R. Kumar, P.K. Rai, R. Malik, V.K. Tomer, R. Ahuja, Y.K. Mishra, Aero-gel based CeO₂ nanoparticles: synthesis, structural properties and detailed humidity sensing response, *J. Mater. Chem. C* 7 (2019) 5477–5487, 1–6.
 - [22] E. Prince, E. Kumacheva, Design and applications of man-made biomimetic fibrillar hydrogels, *Nat. Rev. Mater.* 4 (2019) 99–115.
 - [23] P.K. Sarswat, Y.K. Mishra, M.L. Free, Fabrication and response of alpha-hydroxybutyrate sensors for rapid assessment of cardiometabolic disease risk, *Biosens. Bioelectron.* 89 (2017) 334–342.
 - [24] E.S. Zarie, V. Kaidas, D. Gedamu, Y.K. Mishra, R. Adelung, F.H. Furkert, R. Scherließ, H. Steckel, B. Groessner-Schreiber, Solvent free fabrication of micro and nanostructured drug coatings by thermal evaporation for controlled release and increased effects, *PLoS ONE* 7 (2012) e40746.
 - [25] R. Mohammadinejad, M.A. Moosavi, S. Tavakol, D.Ö. Vardar, A. Hosseini, M. Rahmati, L. Dini, S. Hussain, A. Mandegary, D.J. Klionsky, Necrotic, apoptotic and autophagic cell fates triggered by nanoparticles, *Autophagy* 15 (2019) 4–33.
 - [26] J.E. Gagner, W. Kim, E.L. Chaikof, Designing protein-based biomaterials for biomedical applications, *Acta Biomater.* 10 (2014) 1542–1557.
 - [27] L.S. Nair, C.T. Laurencin, Biodegradable polymers as biomaterials, *Prog. Polym. Sci.* 32 (2007) 762–798.
 - [28] M. Yang, G. Zhou, H. Castano-Izquierdo, Y. Zhu, C. Mao, Biomineralization of natural collagenous nanofibrous membranes and their potential use in bone tissue engineering, *J. Biomed. Nanotechnol.* 11 (2015) 447–456.
 - [29] M. Ajdari, M. Moosavi, M. Rahmati, M. Falahati, M. Mahboubi, A. Mandegary, S. Jangjoo, R. Mohammadinejad, R. Varma, Health concerns of various nanoparticles: a review of their in vitro and in vivo toxicity, *Nanomaterials* 8 (2018) 634.
 - [30] A.E. Nadimi, S.Y. Ebrahimipour, E.G. Afshar, S.K. Falahati-Pour, Z. Ahmadi, R. Mohammadinejad, M. Mohamadi, Nano-scale drug delivery systems for antiarrhythmic agents, *Eur. J. Med. Chem.* 157 (2018) 1153–1163.
 - [31] V.K. Bajpai, I. Park, J. Lee, S. Shukla, S.H. Nile, H.S. Chun, I. Khan, S.Y. Oh, H. Lee, Y.S. Huh, Antioxidant and antimicrobial efficacy of a biflavonoid, amentoflavone from *Nandina domestica* in vitro and in minced chicken meat and apple juice food models, *Food Chem.* 271 (2019) 239–247.
 - [32] D.B. Kovačević, F.J. Barba, D. Granato, C.M. Galanakis, Z. Herceg, V. Dragović-Uzelac, P. Putnik, Pressurized hot water extraction (PHWE) for the green recovery of bioactive compounds and steviol glycosides from *Stevia rebaudiana* Bertoni leaves, *Food Chem.* 254 (2018) 150–157.
 - [33] S. Kumar, A.K. Pandey, Chemistry and biological activities of flavonoids: an overview, *Sci. World J.* (2013) 162750.
 - [34] M.N. Criado, F.J. Barba, A. Frígola, D. Rodrigo, Effect of *Stevia rebaudiana* on oxidative enzyme activity and its correlation with antioxidant capacity and bioactive compounds, *Food Bioprocess Technol.* 7 (2014) 1518–1525.
 - [35] M. Koubaa, E. Rosello-Soto, J. Šić Žlabur, A. Režek Jambrak, M. Brncić, N. Grimi, N. Boussetta, F.J. Barba, Current and new insights in the sustainable and green recovery of nutritionally valuable compounds from *Stevia rebaudiana* Bertoni, *J. Agric. Food Chem.* 63 (2015) 6835–6846.
 - [36] V.K. Bajpai, M.B. Alam, K.T. Quan, M.-K. Ju, R. Majumder, S. Shukla, Y.S. Huh, M. Na, S.H. Lee, Y.-K. Han, Attenuation of inflammatory responses by (+)-syngaresinol via MAP-kinase-mediated suppression of NF-κB signaling in vitro and in vivo, *Sci. Rep.* 8 (2018) 9216.
 - [37] E. Maestri, M. Marmioli, N. Marmioli, Bioactive peptides in plant-derived foodstuffs, *J. Proteomics* 147 (2016) 140–155.
 - [38] S. Painuli, N. Kumar, Prospects in the development of natural radioprotective therapeutics with anti-cancer properties from the plants of Uttarakhand region of India, *J. Ayurveda Integr. Med.* 7 (2016) 62–68.
 - [39] H.S. Saraei, S. Jafarmadar, M. Sayadi, A. Parikhani, J. Kheyrollahi, N. Pourvosoughi, Green fuel production from *Pistacia khinjuk* and its engine test analysis as a promising alternative, *J. Clean. Prod.* 156 (2017) 106–113.
 - [40] R. Sen, M. Chatterjee, Plant derived therapeutics for the treatment of *Leishmaniasis*, *Phytomedicine* 18 (2011) 1056–1069.
 - [41] M.A. Alvarez, Plant Biotechnology for Health: From Secondary Metabolites to Molecular Farming, Springer, 2014.
 - [42] L.N. Joppa, D.L. Roberts, S.L. Pimm, How many species of flowering plants are there? *Proc. R. Soc. Lond. B: Biol. Sci.* 278 (2010), rspb20101004.
 - [43] J.S. Miller, The discovery of medicines from plants: a current biological perspective, *Econ. Bot.* 65 (2011) 396–407.
 - [44] Z. Ahmadi, R. Mohammadinejad, M. Ashrafzadeh, Drug delivery systems for resveratrol, a non-flavonoid polyphenol: emerging evidence in last decades, *J. Drug Deliv. Sci. Technol.* 51 (2019) 591–604.
 - [45] R. Irchhaiya, A. Kumar, A. Yadav, N. Gupta, S. Kumar, N. Gupta, V. Yadav, A. Prakash, H. Gurjar, Metabolites in plants and its classification, *World J. Pharm. Pharm. Sci.* 4 (2015) 287–305.
 - [46] J.N. Kabera, E. Semana, A.R. Mussa, X. He, Plant secondary metabolites: biosynthesis, classification, function and pharmacological properties, *J. Pharm. Pharmacol.* 2 (2014) 377–392.
 - [47] A. Aharoni, G. Galili, Metabolic engineering of the plant primary–secondary metabolism interface, *Curr. Opin. Biotechnol.* 22 (2011) 239–244.
 - [48] M. Ohtani, K. Morisaki, Y. Sawada, R. Sano, A.L.T. Uy, A. Yamamoto, T. Kurata, Y. Nakano, S. Suzuki, M. Matsuda, Primary metabolism during biosynthesis of secondary wall polymers of protoxylem vessel elements, *Plant Physiol.* 172 (2016) 1612–1624.
 - [49] S. Sanchez, A.L. Demain, Metabolic regulation and overproduction of primary metabolites, *Microbial Biotechnol.* 1 (2008) 283–319.
 - [50] B. Haefner, Drugs from the deep: marine natural products as drug candidates, *Drug Discov. Today* 8 (2003) 536–544.
 - [51] R.K. Jha, X. Zi-Rong, Biomedical compounds from marine organisms, *Mar. Drugs* 2 (2004) 123–146.
 - [52] K. Kathiresan, A. Duraisamy, Current issue of microbiology, *ENVIS Cent. Newsl.* 4 (2005) 3–5.
 - [53] B. Singh, L. Varshney, S. Francis, Designing tragacanth gum based sterile hydrogel by radiation method for use in drug delivery and wound dressing applications, *Int. J. Biol. Macromol.* 88 (2016) 586–602.
 - [54] M. Wink, Modes of action of herbal medicines and plant secondary metabolites, *Medicines* 2 (2015) 251–286.
 - [55] Y. Yoshie, W. Wang, Y.-P. Hsieh, T. Suzuki, Compositional difference of phenolic compounds between two seaweeds, *Halimeda* spp., *J.-Tokyo Univ. Fish.* 88 (2002) 21–24.
 - [56] A.H. Gunawardena, J.S. Greenwood, N.G. Dengler, Programmed cell death remodels lace plant leaf shape during development, *Plant Cell* 16 (2004) 60–73.
 - [57] R. Mohammadinejad, Z. Ahmadi, S. Tavakol, M. Ashrafzadeh, Berberine as a potential autophagy modulator, *J. Cell. Physiol.* (2019) 1–13, <http://dx.doi.org/10.1002/jcp.28325>.
 - [58] M. Otani, N. Shitan, K. Sakai, E. Martinoia, F. Sato, K. Yazaki, Characterization of vacuolar transport of the endogenous alkaloid berberine in *Coptis japonica*, *Plant Physiol.* 138 (2005) 1939–1946.
 - [59] R. Wiermann, Secondary plant products and cell and tissue differentiation, *Biochem. Plants* 7 (1981) 85–116.
 - [60] K. Yazaki, Transporters of secondary metabolites, *Curr. Opin. Plant Biol.* 8 (2005) 301–307.
 - [61] S.O. Duke, C.L. Cantrell, K.M. Meepagala, D.E. Wedge, N. Tabanca, K.K. Schrader, Natural toxins for use in pest management, *Toxins* 2 (2010) 1943–1962.
 - [62] A. Gurib-Fakim, Medicinal plants: traditions of yesterday and drugs of tomorrow, *Mol. Aspects Med.* 27 (2006) 1–93.
 - [63] A. Lubbe, R. Verpoorte, Cultivation of medicinal and aromatic plants for specialty industrial materials, *Ind. Crops Prod.* 34 (2011) 785–801.
 - [64] T. Vanhercke, C.C. Wood, S. Stymme, S.P. Singh, A.G. Green, Metabolic engineering of plant oils and waxes for use as industrial feedstocks, *Plant Biotechnol. J.* 11 (2013) 197–210.
 - [65] L. Jones, Mineral components of plant cell walls, *Am. J. Clin. Nutr.* 31 (1978) S94–S98.
 - [66] C. Veeresham, Natural products derived from plants as a source of drugs, *J. Adv. Pharm. Technol. Res.* 3 (2012) 200.
 - [67] G.M. Cragg, D.J. Newman, Natural products: a continuing source of novel drug leads, *Biochim. Biophys. Acta* 1830 (2013) 3670–3695.
 - [68] K.G. Ramawat, J.-M. Mérillon, Bioactive Molecules and Medicinal Plants, Springer, 2008.
 - [69] A.S. Hoffman, Hydrogels for biomedical applications, *Adv. Drug Deliv. Rev.* 64 (2012) 18–23.
 - [70] N.A. Peppas, J.Z. Hilt, A. Khademhosseini, R. Langer, Hydrogels in biology and medicine: from molecular principles to bionanotechnology, *Adv. Mater.* 18 (2006) 1345–1360.
 - [71] E.M. Ahmed, Hydrogel: preparation, characterization, and applications: a review, *J. Adv. Res.* 6 (2015) 105–121.
 - [72] Q. Chai, Y. Jiao, X. Yu, Hydrogels for biomedical applications: their characteristics and the mechanisms behind them, *Gels* 3 (2017) 6.
 - [73] S.B. Ross-Murphy, Physical gelation of biopolymers, *Food Hydrocolloids* 1 (1987) 485–495.
 - [74] N. Reddy, R. Reddy, Q. Jiang, Crosslinking biopolymers for biomedical applications, *Trends Biotechnol.* 33 (2015) 362–369.
 - [75] X. Shen, J.L. Shamshina, P. Berton, G. Gurau, R.D. Rogers, Hydrogels based on cellulose and chitin: fabrication, properties, and applications, *Green Chem.* 18 (2016) 53–75.
 - [76] S.J. Buwalda, T. Vermonden, W.E. Hennink, Hydrogels for therapeutic delivery: current developments and future directions, *Biomacromolecules* 18 (2017) 316–330.
 - [77] S. Utech, A.R. Boccaccini, A review of hydrogel-based composites for biomedical applications: enhancement of hydrogel properties by addition of rigid inorganic fillers, *J. Mater. Sci.* 51 (2016) 271–310.
 - [78] Y.S. Zhang, A. Khademhosseini, Advances in engineering hydrogels, *Science* 356 (2017), eaaf3627.

- [79] C. Chang, L. Zhang, Cellulose-based hydrogels: present status and application prospects, *Carbohydr. Polym.* 84 (2011) 40–53.
- [80] S.J. Eichhorn, R.J. Young, G.R. Davies, Modeling crystal and molecular deformation in regenerated cellulose fibers, *Biomacromolecules* 6 (2005) 507–513.
- [81] J. Schurz, A bright future for cellulose, *Prog. Polym. Sci.* 24 (1999) 481–483.
- [82] A. Sannino, C. Demitri, M. Madaghiele, Biodegradable cellulose-based hydrogels: design and applications, *Materials* 2 (2009) 353–373.
- [83] W.K. Czaja, D.J. Young, M. Kaweck, R.M. Brown, The future prospects of microbial cellulose in biomedical applications, *Biomacromolecules* 8 (2007) 1–12.
- [84] O. Nechyporchuk, M.N. Belgacem, J. Bras, Production of cellulose nanofibrils: a review of recent advances, *Nanocellulose* 93 (2016) 2–25.
- [85] N. Lin, A. Dufresne, Nanocellulose in biomedicine: current status and future prospect, *Eur. Polym. J.* 59 (2014) 302–325.
- [86] A.J. Peñaranda, M. Sabino, Effect of the presence of lignin or peat in IPN hydrogels on the sorption of heavy metals, *Polym. Bull.* 65 (2010) 495–508.
- [87] X. Shen, P. Berton, J.L. Shamsheina, R.D. Rogers, Preparation and comparison of bulk and membrane hydrogels based on Kraft- and ionic-liquid-isolated lignins, *Green Chem.* 18 (2016) 5607–5620.
- [88] S. Stewart, J. Domínguez-Robles, R. Donnelly, E. Larrañeta, Implantable polymeric drug delivery devices: classification, manufacture, materials, and clinical applications, *Polymers* 10 (2018) 1379.
- [89] C. Yu, F. Wang, C. Zha, S. Fu, L.A. Lucia, The synthesis and absorption dynamics of a lignin-based hydrogel for remediation of cationic dye-contaminated effluent, *React. Funct. Polym.* 106 (2016) 137–142.
- [90] A. Sheikhi, T.G. van de Ven, Colloidal aspects of Janus-like hairy cellulose nanocrystallites, *Curr. Opin. Colloid Interface Sci.* (2017).
- [91] T.G. van de Ven, A. Sheikhi, Hairy cellulose nanocrystallites: a novel class of nanocellulose, *Nanoscale* 8 (2016) 15101–15114.
- [92] Y. Habibi, L.A. Lucia, O.J. Rojas, Cellulose nanocrystals: chemistry, self-assembly, and applications, *Chem. Rev.* 110 (2010) 3479–3500.
- [93] H.A. Khalil, Y. Davoudpour, M.N. Islam, A. Mustapha, K. Sudesh, R. Dungani, M. Jawaid, Production and modification of nanofibrillated cellulose using various mechanical processes: a review, *Carbohydr. Polym.* 99 (2014) 649–665.
- [94] D. Klemm, F. Kramer, S. Moritz, T. Lindström, M. Ankerfors, D. Gray, A. Dorris, Nanocelluloses: a new family of nature-based materials, *Angew. Chem. Int. Ed.* 50 (2011) 5438–5466.
- [95] N. Lavoine, I. Desloges, A. Dufresne, J. Bras, Microfibrillated cellulose – its barrier properties and applications in cellulosic materials: a review, *Carbohydr. Polym.* 90 (2012) 735–764.
- [96] R.J. Moon, A. Martini, J. Nairn, J. Simonsen, J. Youngblood, Cellulose nanomaterials review: structure, properties and nanocomposites, *Chem. Soc. Rev.* 40 (2011) 3941–3994.
- [97] A. Sheikhi, J. Hayashi, J. Eichenbaum, M. Gutin, N. Kuntjoro, D. Khorsandi, A. Khademhosseini, Recent advances in nanoengineering cellulose for cargo delivery, *J. Control. Release* 294 (2019) 53–76.
- [98] Y. Nishiyama, P. Langan, H. Chanzy, Crystal structure and hydrogen-bonding system in cellulose I β from synchrotron X-ray and neutron fiber diffraction, *J. Am. Chem. Soc.* 124 (2002) 9074–9082.
- [99] Y. Nishiyama, J. Sugiyama, H. Chanzy, P. Langan, Crystal structure and hydrogen bonding system in cellulose I α from synchrotron X-ray and neutron fiber diffraction, *J. Am. Chem. Soc.* 125 (2003) 14300–14306.
- [100] H. Yang, M.N. Alam, T.G. van de Ven, Highly charged nanocrystalline cellulose and dicarboxylated cellulose from periodate and chlorite oxidized cellulose fibers, *Cellulose* 20 (2013) 1865–1875.
- [101] S. Safari, A. Sheikhi, T.G. van de Ven, Electroacoustic characterization of conventional and electrosterically stabilized nanocrystalline celluloses, *J. Colloid Interface Sci.* 432 (2014) 151–157.
- [102] A. Sheikhi, S. Safari, H. Yang, T.G. van de Ven, Copper removal using electrosterically stabilized nanocrystalline cellulose, *ACS Appl. Mater. Interfaces* 7 (2015) 11301–11308.
- [103] H. Yang, D. Chen, T.G. van de Ven, Preparation and characterization of sterically stabilized nanocrystalline cellulose obtained by periodate oxidation of cellulose fibers, *Cellulose* 22 (2015) 1743–1752.
- [104] H. Yang, A. Tejado, N. Alam, M. Antal, T.G. van de Ven, Films prepared from electrosterically stabilized nanocrystalline cellulose, *Langmuir* 28 (2012) 7834–7842.
- [105] H. Yang, A. Sheikhi, T.G. van de Ven, Reusable green aerogels from cross-linked hairy nanocrystalline cellulose and modified chitosan for dye removal, *Langmuir* 32 (2016) 11771–11779.
- [106] H.P. Fink, P. Weigel, H.J. Purz, J. Ganster, Structure formation of regenerated cellulose materials from NMMO-solutions, *Prog. Polym. Sci.* 26 (2001) 1473–1524.
- [107] H. Zhao, J.H. Kwak, Y. Wang, J.A. Franz, J.M. White, J.E. Holladay, Interactions between cellulose and N-methylmorpholine-N-oxide, *Carbohydr. Polym.* 67 (2007) 97–103.
- [108] W. De Oliveira, W.G. Glasser, Hydrogels from polysaccharides. I. Cellulose beads for chromatographic support, *J. Appl. Polym. Sci.* 60 (1996) 63–73.
- [109] T. Heinze, R. Dicke, A. Koschella, A.H. Kull, E.A. Klor, W. Koch, Effective preparation of cellulose derivatives in a new simple cellulose solvent, *Macromol. Chem. Phys.* 201 (2000) 627–631.
- [110] Å. Östlund, D. Lundberg, L. Nordstierna, K. Holmberg, M. Nydén, Dissolution and gelation of cellulose in TBAF/DMSO solutions: the roles of fluoride ions and water, *Biomacromolecules* 10 (2009) 2401–2407.
- [111] H. Saito, A. Sakurai, M. Sakakibara, H. Saga, Preparation and properties of transparent cellulose hydrogels, *J. Appl. Polym. Sci.* 90 (2003) 3020–3025.
- [112] J. Kadokawa, M. Murakami, Y. Kaneko, A facile preparation of gel materials from a solution of cellulose in ionic liquid, *Carbohydr. Res.* 343 (2008) 769–772.
- [113] R.P. Swatoski, S.K. Spear, J.D. Holbrey, R.D. Rogers, Dissolution of cellulose with ionic liquids, *J. Am. Chem. Soc.* 124 (2002) 4974–4975.
- [114] H. Zhang, J. Wu, J. Zhang, J. He, 1-Allyl-3-methylimidazolium chloride room temperature ionic liquid: a new and powerful nonderivatizing solvent for cellulose, *Macromolecules* 38 (2005) 8272–8277.
- [115] S. Zhu, Y. Wu, Q. Chen, Z. Yu, C. Wang, S. Jin, Y. Ding, G. Wu, Dissolution of cellulose with ionic liquids and its application: a mini-review, *Green Chem.* 8 (2006) 325–327.
- [116] J. Cai, L. Zhang, Unique gelation behavior of cellulose in NaOH/urea aqueous solution, *Biomacromolecules* 7 (2006) 183–189.
- [117] J. Cai, L. Zhang, S. Liu, Y. Liu, X. Xu, X. Chen, B. Chu, X. Guo, J. Xu, H. Cheng, C.C. Han, S. Kuga, Dynamic self-assembly induced rapid dissolution of cellulose at low temperatures, *Macromolecules* 41 (2008) 9345–9351.
- [118] A. Lue, L. Zhang, D. Ruan, Inclusion complex formation of cellulose in NaOH–thiourea aqueous system at low temperature, *Macromol. Chem. Phys.* 208 (2007) 2359–2366.
- [119] S. Liang, L. Zhang, Y. Li, J. Xu, Fabrication and properties of cellulose hydrated membrane with unique structure, *Macromol. Chem. Phys.* 208 (2007) 594–602.
- [120] Y. Mao, J. Zhou, J. Cai, L. Zhang, Effects of coagulants on porous structure of membranes prepared from cellulose in NaOH/urea aqueous solution, *J. Membr. Sci.* 279 (2006) 246–255.
- [121] S.J. Eichhorn, Cellulose nanowhiskers: promising materials for advanced applications, *Soft Matter* 7 (2011) 303–315.
- [122] J. Araki, S. Kuga, Effect of trace electrolyte on liquid crystal type of cellulose microcrystals, *Langmuir* 17 (2001) 4493–4496.
- [123] L. Heath, W. Thielemans, Cellulose nanowhisker aerogels, *Green Chem.* 12 (2010) 1448–1453.
- [124] J.R. Capadona, K. Shanmuganathan, S. Trittschuh, S. Seidel, S.J. Rowan, C. Weder, Polymer nanocomposites with nanowhiskers isolated from microcrystalline cellulose, *Biomacromolecules* 10 (2009) 712–716.
- [125] R.M. Domingues, M. Silva, P. Gershovitch, S. Betta, P. Babo, S.G. Caridade, J.o.F. Mano, A. Motta, R.L. Reis, M.E. Gomes, Development of injectable hyaluronic acid/cellulose nanocrystals bionanocomposite hydrogels for tissue engineering applications, *Bioconjug. Chem.* 26 (2015) 1571–1581.
- [126] L. Li, H. Shan, C.Y. Yue, Y.C. Lam, K.C. Tam, X. Hu, Thermally induced association and dissociation of methylcellulose in aqueous solutions, *Langmuir* 18 (2002) 7291–7298.
- [127] C. Sammon, G. Bajwa, P. Timmins, C.D. Melia, The application of attenuated total reflectance Fourier transform infrared spectroscopy to monitor the concentration and state of water in solutions of a thermally responsive cellulose ether during gelation, *Polymer* 47 (2006) 577–584.
- [128] N. Ninan, M. Muthiah, I.K. Park, A. Elain, S. Thomas, Y. Grohens, Pectin/carboxymethyl cellulose/microfibrillated cellulose composite scaffolds for tissue engineering, *Carbohydr. Polym.* 98 (2013) 877–885.
- [129] G. Yang, L. Zhang, T. Peng, W. Zhong, Effects of Ca²⁺ bridge cross-linking on structure and pervaporation of cellulose/alginate blend membranes, *J. Membr. Sci.* 175 (2000) 53–60.
- [130] E. Larrañeta, S. Stewart, M. Ervine, R. Al-Kasasbeh, R. Donnelly, Hydrogels for hydrophobic drug delivery. Classification, synthesis and applications, *J. Funct. Biomater.* 9 (2018) 13.
- [131] H. Kono, M. Zakimi, Preparation, water absorbency, and enzyme degradability of novel chitin- and cellulose/chitin-based superabsorbent hydrogels, *J. Appl. Polym. Sci.* 128 (2013) 572–581.
- [132] T. Yoshimura, K. Matsuo, R. Fujioka, Novel biodegradable superabsorbent hydrogels derived from cotton cellulose and succinic anhydride: synthesis and characterization, *J. Appl. Polym. Sci.* 99 (2006) 3251–3256.
- [133] C. Chang, B. Duan, L. Zhang, Fabrication and characterization of novel macroporous cellulose–alginate hydrogels, *Polymer* 50 (2009) 5467–5473.
- [134] J. Zhou, C. Chang, R. Zhang, L. Zhang, Hydrogels prepared from unsubstituted cellulose in NaOH/urea aqueous solution, *Macromol. Biosci.* 7 (2007) 804–809.
- [135] R. Rodríguez, C. Alvarez-Lorenzo, A. Concheiro, Cationic cellulose hydrogels: kinetics of the cross-linking process and characterization as pH-/ion-sensitive drug delivery systems, *J. Control. Release* 86 (2003) 253–265.
- [136] X. Lu, Z. Hu, J. Gao, Synthesis and light scattering study of hydroxypropyl cellulose microgels, *Macromolecules* 33 (2000) 8698–8702.
- [137] H. Kono, S. Fujita, Biodegradable superabsorbent hydrogels derived from cellulose by esterification crosslinking with 1,2,3,4-butanetetracarboxylic dianhydride, *Carbohydr. Polym.* 87 (2012) 2582–2588.
- [138] A. Sakakura, K. Kawajiri, T. Ohkubo, Y. Kosugi, K. Ishihara, Widely useful DMAP-catalyzed esterification under auxiliary base- and solvent-free conditions, *J. Am. Chem. Soc.* 129 (2007) 14775–14779.
- [139] A. Sannino, M. Madaghiele, M.G. Lionetto, T. Schettino, A. Maffezzoli, A cellulose-based hydrogel as a potential bulking agent for hypocaloric diets: an in vitro biocompatibility study on rat intestine, *J. Appl. Polym. Sci.* 102 (2006) 1524–1530.
- [140] A. Kimura, N. Nagasawa, M. Taguchi, Cellulose gels produced in room temperature ionic liquids by ionizing radiation, *Radiat. Phys. Chem.* 103 (2014) 216–221.

- [141] L. Zhao, H. Mitomo, F. Yosh, Synthesis of pH-sensitive and biodegradable CM-cellulose/chitosan polyampholytic hydrogels with electron beam irradiation, *J. Bioact. Compat. Polym.* 23 (2008) 319–333.
- [142] P. Petrov, E. Petrova, R. Stamenova, C.B. Tsvetanov, G. Riess, Cryogels of cellulose derivatives prepared by UV irradiation of moderately frozen systems, *Polymer* 47 (2006) 6481–6484.
- [143] B.J. Kong, A. Kim, S.N. Park, Properties and in vitro drug release of hyaluronic acid-hydroxyethyl cellulose hydrogels for transdermal delivery of isoliquiritigenin, *Carbohydr. Polym.* 147 (2016) 473–481.
- [144] S. Napso, D.M. Rein, R. Khalifin, O. Kleinerman, Y. Cohen, Cellulose gel dispersion: from pure hydrogel suspensions to encapsulated oil-in-water emulsions, *Colloids Surf. B: Biointerfaces* 137 (2016) 70–76.
- [145] S.G. Hirsch, R.J. Spontak, Temperature-dependent property development in hydrogels derived from hydroxypropylcellulose, *Polymer* 43 (2002) 123–129.
- [146] S.V. Madhally, H.W.T. Matthew, Porous chitosan scaffolds for tissue engineering, *Biomaterials* 20 (1999) 1133–1142.
- [147] J. Innerlohinger, H.K. Weber, G. Kraft, Aerocellulose: aerogels and aerogel-like materials made from cellulose, *Macromol. Symp.* 244 (2006) 126–135.
- [148] M. He, Y. Zhao, J. Duan, Z. Wang, Y. Chen, L. Zhang, Fast contact of solid–liquid interface created high strength multi-layered cellulose hydrogels with controllable size, *ACS Appl. Mater. Interfaces* 6 (2014) 1872–1878.
- [149] D. Zhao, J. Huang, Y. Zhong, K. Li, L. Zhang, J. Cai, High-strength and high-toughness double-cross-linked cellulose hydrogels: a new strategy using sequential chemical and physical cross-linking, *Adv. Funct. Mater.* 26 (2016) 6279–6287.
- [150] B. Al-Rudainy, M. Galbe, M. Arcos Hernandez, P. Jannasch, O. Wallberg, Impact of lignin content on the properties of hemicellulose hydrogels, *Polymers* 11 (2019) 35.
- [151] L. Maleki, U. Edlund, A.-C. Albertsson, Synthesis of full interpenetrating hemicellulose hydrogel networks, *Carbohydr. Polym.* 170 (2017) 254–263.
- [152] L. Maleki, U. Edlund, A.-C. Albertsson, Unrefined wood hydrolysates are viable reactants for the reproducible synthesis of highly swellable hydrogels, *Carbohydr. Polym.* 108 (2014) 281–290.
- [153] X.F. Sun, Z. Gan, Z. Jing, H. Wang, D. Wang, Y. Jin, Adsorption of methylene blue on hemicellulose-based stimuli-responsive porous hydrogel, *J. Appl. Polym. Sci.* 132 (2015).
- [154] P. Oyarce, B. De Meester, F. Fonseca, L. de Vries, G. Goeminne, A. Pallidis, R. De Rycke, Y. Tsuji, Y. Li, S. Van den Bosch, Introducing curcumin biosynthesis in *Arabidopsis* enhances lignocellulosic biomass processing, *Nat. Plants* 5 (2019) 225.
- [155] V.K. Thakur, M.K. Thakur, R.K. Gupta, Graft copolymers from cellulose: synthesis, characterization and evaluation, *Carbohydr. Polym.* 97 (2013) 18–25.
- [156] R. Vanholme, B. De Meester, J. Ralph, W. Boerjan, Lignin biosynthesis and its integration into metabolism, *Curr. Opin. Biotechnol.* 56 (2019) 230–239.
- [157] S. Laurichesse, L. Avérous, Chemical modification of lignins: towards biobased polymers, *Top. Issue Biomater.* 39 (2014) 1266–1290.
- [158] W.O.S. Doherty, P. Mousavioun, C.M. Fellows, Value-adding to cellulosic ethanol: lignin polymers, *Ind. Crops Prod.* 33 (2011) 259–276.
- [159] R. Sánchez, E. Espinosa, J. Domínguez-Robles, J.M. Loaiza, A. Rodríguez, Isolation and characterization of lignocellulose nanofibers from different wheat straw pulps, *Int. J. Biol. Macromol.* 92 (2016) 1025–1033.
- [160] R. Sánchez, E. Espinosa, J. Domínguez-Robles, J.M. Loaiza, A. Rodríguez, Isolation and characterization of lignocellulose nanofibers from different wheat straw pulps, *Int. J. Biol. Macromol.* 92 (2016) 1025–1033.
- [161] V.K. Thakur, M.K. Thakur, Recent advances in green hydrogels from lignin: a review, *Int. J. Biol. Macromol.* 72 (2015) 834–847.
- [162] H.V. Lee, S.B.A. Hamid, S.K. Zain, Conversion of lignocellulosic biomass to nanocellulose: structure and chemical process, *Sci. World J.* (2014).
- [163] M. Palm, G. Zacchi, Separation of hemicellulosic oligomers from steam-treated spruce wood using gel filtration, *Sep. Purif. Technol.* 36 (2004) 191–201.
- [164] V.K. Thakur, Green Composites from Natural Resources, Taylor & Francis, 2013.
- [165] A. Naseem, S. Tabasum, K.M. Zia, M. Zuber, M. Ali, A. Noreen, Lignin-derivatives based polymers, blends and composites: a review, *Int. J. Biol. Macromol.* 93 (2016) 296–313.
- [166] Q. Tarrés, E. Espinosa, J. Domínguez-Robles, A. Rodríguez, P. Mutjé, M. Delgado-Aguilar, The suitability of banana leaf residue as raw material for the production of high lignin content micro/nano fibers: from residue to value-added products, *Ind. Crops Prod.* 99 (2017) 27–33.
- [167] J. Domínguez-Robles, Q. Tarrés, M. Delgado-Aguilar, A. Rodríguez, F.X. Espinach, P. Mutjé, Approaching a new generation of fiberboards taking advantage of self lignin as green adhesive, *Int. J. Biol. Macromol.* 108 (2018) 927–935.
- [168] J. Domínguez-Robles, M.S. Peresin, T. Tamminen, A. Rodríguez, E. Larrañeta, A.-S. Jääskeläinen, Lignin-based hydrogels with “super-swelling” capacities for dye removal, *Int. J. Biol. Macromol.* 115 (2018) 1249–1259.
- [169] S. Thakur, P.P. Govender, M.A. Mamo, S. Tamulevicius, Y.K. Mishra, V.K. Thakur, Progress in lignin hydrogels and nanocomposites for water purification: future perspectives, *Vacuum* 146 (2017) 342–355.
- [170] X. Wang, Y. Xiong, F.L. Sun, Y.Q. Yang, X.D. Zhang, Ultrasonic-assisted synthesis of a superabsorbent composite hydrogel for the responsive and removal properties of Pb(II), *Acta Phys.-Chim. Sin.* 32 (2016) 2563–2573.
- [171] S. Sathawong, W. Sridach, K.-A. Techato, Lignin: Isolation and preparing the lignin based hydrogel, *J. Environ. Chem. Eng.* 6 (2018) 5879–5888.
- [172] W.K. El-Zawawy, Preparation of hydrogel from green polymer, *Polym. Adv. Technol.* 16 (2005) 48–54.
- [173] B.L. Xue, J.L. Wen, R.C. Sun, Ethanol organosolv lignin as a reactive filler for acrylamide-based hydrogels, *J. Appl. Polym. Sci.* 132 (2015).
- [174] W.K. El-Zawawy, M.M. Ibrahim, Preparation and characterization of novel polymer hydrogel from industrial waste and copolymerization of poly(vinyl alcohol) and polyacrylamide, *J. Appl. Polym. Sci.* 124 (2012) 4362–4370.
- [175] Q. Feng, F. Chen, H. Wu, Preparation and characterization of a temperature-sensitive lignin-based hydrogel, *Bioresources* 6 (2011) 4942–4952.
- [176] Z. Peng, F. Chen, Synthesis and properties of lignin-based polyurethane hydrogels, *Int. J. Polym. Mater.* 60 (2011) 674–683.
- [177] L.I. Grishechko, G. Amaral-Labat, A. Szczurek, V. Fierro, B.N. Kuznetsov, A. Pizzi, A. Celzard, New tannin–lignin aerogels, *Ind. Crops Prod.* 41 (2013) 347–355.
- [178] S. Quraishi, M. Martins, A.A. Barros, P. Gurikov, S.P. Raman, I. Smirnova, A.R.C. Duarte, R.L. Reis, Novel non-cytotoxic alginate–lignin hybrid aerogels as scaffolds for tissue engineering, in: Special Issue of the 14th European Meeting on Supercritical Fluids, vol. 105, 2015, pp. 1–8.
- [179] L. Passauer, M. Struch, S. Schuldt, J. Appelt, Y. Schneider, D. Jaros, H. Rohm, Dynamic moisture sorption characteristics of xerogels from water-swellable oligo(oxyethylene) lignin derivatives, *ACS Appl. Mater. Interfaces* 4 (2012) 5852–5862.
- [180] M.J. de la Torre, A. Moral, M.D. Hernández, E. Cabeza, A. Tijero, Organosolv lignin for biofuel, *Ind. Crops Prod.* 45 (2013) 58–63.
- [181] M. Nishida, Y. Uraki, Y. Sano, Lignin gel with unique swelling property, *Bioresour. Technol.* 88 (2003) 81–83.
- [182] D. Ciolacu, A.M. Oprea, N. Anghel, G. Cazacu, M. Cazacu, New cellulose–lignin hydrogels and their application in controlled release of polyphenols, *Mater. Sci. Eng. C* 32 (2012) 452–463.
- [183] D. Ciolacu, F. Doroftei, G. Cazacu, M. Cazacu, Morphological and surface aspects of cellulose–lignin hydrogels, *Cell. Chem. Technol.* 47 (2013) 377–386.
- [184] I.E. Raschpi, E.G. Hitruc, C. Vasile, Semi-interpenetrating polymer networks containing polysaccharides. II. Xanthan/lignin networks: a spectral and thermal characterization, *High Perform. Polym.* 23 (2011) 219–229.
- [185] I.E. Raschpi, G.E. Hitruc, C. Vasile, M.C. Popescu, Effect of the lignin type on the morphology and thermal properties of the xanthan/lignin hydrogels, *Int. J. Biol. Macromol.* 54 (2013) 230–237.
- [186] H. Yamamoto, M. Amaike, H. Saitoh, Y. Sano, Gel formation of lignin and biodegradation of the lignin gels by microorganisms, *Mater. Sci. Eng. C* 7 (2000) 143–147.
- [187] X.H. Wang, Z.L. Zhou, X.W. Guo, Q. He, C. Hao, C.W. Ge, Ultrasonic-assisted synthesis of sodium lignosulfonate-grafted poly(acrylic acid-co-poly(vinyl pyrrolidone)) hydrogel for drug delivery, *RSC Adv.* 6 (2016) 35550–35558.
- [188] D. Kai, Z.W. Low, S.S. Liow, A. Abdul Karim, H. Ye, G. Jin, K. Li, X.J. Loh, Development of lignin supramolecular hydrogels with mechanically responsive and self-healing properties, *ACS Sustain. Chem. Eng.* 3 (2015) 2160–2169.
- [189] E. Larraneta, M. Imizcoz, J.X. Toh, N.J. Irwin, A. Ripolin, A. Perminova, J. Domínguez-Robles, A. Rodríguez, R.F. Donnelly, Synthesis and characterization of lignin hydrogels for potential applications as drug eluting antimicrobial coatings for medical materials, *ACS Sustain. Chem. Eng.* (2018).
- [190] J. Chen, L. Chen, F. Xie, X. Li, Starch, in: *Drug Delivery Applications of Starch Biopolymer Derivatives*, Springer Singapore, Singapore, 2019, pp. 29–40.
- [191] F. Haq, H. Yu, L. Wang, L. Teng, M. Haroon, R.U. Khan, S. Mehmood, R.S. Ullah, A. Khan, A. Nazir, Advances in chemical modifications of starches and their applications, *Carbohydr. Res.* (2019).
- [192] H. Ismail, M. Irani, Z. Ahmad, Starch-based hydrogels: present status and applications, *Int. J. Polym. Mater. Polym. Biomater.* 62 (2013) 411–420.
- [193] V. Athawale, V. Lele, Graft copolymerization onto starch. II. Grafting of acrylic acid and preparation of it's hydrogels, *Carbohydr. Polym.* 35 (1998) 21–27.
- [194] E.S. Dragan, D.F. Apopei, Synthesis and swelling behavior of pH-sensitive semi-interpenetrating polymer network composite hydrogels based on native and modified potatoes starch as potential sorbent for cationic dyes, *Chem. Eng. J.* 178 (2011) 252–263.
- [195] A. Pourjavadi, A. Harzandi, H. Hosseinzadeh, Modified carrageenan 3, synthesis of a novel polysaccharide-based superabsorbent hydrogel via graft copolymerization of acrylic acid onto kappa-carrageenan in air, *Eur. Polym. J.* 40 (2004) 1363–1370.
- [196] M. Fariña, M.D. Torres, R. Moreira, Starch hydrogels from discarded chestnuts produced under different temperature-time gelatinisation conditions, *Int. J. Food Sci. Technol.* (2019).
- [197] W. Tanan, J. Panichpakdee, S. Saengsuwan, Novel biodegradable hydrogel based on natural polymers: synthesis, characterization, swelling/reswelling and biodegradability, *Eur. Polym. J.* 112 (2019) 678–687.

- [198] A.E.-H. Ali, A. AlArifi, Characterization and in vitro evaluation of starch based hydrogels as carriers for colon specific drug delivery systems, *Carbohydr. Polym.* 78 (2009) 725–730.
- [199] J. Ngoenkam, A. Faikrua, S. Yasothornsrikul, J. Viyoch, Potential of an injectable chitosan/starch/ β -glycerol phosphate hydrogel for sustaining normal chondrocyte function, *Int. J. Pharm.* 391 (2010) 115–124.
- [200] D.N. Sila, S. Van Buggenhout, T. Duvetter, I. Fraeye, A. De Roeck, A. Van Loey, M. Hendrickx, Pectins in processed fruit and vegetables: Part II – structure–function relationships, *Comprehens. Rev. Food Sci. Food Saf.* 8 (2009) 86–104.
- [201] M. Mehrali, A. Thakur, F.B. Kadumudi, M.K. Pierchala, J.A.V. Cordova, M.-A. Shahbazi, M. Mehrali, C.P. Pennisi, G. Orive, A.K. Gaharwar, Pectin methacrylate (PEMA) and gelatin-based hydrogels for cell-delivery: converting waste-materials into biomaterials, *ACS Appl. Mater. Interfaces* (2019).
- [202] B.R. Thakur, R.K. Singh, A.K. Handa, Chemistry and uses of pectin – a review, *Crit. Rev. Food Sci. Nutr.* 37 (1997) 47–73.
- [203] D. Mohnen, Pectin structure and biosynthesis, *Curr. Opin. Plant Biol.* 11 (2008) 266–277.
- [204] F.P.C. Blamey, D.C. Edmeades, D.M. Wheeler, Role of root cation-exchange capacity in differential aluminum tolerance of lotus species, *J. Plant Nutr.* 13 (1990) 729–744.
- [205] S. Seslija, D. Veljovic, M.K. Krusic, J. Stevanovic, S. Velickovic, I. Popovic, Cross-linking of highly methoxylated pectin with copper: the specific anion influence, *New J. Chem.* 40 (2016) 1618–1625.
- [206] C.W. Tibbitts, A.J. MacDougall, S.G. Ring, Calcium binding and swelling behaviour of a high methoxyl pectin gel, *Carbohydr. Res.* 310 (1998) 101–107.
- [207] V. Evageliou, R.K. Richardson, E.R. Morris, Effect of pH, sugar type and thermal annealing on high-methoxy pectin gels, *Carbohydr. Polym.* 42 (2000) 245–259.
- [208] R. Rakhshae, M. Panahandeh, Stabilization of a magnetic nano-adsorbent by extracted pectin to remove methylene blue from aqueous solution: a comparative studying between two kinds of cross-linked pectin, *J. Hazard. Mater.* 189 (2011) 158–166.
- [209] R. Semde, A.J. Moes, M.J. Devleeschouwer, K. Amighi, Synthesis and enzymatic degradation of epichlorohydrin cross-linked pectins, *Drug Dev. Ind. Pharm.* 29 (2003) 203–213.
- [210] T. Yoshimura, K. Sengoku, R. Fujioka, Pectin-based superabsorbent hydrogels crosslinked by some chemicals: synthesis and characterization, *Polym. Bull.* 55 (2005) 123–129.
- [211] S. Hauptstein, F. Hintzen, C. Muller, M. Ohm, A. Bernkop-Schnurch, Development and in vitro evaluation of a buccal drug delivery system based on preactivated thiolated pectin, *Drug Dev. Ind. Pharm.* 40 (2014) 1530–1537.
- [212] C. Alvarez-Lorenzo, B. Blanco-Fernandez, A.M. Puga, A. Concheiro, Crosslinked ionic polysaccharides for stimuli-sensitive drug delivery, *Adv. Drug Deliv. Rev.* 65 (2013) 1148–1171.
- [213] L.S. Liu, J. Kost, F. Yan, R.C. Spiro, Hydrogels from biopolymer hybrid for biomedical, food, and functional food applications, *Polymers* 4 (2012) 997–1011.
- [214] L.C. Lopes, F.F. Simas-Tosin, T.R. Cipriani, L.F. Marchesi, M. Vidotti, I.C. Riegel-Vidotti, Effect of low and high methoxyl citrus pectin on the properties of polypyrrole based electroactive hydrogels, *Carbohydr. Polym.* 155 (2017) 11–18.
- [215] E.F. Lessa, M.S. Gualarte, E.S. Garcia, A.R. Fajardo, Orange waste: a valuable carbohydrate source for the development of beads with enhanced adsorption properties for cationic dyes, *Carbohydr. Polym.* (2016).
- [216] E. Kirtil, M.H. Oztop, A. Sirijariyawat, P. Ngamchuachit, D.M. Barrett, M.J. McCarthy, Effect of pectin methyl esterase (PME) and CaCl_2 infusion on the cell integrity of fresh-cut and frozen-thawed mangoes: an NMR relaxometry study, *Food Res. Int.* 66 (2014) 409–416.
- [217] M. Haghighi, K. Rezaei, General analytical schemes for the characterization of pectin-based edible gelled systems, *Sci. World J.* (2012).
- [218] X.J. Guo, H.Y. Duan, C. Wang, X.S. Huang, Characteristics of two calcium pectinates prepared from citrus pectin using either calcium chloride or calcium hydroxide, *J. Agric. Food Chem.* 62 (2014) 6354–6361.
- [219] H.R. Moreira, F. Munarin, R. Gentilini, L. Visai, P.L. Granja, M.C. Tanzi, P. Petrini, Injectable pectin hydrogels produced by internal gelation: pH dependence of gelling and rheological properties, *Carbohydr. Polym.* 103 (2014) 339–347.
- [220] P. Opanasopit, A. Apirakaramwong, T. Ngawhirunpat, T. Rojanarata, U. Ruktanonchai, Development and characterization of pectinate micro/nanoparticles for gene delivery, *AAPS PharmSciTech* 9 (2008) 67–74.
- [221] O. Chambin, G. Dupuis, D. Champion, A. Voilley, Y. Pourcelot, Colon-specific drug delivery: influence of solution reticulation properties upon pectin beads performance, *Int. J. Pharm.* 321 (2006) 86–93.
- [222] C.A. Garcia-Gonzalez, E. Carenza, M.L. Zeng, I. Smirnova, A. Roig, Design of biocompatible magnetic pectin aerogel monoliths and microspheres, *RSC Adv.* 2 (2012) 9816–9823.
- [223] F.N. Souza, C. Gebara, M.C.E. Ribeiro, K.S. Chaves, M.L. Gigante, C.R.F. Grosso, Production and characterization of microparticles containing pectin and whey proteins, *Food Res. Int.* 49 (2012) 560–566.
- [224] C. Kim, K.S. Park, J. Kim, S.G. Jeong, C.S. Lee, Microfluidic synthesis of monodisperse pectin hydrogel microspheres based on in situ gelation and settling collection, *J. Chem. Technol. Biotechnol.* 92 (2017) 201–209.
- [225] P. Jantrawut, A. Assifaoui, O. Chambin, Influence of low methoxyl pectin gel textures and in vitro release of rutin from calcium pectinate beads, *Carbohydr. Polym.* 97 (2013) 335–342.
- [226] V.B.V. Maciel, C.M.P. Yoshida, T.T. Franco, Chitosan/pectin polyelectrolyte complex as a pH indicator, *Carbohydr. Polym.* 132 (2015) 537–545.
- [227] N.P. Birch, L.E. Barney, E. Pandres, S.R. Peyton, J.D. Schiffman, Thermal-responsive behavior of a cell compatible chitosan/pectin hydrogel, *Biomacromolecules* 16 (2015) 1837–1843.
- [228] B. Hastuti, Mudasir, D. Siswanta, Triyono, The preparation of polyelectrolyte complexes carboxymethyl chitosan (CMC)-pectin by reflux method as a Pb(II) metal ion adsorbent, in: A. Purwanto, A. Nur, F. Rahmawati, E.R. Dyartanti, A. Jumari (Eds.), 6th Nanoscience and Nanotechnology Symposium, vol. 1710, 2016.
- [229] A. Rampino, M. Borgogna, B. Bellich, P. Blasi, F. Virgilio, A. Cesaro, Chitosan-pectin hybrid nanoparticles prepared by coating and blending techniques, *Eur. J. Pharm. Sci.* 84 (2016) 37–45.
- [230] L. Leclercq, M. Boustta, M. Vert, Dynamics of polyelectrolyte complex formation and stability as a polyanion is progressively added to a polycation under modeled physicochemical blood conditions, *J. Bioact. Compat. Polym.* 26 (2011) 301–316.
- [231] P. Bernabe, C. Peniche, W. Arguelles-Monal, Swelling behavior of chitosan/pectin polyelectrolyte complex membranes. Effect of thermal cross-linking, *Polym. Bull.* 55 (2005) 367–375.
- [232] I. Ventura, H. Bianco-Peled, Small-angle X-ray scattering study on pectin-chitosan mixed solutions and thermoreversible gels, *Carbohydr. Polym.* 123 (2015) 122–129.
- [233] D.G. Oakenfull, The Chemistry of High Methoxyl Pectins, Academic Press, San Diego, USA, 1991, pp. 21.
- [234] A. Pourjavadi, S. Barzegar, Synthesis and evaluation of pH and thermosensitive pectin-based superabsorbent hydrogel for oral drug delivery systems, *Starch-Starke* 61 (2009) 161–172.
- [235] S.Y. Chan, W.S. Choo, D.J. Young, X.J. Loh, Thixotropic supramolecular pectin-poly(ethylene glycol) methacrylate (PEGMA) hydrogels, *Polymers* 8 (2016).
- [236] J.F.A. Souto-Maior, A.V. Reis, L.N. Pedreiro, O.A. Cavalcanti, Phosphated crosslinked pectin as a potential excipient for specific drug delivery: preparation and physicochemical characterization, *Polym. Int.* 59 (2010) 127–135.
- [237] J. Chen, W. Liu, C.M. Liu, T. Li, R.H. Liang, S.J. Luo, Pectin modifications: a review, *Crit. Rev. Food Sci. Nutr.* 55 (2015) 1684–1698.
- [238] R.H. Kollarigowda, Novel polysaccharide nanowires; synthesized from pectin-modified methacrylate, *RSC Adv.* 5 (2015) 102143–102146.
- [239] V. Sekkar, K. Narayanaswamy, K.J. Scaria, P.R. Nair, K.S. Sastri, H.G. Ang, Evaluation by various experimental approaches of the crosslink density of urethane networks based on hydroxyl-terminated polybutadiene, *J. Appl. Polym. Sci.* 103 (2007) 3129–3133.
- [240] J. Maior, A.V. Reis, E.C. Muniz, O.A. Cavalcanti, Reaction of pectin and glycidyl methacrylate and ulterior formation of free films by reticulation, *Int. J. Pharm.* 355 (2008) 184–194.
- [241] N. Karaki, A. Aljawish, L. Muniglia, C. Humeau, J. Jasiewicz, Physicochemical characterization of pectin grafted with exogenous phenols, *Food Hydrocolloids* 60 (2016) 486–493.
- [242] R.K. Mishra, A.B.A. Majeed, A.K. Banthia, Synthesis, characterization and material properties of novel poly vinyl acetate grafted pectin, *Int. J. Plastics Technol.* 20 (2016) 79–92.
- [243] P.B. Sutar, R.K. Mishra, K. Pal, A.K. Banthia, Development of pH sensitive polyacrylamide grafted pectin hydrogel for controlled drug delivery system, *J. Mater. Sci.-Mater. Med.* 19 (2008) 2247–2253.
- [244] B. Kazemzadeh, H. Hosseinzadeh, M. Babazadeh, Synthesis of a novel pectin-based superabsorbent hydrogel with salt and pH-responsiveness, *Biomed. Pharmacol. J.* 6 (2013) 41–48.
- [245] M.P.M. da Costa, I.L.D. Ferreira, M.T.D. Cruz, New polyelectrolyte complex from pectin/chitosan and montmorillonite clay, *Carbohydr. Polym.* 146 (2016) 123–130.
- [246] J. Namanga, J. Foba, D.T. Ndiinteh, D.M. Yufanyi, R.W.M. Krause, Synthesis and magnetic properties of a superparamagnetic nanocomposite "pectin-magnetite nanocomposite", *J. Nanomater.* (2013).
- [247] S. Sahu, R.K. Dutta, Novel hybrid nanostructured materials of magnetite nanoparticles and pectin, *J. Magn. Magn. Mater.* 323 (2011) 980–987.
- [248] V. Mami, R. Devasenathipathy, S.M. Chen, S.F. Wang, P. Devi, Y. Tai, Electrodeposition of copper nanoparticles using pectin scaffold at graphene nanosheets for electrochemical sensing of glucose and hydrogen peroxide, *Electrochim. Acta* 176 (2015) 804–810.
- [249] V.V. Padil, S. Wacławek, M. Černík, R.S. Varma, Tree gum-based renewable materials: sustainable applications in nanotechnology, biomedical and environmental fields, *Biotechnol. Adv.* (2018).
- [250] A. Saha, S. Tyagi, R.K. Gupta, Y.K. Tyagi, Natural gums of plant origin as edible coatings for food industry applications, *Crit. Rev. Biotechnol.* (2017) 1–15.
- [251] K. Sharma, V. Kumar, B. Chaudhary, B. Kaith, S. Kalia, H. Swart, Application of biodegradable superabsorbent hydrogel composite based on Gum ghatti-co-poly (acrylic acid-aniline) for controlled drug delivery, *Polym. Degrad. Stab.* 124 (2016) 101–111.
- [252] B. Singh, V. Sharma, Influence of polymer network parameters of tragacanth gum-based pH responsive hydrogels on drug delivery, *Carbohydr. Polym.* 101 (2014) 928–940.

- [253] H. Mirhosseini, B.T. Amid, A review study on chemical composition and molecular structure of newly plant gum exudates and seed gums, *Food Res. Int.* 46 (2012) 387–398.
- [254] D. Pathania, C. Verma, P. Negi, I. Tyagi, M. Asif, N.S. Kumar, E.H. Al-Ghurabi, S. Agarwal, V.K. Gupta, Novel nanohydrogel based on itaconic acid grafted tragacanth gum for controlled release of ampicillin, *Carbohydr. Polym.* 196 (2018) 262–271.
- [255] S. Sharma, S. Afgan, A. Kumar, R. Kumar, L-Alanine induced thermally stable self-healing guar gum hydrogel as potential drug vehicle for sustained release of hydrophilic drug, *Mater. Sci. Eng. C* 99 (2019) 1384–1391.
- [256] P. Sharma, H. Mittal, R. Jindal, D. Jindal, S.M. Alhassan, Sustained delivery of atenolol drug using gum dammar crosslinked polyacrylamide and zirconium based biodegradable hydrogel composites, *Colloids Surf. A: Physicochem. Eng. Asp.* 562 (2019) 136–145.
- [257] B. Laha, R. Goswami, S. Maiti, K.K. Sen, Smart karaya-locust bean gum hydrogel particles for the treatment of hypertension: optimization by factorial design and pre-clinical evaluation, *Carbohydr. Polym.* 210 (2019) 274–288.
- [258] E. Tolba, X. Wang, M. Ackermann, M. Neufurth, R. Muñoz-Espí, H.C. Schröder, W.E. Müller, In situ polyphosphate nanoparticle formation in hybrid poly (vinyl alcohol)/karaya gum hydrogels: a porous scaffold inducing infiltration of mesenchymal stem cells, *Adv. Sci.* 6 (2019) 1801452.
- [259] J.S. Maciel, S. Azevedo, C.R. Correia, A.M. Costa, R.R. Costa, F.A. Magalhães, A.A. de Sousa Monteiro, J.F.G. Costa, R.C.M. de Paula, J.P. Feitosa, Oxidized cashew gum scaffolds for tissue engineering, *Macromol. Mater. Eng.* 304 (2019) 1800574.
- [260] R. Mohammadinejad, A. Shavandi, D.S. Raie, J. Sangeetha, M. Soleimani, S.S. Hajibehzad, D. Thangadurai, R. Hospe, J.O. Popoola, A. Arzani, Plant molecular farming: production of metallic nanoparticles and therapeutic proteins using green factories, *Green Chem.* (2019), <http://dx.doi.org/10.1039/C1039GC00335E>.
- [261] A. Sheikhi, J. de Rutte, R. Haghniaz, O. Akouissi, A. Sohrabi, D. Di Carlo, A. Khademhosseini, Microfluidic-enabled bottom-up hydrogels from annealed naturally-derived protein microbeads, *Biomaterials* 192 (2019) 560–568.
- [262] W. Shi, M.-J. Dumont, E.B. Ly, Synthesis and properties of canola protein-based superabsorbent hydrogels, *Eur. Polym. J.* 54 (2014) 172–180.
- [263] X. Hu, P. Cebe, A.S. Weiss, F. Omenetto, D.L. Kaplan, Protein-based composite materials, *Mater. Today* 15 (2012) 208–215.
- [264] C. Rinoldi, M. Costantini, E. Kijęńska-Gawrońska, S. Testa, E. Fornetti, M. Heljak, M. Ćwiklińska, R. Buda, J. Baldi, S. Cannata, Tendon tissue engineering: effects of mechanical and biochemical stimulation on stem cell alignment on cell-laden hydrogel yarns, *Adv. Healthc. Mater.* 8 (2019) 1801218.
- [265] E.S. Sani, A. Kheirkhah, D. Rana, Z. Sun, W. Foulsham, A. Sheikhi, A. Khademhosseini, R. Dana, N. Annabi, Sutureless repair of corneal injuries using naturally derived bioadhesive hydrogels, *Sci. Adv.* 5 (2019), eaav1281.
- [266] C. Liu, W. Yao, L. Zhang, H. Qian, W. Wu, X. Jiang, Cell-penetrating hollow spheres based on milk protein, *Chem. Commun.* 46 (2010) 7566–7568.
- [267] M. Santin, L. Ambrosio, Soybean-based biomaterials: preparation, properties and tissue regeneration potential, *Expert Rev. Med. Dev.* 5 (2008) 349–358.
- [268] R. Mohammadinejad, S. Karimi, S. Irvani, R.S. Varma, Plant-derived nanostructures: types and applications, *Green Chem.* 18 (2016) 20–52.
- [269] R. Shukla, M. Cheryan, Zein: the industrial protein from corn, *Ind. Crops Prod.* 13 (2001) 171–192.
- [270] J. Keefe, L. Wauk, S. Chu, F. DeLustro, Clinical use of injectable bovine collagen – a decade of experience, *Clin. Mater.* 9 (1992) 155–162.
- [271] L. Cooperman, D. Michaeli, The immunogenicity of injectable collagen. I. A 1-year prospective study, *J. Am. Acad. Dermatol.* 10 (1984) 638–646.
- [272] L. Cooperman, D. Michaeli, P. Alto, S. Francisco, C. Corporation, The immunogenicity of injectable collagen. II. A retrospective review of seventy-two tested and treated patients, *J. Am. Acad. Dermatol.* 10 (1984) 647–651.
- [273] Y.Y. Peng, V. Glattau, J. Ramshaw, J. Werkmeister, Evaluation of the immunogenicity and cell compatibility of avian collagen for biomedical applications, *J. Biomed. Mater. Res. A* 93 (2010) 1235–1244.
- [274] A.O. Elzoghby, W.M. Samy, N.A. Elgindy, Protein-based nanocarriers as promising drug and gene delivery systems, *J. Control. Release* 161 (2012) 38–49.
- [275] V. Urbonaite, H.H.J. de Jongh, E. van der Linden, L. Pouvreau, Origin of water loss from soy protein gels, *J. Agric. Food Chem.* 62 (2014) 7550–7558.
- [276] D. Sağlam, P. Venem, R. de Vries, E. van der Linden, The influence of pH and ionic strength on the swelling of dense protein particles, *Soft Matter* 9 (2013) 4598–4606.
- [277] R.R. Brentin, Soy-based Chemicals and Materials, ACS Publications, 2014.
- [278] R.P. Koshy, S.K. Mary, S. Thomas, L.A. Pothan, Environment friendly green composites based on soy protein isolate – a review, *Food Hydrocolloids* 50 (2015) 174–192.
- [279] C. Liu, H. Wang, Z. Cui, X. He, X. Wang, X. Zeng, H. Ma, Optimization of extraction and isolation for 11S and 7S globulins of soybean seed storage protein, *Food Chem.* 102 (2007) 1310–1316.
- [280] F. Song, D.-L. Tang, X.-L. Wang, Y.-Z. Wang, Biodegradable soy protein isolate-based materials: a review, *Biomacromolecules* 12 (2011) 3369–3380.
- [281] E.M. Ciannamea, P.M. Stefani, R.A. Ruseckaite, Physical and mechanical properties of compression molded and solution casting soybean protein concentrate based films, *Food Hydrocolloids* 38 (2014) 193–204.
- [282] J.F. Hsieh, C.J. Yu, J.Y. Chang, S.T. Chen, H.Y. Tsai, Microbial transglutaminase-induced polymerization of b-conglycinin and glycinin in soymilk: a proteomics approach, *Food Hydrocolloids* 35 (2014) 678–685.
- [283] W.J. Wolf, G.E. Babcock, A.K. Smith, Ultracentrifugal differences in soybean protein composition, *Nature* 191 (1961) 1395–1396.
- [284] V.H. Thanh, K. Shibasaki, Major proteins of soybean seeds. Reconstitution of β -conglycinin from its subunits, *J. Agric. Food Chem.* 26 (1978) 695–698.
- [285] M. Felix, J.E. Martín-Alfonso, A. Romero, A. Guerrero, Development of albumen/soy biobased plastic materials processed by injection molding, *J. Food Eng.* 125 (2014) 7–16.
- [286] R.G. Aswathy, B. Sivakumar, D. Brahatheeswaran, T. Fukuda, Y. Yoshida, T. Maekawa, D.S. Kumar, Biocompatible fluorescent zein nanoparticles for simultaneous bioimaging and drug delivery application, *Adv. Nat. Sci.: Nanosci. Nanotechnol.* 3 (2012), <http://dx.doi.org/10.1088/2043-6262/3/2/025006>.
- [287] R. Palwal, S. Palakurthi, Zein in controlled drug delivery and tissue engineering, *J. Control. Release* 189 (2014) 108–122.
- [288] Y. Luo, Q. Wang, Zein-based micro- and nano-particles for drug and nutrient delivery: a review, *J. Appl. Polym. Sci.* 131 (2014) 1–12.
- [289] F. Song, L.-M. Zhang, Gelation modification of soy protein isolate by a naturally occurring cross-linking agent and its potential biomedical application, *Ind. Eng. Chem. Res.* 48 (2009) 7077–7083.
- [290] K.B. Chien, E.J. Chung, R.N. Shah, Investigation of soy protein hydrogels for biomedical applications: materials characterization, drug release, and biocompatibility, *J. Biomater. Appl.* 28 (2014) 1085–1096.
- [291] T.M. Bikbov, V. Grinberg, H. Schmandke, T.S. Chaika, I.A. Vaintraub, B. Tolstoguzov, A study on gelation of soybean globulin solution, *Colloid. Polym. Sci.* 259 (1981) 536–547.
- [292] C.V. Morr, E.A. Foegeding, Composition and functionality of commercial whey and milk protein concentrates and isolates: a status report, *Food Technol.* 44 (2003) 100–104.
- [293] N. Shen, J. Hu, L. Zhang, L. Zhang, Y. Sun, Y. Xie, S. Wu, L. Liu, Z. Gao, Doxorubicin-loaded zein in situ gel for interstitial chemotherapy of colorectal cancer, *Acta Pharm. Sin. B* 2 (2012) 610–614.
- [294] H. Yuan, J. Xu, E.P. Van Dam, G. Giubertoni, Y.L. Rezus, R. Hammink, H.J. Bakker, Y. Zhan, A.E. Rowan, C. Xing, Strategies to increase the thermal stability of truly biomimetic hydrogels: combining hydrophobicity and directed hydrogen bonding, *Macromolecules* 50 (2017) 9058–9065.
- [295] J. Guo, Y.-C. Jin, X.-Q. Yang, S.-J. Yu, S.-W. Yin, J.-R. Qi, Computed microtomography and mechanical property analysis of soy protein porous hydrogel prepared by homogenizing and microbial transglutaminase cross-linking, *Food Hydrocolloids* 31 (2013) 220–226.
- [296] R. Mercadé-Prieto, H. Zhao, M. Zhang, H. Li, L. Zhao, X.D. Chen, Dissolution and swelling of soy protein isolate hydrogels in alkali, *Food Hydrocolloids* 56 (2016) 285–291.
- [297] J.M.S. Renkema, T. Van Vliet, Heat-induced gel formation by soy proteins at neutral pH, *J. Agric. Food Chem.* 50 (2002) 1569–1573.
- [298] M. Dumoulin, S. Ozawa, R. Hayashi, Textural properties of pressure-induced gels of food proteins obtained under different temperatures including subzero, *J. Food Sci.* 63 (1998) 92–95.
- [299] M.C. Puppo, M.C. Anon, Structural properties of heat-induced soy protein gels as affected by ionic strength and pH, *J. Agric. Food Chem.* 46 (1998) 3583–3589.
- [300] E. Molina, D.A. Ledward, Effects of combined high-pressure and heat treatment on the textural properties of soya gels, *Food Chem.* 80 (2003) 367–370.
- [301] D.-C. Hwang, S. Damodaran, Chemical modification strategies for synthesis of protein-based hydrogel, *J. Agric. Food Chem.* 44 (1996) 751–758.
- [302] S.S. Wong, Chemistry of Protein Conjugation and Cross-linking, CRC Press, Boca Raton, FL, 1991.
- [303] J. Guo, Y. Zhang, X.-Q. Yang, A novel enzyme cross-linked gelation method for preparing food globular protein-based transparent hydrogel, *Food Hydrocolloids* 26 (2012) 277–285.
- [304] K. Seguro, N. Nio, M. Motoki, Some characteristics of a microbial protein cross-linking enzyme: transglutaminase, in: *Macromolecular Interactions in Food Technology*, 1996, pp. 271–280 (Chapter 21).
- [305] M. Jin, Q. Zhong, Transglutaminase cross-linking to enhance elastic properties of soy protein hydrogels with intercalated montmorillonite nanoclay, *J. Food Eng.* 115 (2013) 33–40.
- [306] Y. Zhu, J. Bol, A. Rinze, J. Trammer, G. Wijngaards, Transglutaminase as a potential tool in developing novel protein foods, *Agro Food Ind. Hi-Tech.* 10 (1999) 8–10.
- [307] J. Guo, Q. Zhou, Y.-C. Liu, X.-Q. Yang, J.-M. Wang, S.-W. Yin, J.-R. Qi, Preparation of soy protein-based microgel particles using a hydrogel homogenizing strategy and their interfacial properties, *Food Hydrocolloids* 58 (2016) 324–334.
- [308] K. Nishinari, Y. Fang, S. Guo, G.O. Phillips, Soy proteins: a review on composition, aggregation and emulsification, *Food Hydrocolloids* 39 (2014) 301–318.
- [309] R.S.H. Lam, M.T. Nickerson, Food proteins: a review on their emulsifying properties using a structure–function approach, *Food Chem.* 141 (2013) 975–984.
- [310] M. Jin, S. Ikeda, Q. Zhong, Strengthening soy protein hydrogels filled with protein-coated montmorillonite nanoclay by glutaraldehyde crosslinking, *LWT – Food Sci. Technol.* 51 (2013) 23–29.

- [311] Y. Liua, Y. Cui, Preparation and properties of temperature-sensitive soyprotein/poly(N-isopropylacrylamide) interpenetrating polymer network hydrogels, *Polym. Int.* 60 (2011) 1117–1122.
- [312] X. Cao, J. Geng, S. Su, L. Zhang, Q. Xu, L. Zhang, Y. Xie, S. Wu, Y. Sun, Z. Gao, Doxorubicin-loaded zein in situ gel for interstitial chemotherapy, *Chem. Pharm. Bull.* 60 (2012) 1227–1233.
- [313] Z. Gao, P. Ding, L. Zhang, J. Shi, S. Yuan, J. Wei, D. Chen, Study of a pingyangmycin delivery system: zein/zein-SALB in situ gels, *Int. J. Pharm.* 328 (2007) 57–64.
- [314] L. Liu, M.L. Fishman, K.B. Hicks, M. Kende, G. Ruthel, Pectin/zein beads for potential colon-specific drug delivery: synthesis and in vitro evaluation, *Drug Deliv.* 13 (2006) 417–423.
- [315] A. de Vries, C.V. Nikiforidis, E. Scholten, Natural amphiphilic proteins as tri-block Janus particles: self-sorting into thermo-responsive gels, *Europhys. Lett.* 107 (2014), pp. 58003 P58001–58003 P58006.
- [316] N.A. Peppas, Hydrogels and drug delivery, *Curr. Opin. Colloid Interface Sci.* 2 (1997) 531–537.
- [317] L. Chen, G.E. Remondetto, M. Subirade, Food protein-based materials as nutraceutical delivery systems, *Trends Food Sci. Technol.* 17 (2006) 272–283.
- [318] N. Purdie, Analytical Applications of Circular Dichroism (Techniques and Instrumentation in Analytical Chemistry, 1st ed., Elsevier Science Ltd., 1994.
- [319] N. Matsushima, G. Danno, H. Takezawa, Y. Izumi, Three-dimensional structure of maize alpha-zein proteins studied by small-angle X-ray scattering, *Biochim. Biophys. Acta* 1339 (1997) 14–22.
- [320] J.-J. Hou, J. Guo, J.-M. Wang, X.-T. He, Y. Yuan, S.-W. Yin, X.-Q. Yang, Edible double-network gels based on soy protein and sugar beet pectin with hierarchical microstructure, *Food Hydrocolloids* 50 (2015) 94–101.
- [321] R. Caillard, G.E. Remondetto, M. Subirade, Physicochemical properties and microstructure of soy protein hydrogels co-induced by Maillard type cross-linking and salts, *Food Res. Int.* 42 (2009) 98–106.
- [322] K.J. Edgar, Cellulose esters in drug delivery, *Cellulose* 14 (2007) 49–64.
- [323] Y. Shen, X. Li, Y. Huang, G. Chang, K. Cao, J. Yang, R. Zhang, X. Sheng, X. Ye, pH and redox dual stimuli-responsive injectable hydrogels based on carboxymethyl cellulose derivatives, *Macromol. Res.* 24 (2016) 602–608.
- [324] C. Chang, B. Duan, J. Cai, L. Zhang, Super absorbent hydrogels based on cellulose for smart swelling and controllable delivery, *Eur. Polym. J.* 46 (2010) 92–100.
- [325] Y. Wang, L. Chen, Impacts of nanowhisker on formation kinetics and properties of all-cellulose composite gels, *Carbohydr. Polym.* 83 (2011) 1937–1946.
- [326] H.M. Nizam El-Din, S.G. Abd Alla, A.W.M. El-Naggar, Swelling and drug release properties of acrylamide/carboxymethyl cellulose networks formed by gamma irradiation, *Radiat. Phys. Chem.* 79 (2010) 725–730.
- [327] J.F. Mano, Stimuli-responsive polymeric systems for biomedical applications, *Adv. Eng. Mater.* 10 (2008) 515–527.
- [328] M. Prabakaran, J.F. Mano, Stimuli-responsive hydrogels based on polysaccharides incorporated with thermo-responsive polymers as novel biomaterials, *Macromol. Biosci.* 6 (2006) 991–1008.
- [329] J. Wang, X. Zhou, H. Xiao, Structure and properties of cellulose/poly(N-isopropylacrylamide) hydrogels prepared by SIPN strategy, *Carbohydr. Polym.* 94 (2013) 749–754.
- [330] H. Zhou, H. Zhu, X. Yang, Y. Zhang, X. Zhang, K. Cui, L. Shao, J. Yao, Temperature/pH sensitive cellulose-based hydrogel: synthesis, characterization, loading, and release of model drugs for potential oral drug delivery, *Bioresources* 10 (2014).
- [331] A.K. Bajpai, A. Mishra, Carboxymethyl cellulose (CMC) based semi-IPNs as carriers for controlled release of ciprofloxacin: an in-vitro dynamic study, *J. Mater. Sci. Mater. Med.* 19 (2008) 2121–2130.
- [332] X. Luo, S. Liu, J. Zhou, L. Zhang, In situ synthesis of Fe₃O₄/cellulose microspheres with magnetic-induced protein delivery, *J. Mater. Chem.* 19 (2009) 3538–3545.
- [333] J.D. Kretlow, L. Klouda, A.G. Mikos, Injectable matrices and scaffolds for drug delivery in tissue engineering, *Adv. Drug Deliv. Rev.* 59 (2007) 263–273.
- [334] M.D. Baumann, C.E. Kang, J.C. Stanwick, Y. Wang, H. Kim, Y. Lapitsky, M.S. Shoichet, An injectable drug delivery platform for sustained combination therapy, in: *Sixth International Nanomedicine and Drug Delivery Symposium*, vol. 138, 2009, pp. 205–213.
- [335] A. Ebringerová, T. Heinze, Xylan and xylan derivatives – biopolymers with valuable properties. 1. Naturally occurring xylans structures, isolation procedures and properties, *Macromol. Rapid Commun.* 21 (2000) 542–556.
- [336] V.R. Sinha, R. Kumria, Polysaccharides in colon-specific drug delivery, *Int. J. Pharm.* 224 (2001) 19–38.
- [337] I. Gabrieli, P. Gatenholm, Preparation and properties of hydrogels based on hemicellulose, *J. Appl. Polym. Sci.* 69 (1998) 1661–1667.
- [338] I. Gabrieli, P. Gatenholm, W.G. Glasser, R.K. Jain, L. Kenne, Separation, characterization and hydrogel-formation of hemicellulose from aspen wood, *Carbohydr. Polym.* 43 (2000) 367–374.
- [339] X.F. Sun, H.H. Wang, Z.X. Jing, R. Mohanathas, Hemicellulose-based pH-sensitive and biodegradable hydrogel for controlled drug delivery, *Carbohydr. Polym.* 92 (2013) 1357–1366.
- [340] R.A. Green, R.T. Hassarati, J.A. Goding, S. Baek, N.H. Lovell, P.J. Martens, L.A. Poole-Warren, Conductive hydrogels: mechanically robust hybrids for use as biomaterials, *Macromol. Biosci.* 12 (2012) 494–501.
- [341] W. Zhao, L. Glavas, K. Odelius, U. Edlund, A.-C. Albertsson, Facile and green approach towards electrically conductive hemicellulose hydrogels with tunable conductivity and swelling behavior, *Chem. Mater.* 26 (2014) 4265–4273.
- [342] W. Zhao, K. Odelius, U. Edlund, C. Zhao, A.-C. Albertsson, In situ synthesis of magnetic field-responsive hemicellulose hydrogels for drug delivery, *Biomacromolecules* 16 (2015) 2522–2528.
- [343] Y. Sun, Y. Ma, G. Fang, S. Ren, Y. Fu, Controlled pesticide release from porous composite hydrogels based on lignin and polyacrylic acid, *Bioresources* 11 (2016).
- [344] P. Figueiredo, K. Lintinen, A. Kiriazis, V. Hynninen, Z. Liu, T. Bauleth-Ramos, A. Rahikkala, A. Correia, T. Kohout, B. Sarmiento, In vitro evaluation of biodegradable lignin-based nanoparticles for drug delivery and enhanced antiproliferation effect in cancer cells, *Biomaterials* 121 (2017) 97–108.
- [345] C. Elvira, J.F. Mano, J. San Román, R.L. Reis, Starch-based biodegradable hydrogels with potential biomedical applications as drug delivery systems, *Biomaterials* 23 (2002) 1955–1966.
- [346] C. Liu, X. Gan, Y. Chen, A novel pH-sensitive hydrogels for potential colon-specific drug delivery: characterization and in vitro release studies, *Starch-Stärke* 63 (2011) 503–511.
- [347] A. El-Hag Ali, A. AlArifi, Characterization and in vitro evaluation of starch based hydrogels as carriers for colon specific drug delivery systems, *Carbohydr. Polym.* 78 (2009) 725–730.
- [348] M.R. Guilherme, R.S. Oliveira, M.R. Mauricio, T.S.P. Cellet, G.M. Pereira, M.H. Kunita, E.C. Muniz, A.F. Rubira, Albumin release from a brain-resembling superabsorbent magnetic hydrogel based on starch, *Soft Matter* 8 (2012) 6629–6637.
- [349] H. Hamidian, T. Tavakoli, Preparation of a new Fe₃O₄/starch-g-polyester nanocomposite hydrogel and a study on swelling and drug delivery properties, *Carbohydr. Polym.* 144 (2016) 140–148.
- [350] V.M.d. Oliveira Cardoso, B. Stringhetti Ferreira Cury, R.C. Evangelista, M.P. Daflon Gremião, Development and characterization of cross-linked gellan gum and retrograded starch blend hydrogels for drug delivery applications, *J. Mech. Behav. Biomed. Mater.* 65 (2017) 317–333.
- [351] R.K. Mishra, A.K. Bathia, A.B.A. Majeed, Pectin based formulations for biomedical applications: a review, *Asian J. Pharm. Clin. Res.* 5 (2012) 1–7.
- [352] T.F. Vandamme, A. Lenourry, C. Charrueau, J. Chaumeil, The use of polysaccharides to target drugs to the colon, *Carbohydr. Polym.* 48 (2002) 219–231.
- [353] S.K. Jain, A. Jain, Y. Gupta, M. Ahirwar, Design and development of hydrogel beads for targeted drug delivery to the colon, *AAPS PharmSciTech* 8 (2007) E34–E41.
- [354] T. Takei, K. Sugihara, M. Yoshida, K. Kawakami, Injectable and biodegradable sugar beet pectin/gelatin hydrogels for biomedical applications, *J. Biomater. Sci.-Polym. Ed.* 24 (2013) 1333–1342.
- [355] S.I. Hadebe, P.S. Ngubane, M.R. Serumula, C.T. Musabayane, Transdermal delivery of insulin by amidated pectin hydrogel matrix patch in streptozotocin-induced diabetic rats: effects on some selected metabolic parameters, *PLoS ONE* 9 (2014) e101461.
- [356] R.K. Dutta, S. Sahu, Development of oxalipatin encapsulated in magnetic nanocarriers of pectin as potential target drug delivery for cancer therapy, *Results Pharma Sci.* 2 (2012) 38–45.
- [357] T. Marras-Marquez, J. Pena, M.D. Veiga-Ochoa, Robust and versatile pectin-based drug delivery systems, *Int. J. Pharm.* 479 (2015) 265–276.
- [358] B. Singh, L. Varshney, S. Francis, Synthesis and characterization of tragacanth gum based hydrogels by radiation method for use in wound dressing application, *Radiat. Phys. Chem.* 135 (2017) 94–105.
- [359] A.K. Nayak, D. Pal, Sterculia gum-based hydrogels for drug delivery applications, in: *Polymeric Hydrogels as Smart Biomaterials*, Springer, 2016, pp. 105–151.
- [360] V.K. Singh, I. Banerjee, T. Agarwal, K. Pramanik, M.K. Bhattacharya, K. Pal, Guar gum and sesame oil based novel bigels for controlled drug delivery, *Colloids Surf. B: Biointerfaces* 123 (2014) 582–592.
- [361] H. Kono, F. Otaka, M. Ozaki, Preparation and characterization of guar gum hydrogels as carrier materials for controlled protein drug delivery, *Carbohydr. Polym.* 111 (2014) 830–840.
- [362] D.S. Seeli, S. Dhivya, N. Selvamurugan, M. Prabakaran, Guar gum succinate-sodium alginate beads as a pH-sensitive carrier for colon-specific drug delivery, *Int. J. Biol. Macromol.* 91 (2016) 45–50.
- [363] R. Murali, P. Vidhya, P. Thanikaivelan, Thermoresponsive magnetic nanoparticle-aminated guar gum hydrogel system for sustained release of doxorubicin hydrochloride, *Carbohydr. Polym.* 110 (2014) 440–445.
- [364] D.S. Seeli, M. Prabakaran, Guar gum oleate-graft-poly (methacrylic acid) hydrogel as a colon-specific controlled drug delivery carrier, *Carbohydr. Polym.* 158 (2017) 51–57.
- [365] A.S. Deshmukh, C.M. Setty, A.M. Badiger, K. Muralikrishna, Gum ghatti: a promising polysaccharide for pharmaceutical applications, *Carbohydr. Polym.* 87 (2012) 980–986.
- [366] Y. Liu, Y. Cui, G. Yin, H. Ma, Synthesis, characterization, and drug release behaviour of novel soy protein/poly(acrylic acid) IPN hydrogels, *Iran. Polym. J.* 18 (2009) 339–348.
- [367] N. Reddy, Y. Yang, Potential of plant proteins for medical applications, *Trends Biotechnol.* 29 (2011) 490–498.
- [368] L. Chen, G. Remondetto, M. Rouabhi, M. Subirade, Kinetics of the breakdown of cross-linked soy protein films for drug delivery, *Biomaterials* 29 (2008) 3750–3756.

- [369] W. Lohcharoenkal, L. Wang, Y.C. Chen, Y. Rojanasakul, Protein nanoparticles as drug delivery carriers for cancer therapy, *Biomed. Res. Int.* 2014 (2014) 180549.
- [370] Z.-L. Wan, J. Guo, X.-Q. Yang, Plant protein-based delivery systems for bioactive ingredients in foods, *Food Funct.* 6 (2015) 2876–2889.
- [371] A. Maltais, G.E. Remondetto, M. Subirade, Soy protein cold-set hydrogels as controlled delivery devices for nutraceutical compounds, *Food Hydrocolloids* 23 (2009) 1647–1653.
- [372] A. Maltais, G.E. Remondetto, M. Subirade, Tableted soy protein cold-set hydrogels as carriers of nutraceutical substances, *Food Hydrocolloids* 24 (2010) 518–524.
- [373] J. Guo, Y.C. Jin, X.Q. Yang, S.J. Yu, S.W. Yin, J.R. Qi, Computed microtomography and mechanical property analysis of soy protein porous hydrogel prepared by homogenizing and microbial transglutaminase cross-linking, *Food Hydrocolloids* 31 (2013) 220–226.
- [374] R. Caillard, G.E. Remondetto, M.A. Mateescu, M. Subirade, Characterization of aminocross-linked soy protein hydrogels, *J. Food Sci.* 73 (2008) C283–C291.
- [375] R. Caillard, M.A. Mateescu, M. Subirade, Maillard-type cross-linked soy protein hydrogels as devices for the release of ionic compounds: an in vitro study, *Food Res. Int.* 43 (2010) 2349–2355.
- [376] L. Yu, L. Gu, Hydrolyzed polyacrylonitrile-blend-soy protein hydrogel fibers: a study of structure and dynamic pH response, *Polym. Int.* 58 (2009) 66–73.
- [377] T. Kobayashi, Cellulose hydrogels; fabrication, properties, and their application to biocompatible and tissue engineering, in: *Hydrogels*, Springer, 2018, pp. 297–314.
- [378] H. Du, W. Liu, M. Zhang, C. Si, X. Zhang, B. Li, Cellulose nanocrystals and cellulose nanofibrils based hydrogels for biomedical applications, *Carbohydr. Polym.* 209 (2019) 130–144.
- [379] L.-H. Fu, C. Qi, M.-G. Ma, P. Wan, Multifunctional cellulose-based hydrogels for biomedical applications, *J. Mater. Chem. B* 7 (2019) 1541–1562.
- [380] H.L. Cai, S. Sharma, W.Y. Liu, W. Mu, W. Liu, X.D. Zhang, Y.L. Deng, Aerogel microspheres from natural cellulose nanofibrils and their application as cell culture scaffold, *Biomacromolecules* 15 (2014) 2540–2547.
- [381] X. Yang, E. Bakaic, T. Hoare, E.D. Cranston, Injectable polysaccharide hydrogels reinforced with cellulose nanocrystals: morphology, rheology, degradation, and cytotoxicity, *Biomacromolecules* 14 (2013) 4447–4455.
- [382] S. Zadeegan, M. Hosainilipour, H.R. Rezaie, H. Ghassai, M.A. Shokrgozar, Synthesis and biocompatibility evaluation of cellulose/hydroxyapatite nanocomposite scaffold in 1-n-allyl-3-methylimidazolium chloride, *Mater. Sci. Eng. C* 31 (2011) 954–961.
- [383] Y. Tang, X. Wang, Y. Li, M. Lei, Y. Du, J.F. Kennedy, C.J. Knill, Production and characterisation of novel injectable chitosan/methylcellulose/salt blend hydrogels with potential application as tissue engineering scaffolds, *Carbohydr. Polym.* 82 (2010) 833–841.
- [384] C. Vinatier, O. Gauthier, A. Fatimi, C. Merceron, M. Masson, A. Moreau, F. Moreau, B. Fellah, P. Weiss, J. Guicheux, An injectable cellulose-based hydrogel for the transfer of autologous nasal chondrocytes in articular cartilage defects, *Biotechnol. Bioeng.* 102 (2009) 1259–1267.
- [385] S. Shin, S. Park, M. Park, E. Jeong, K. Na, H.J. Youn, J. Hyun, Cellulose nanofibers for the enhancement of printability of low viscosity gelatin derivatives, *Bioresources* 12 (2017) 2941–2954.
- [386] K. Markstedt, A. Mantas, I. Tournier, H.C. Martínez Ávila, D. Hägg, P. Gatenholm, 3D bioprinting human chondrocytes with nanocellulose–alginate bioink for cartilage tissue engineering applications, *Biomacromolecules* 16 (2015) 1489–1496.
- [387] H.M. Ávila, S. Schwarz, N. Rotter, P. Gatenholm, 3D bioprinting of human chondrocyte-laden nanocellulose hydrogels for patient-specific auricular cartilage regeneration, *Bioprinting* 1 (2016) 22–35.
- [388] B. Balli, M.H. Calimli, E. Kuyuldar, F. Sen, Synthesis, characterization, and applications of hemicellulose based eco-friendly polymer composites, in: *Sustainable Polymer Composites and Nanocomposites*, Springer, 2019, pp. 293–311.
- [389] W. Kong, Q. Dai, C. Gao, J. Ren, C. Liu, R. Sun, Hemicellulose-based hydrogels and their potential application, in: V.K. Thakur, M.K. Thakur (Eds.), *Polymer Gels: Science and Fundamentals*, Springer Singapore, Singapore, 2018, pp. 87–127.
- [390] V. Kuzmenko, D. Hägg, G. Toriz, P. Gatenholm, In situ forming spruce xylan-based hydrogel for cell immobilization, *Carbohydr. Polym.* 102 (2014) 862–868.
- [391] X. Liu, Q. Lin, Y. Yan, F. Peng, R. Sun, J. Ren, Hemicellulose from plant biomass in medical and pharmaceutical application: a critical review, *Curr. Med. Chem.* 24 (2017), 1.
- [392] J. Liu, G. Chinga-Carrasco, F. Cheng, W. Xu, S. Willför, K. Syverud, C. Xu, Hemicellulose-reinforced nanocellulose hydrogels for wound healing application, *Cellulose* 23 (2016) 3129–3143.
- [393] M. Arcari, E. Zuccarella, R. Axelrod, J. Adamcik, A. Sánchez Ferrer, R. Mezzenga, G. Nystrom, Nanostructural properties and twist periodicity of cellulose nanofibrils with variable charge density, *Biomacromolecules* 20 (2019) 1288–1296.
- [394] L.M. Ferreira, L. Blanes, A. Gragnani, D.F. Veiga, F.P. Veiga, G.B. Nery, G.H.H.R. Rocha, H.C. Gomes, M.G. Rocha, R. Okamoto, Hemicellulose dressing versus rayon dressing in the re-epithelialization of split-thickness skin graft donor sites: a multicenter study, *J. Tissue Viability* 18 (2009) 88–94.
- [395] D.S. Naidu, S.P. Hlangothi, M.J. John, Bio-based products from xylan: a review, *Carbohydr. Polym.* 179 (2018) 28–41.
- [396] J. Venugopal, R. Rajeswari, M. Shayanti, R. Sridhar, S. Sundararajan, R. Balamurugan, S. Ramakrishna, Xylan polysaccharides fabricated into nanofibrous substrate for myocardial infarction, *Mater. Sci. Eng. C* 33 (2013) 1325–1331.
- [397] L.D. Black 3rd, J.D. Meyers, J.S. Weinbaum, Y.A. Shvelidze, R.T. Tranquillo, Cell-induced alignment augments twitch force in fibrin gel-based engineered myocardium via gap junction modification, *Tissue Eng. A* 15 (2009) 3099–3108.
- [398] M.P. Prabhakaran, J. Venugopal, D. Kai, S. Ramakrishna, Biomimetic material strategies for cardiac tissue engineering, *Mater. Sci. Eng. C* 31 (2011) 503–513.
- [399] D. Kundu, T. Banerjee, Carboxymethyl cellulose–xylan hydrogel: synthesis, characterization, and in vitro release of vitamin B12, *ACS Omega* 4 (2019) 4793–4803.
- [400] L. Berglund, F. Forsberg, M. Jonoobi, K. Oksman, Promoted hydrogel formation of lignin-containing arabinoxylan aerogel using cellulose nanofibers as a functional biomaterial, *RSC Adv.* 8 (2018) 38219–38228.
- [401] H. Bian, L. Wei, C. Lin, Q. Ma, H. Dai, J. Zhu, Lignin-containing cellulose nanofibril-reinforced polyvinyl alcohol hydrogels, *ACS Sustain. Chem. Eng.* 6 (2018) 4821–4828.
- [402] Y. Chen, K. Zheng, L. Niu, Y. Zhang, Y. Liu, C. Wang, F. Chu, Highly mechanical properties nanocomposite hydrogels with biorenewable lignin nanoparticles, *Int. J. Biol. Macromol.* 128 (2019) 414–420.
- [403] M. Witzler, A. Alzagameem, M. Berge, B.E. Khaldi-Hansen, S.E. Klein, D. Hielscher, B. Kamm, J. Kreyenschmidt, E. Tobiasch, M. Schulze, Lignin-derived biomaterials for drug release and tissue engineering, *Molecules* 23 (2018) 1885.
- [404] D. Zmejkoski, D. Spasojević, I. Orlovsk, N. Kozyrovsk, M. Soković, J. Glamočlija, S. Dmitrović, B. Matović, N. Tasić, V. Maksimović, Bacterial cellulose–lignin composite hydrogel as a promising agent in chronic wound healing, *Int. J. Biol. Macromol.* 118 (2018) 494–503.
- [405] L. Musilová, A. Mráček, A. Kovalčík, P. Smolka, A. Minařík, P. Humpolíček, R. Vícha, P. Ponížil, Hyaluronan hydrogels modified by glycinated Kraft lignin: morphology, swelling, viscoelastic properties and biocompatibility, *Carbohydr. Polym.* 181 (2018) 394–403.
- [406] K. Nakasone, T. Kobayashi, Cytocompatible cellulose hydrogels containing trace lignin, *Mater. Sci. Eng. C* 64 (2016) 269–277.
- [407] Z. Sun, B.I. Fridrich, A. de Santi, S. Elangovan, K. Barta, Bright side of lignin depolymerization: toward new platform chemicals, *Chem. Rev.* 118 (2018) 614–678.
- [408] N.A. Afratis, I. Sagi, Novel approaches for extracellular matrix targeting in disease treatment, in: *The Extracellular Matrix*, Springer, 2019, pp. 261–275.
- [409] Y.S. Kim, M. Majid, A.J. Melchiorri, A.G. Mikos, Applications of decellularized extracellular matrix in bone and cartilage tissue engineering, *Bioeng. Transl. Med.* 4 (2019) 83–95.
- [410] I. Van Nieuwenhove, A. Salamon, K. Peters, G.-J. Graulus, J.C. Martins, D. Frankel, K. Kersemans, F. De Vos, S. Van Vlierberghe, P. Dubruel, Gelatin- and starch-based hydrogels. Part A: Hydrogel development, characterization and coating, *Carbohydr. Polym.* 152 (2016) 129–139.
- [411] I. Van Nieuwenhove, A. Salamon, S. Adam, P. Dubruel, S. Van Vlierberghe, K. Peters, Gelatin- and starch-based hydrogels. Part B: in vitro mesenchymal stem cell behavior on the hydrogels, *Carbohydr. Polym.* 161 (2017) 295–305.
- [412] A. Ashri, N. Amalina, A. Kamil, S. Fazry, M.F. Sairi, M.F. Nazar, A.M. Lazim, Modified dioscorea hispida starch-based hydrogels and their in-vitro cytotoxicity study on small intestine cell line (FHS-74 Int), *Int. J. Biol. Macromol.* 107 (2018) 2412–2421.
- [413] S. Minzanova, V. Mironov, D. Arkhipova, A. Khabibullina, L. Mironova, Y. Zakirova, V. Milyukov, Biological activity and pharmacological application of pectic polysaccharides: a review, *Polymers* 10 (2018) 1407.
- [414] I.L. Kim, R.L. Mauck, J.A. Burdick, Hydrogel design for cartilage tissue engineering: a case study with hyaluronic acid, *Biomaterials* 32 (2011) 8771–8782.
- [415] F. Munarin, S. Guerreiro, M. Grellier, M.C. Tanzi, M. Barbosa, P. Petrini, P. Granja, Pectin-based injectable biomaterials for bone tissue engineering, *Biomacromolecules* 12 (2011) 568–577.
- [416] F. Munarin, P. Petrini, M.C. Tanzi, M.A. Barbosa, P.L. Granja, Biofunctional chemically modified pectin for cell delivery, *Soft Matter* 8 (2012) 4731–4739.
- [417] S. Chen, S. Cui, H. Zhang, X. Pei, J. Hu, Y. Zhou, Y. Liu, Cross-linked pectin nanofibers with enhanced cell adhesion, *Biomacromolecules* 19 (2018) 490–498.
- [418] J. Amirian, N.T.B. Linh, Y.K. Min, B.T. Lee, The effect of BMP-2 and VEGF loading of gelatin–pectin–BCP scaffolds to enhance osteoblast proliferation, *J. Appl. Polym. Sci.* 132 (2015) 41241.
- [419] T.B. Nguyen, Y.K. Min, B.T. Lee, Nanoparticle biphasic calcium phosphate loading on gelatin–pectin scaffold for improved bone regeneration, *Tissue Eng. A* 21 (2015) 1376–1378.
- [420] F. Barrere, C.A. van Blitterswijk, K. de Groot, Bone regeneration: molecular and cellular interactions with calcium phosphate ceramics, *Int. J. Nanomed.* 1 (2006) 317–332.
- [421] L.S. Zhao, J.J. Li, L. Zhang, Y. Wang, J.X. Wang, B. Gu, J.F. Chen, T. Hao, C.Y. Wang, N. Wen, Preparation and characterization of calcium phosphate/pectin scaffolds for bone tissue engineering, *RSC Adv.* 6 (2016) 62071–62082.

- [422] R.F. Pereira, C.C. Barrias, P.J. Bártolo, P.L. Granja, Cell-instructive pectin hydrogels crosslinked via thiol-norbornene photo-click chemistry for skin tissue engineering, *Acta Biomater.* 66 (2018) 282–293.
- [423] R. Snyders, K.I. Shingel, O. Zabeida, C. Roberge, M.-P. Faure, L. Martinu, J.E. Klemberg-Sapieha, Mechanical and microstructural properties of hybrid poly(ethylene glycol)–soy protein hydrogels for wound dressing applications, *J. Biomed. Mater. Res. A* 83 (2007) 88–97.
- [424] M. Santin, L. Nicolais, L. Ambrosio, Soybean-based Biomaterials. Patent International Application, 2002, Vol. CA2456006 A1.
- [425] S.T. Meikle, G. Standen, J. Salvage, R. De Santis, L. Nicolais, L. Ambrosio, M. Santin, Synthesis and characterization of soybean-based hydrogels with an intrinsic activity on cell differentiation, *Tissue Eng. A* 17–18 (2012) 1932–1939.
- [426] H.-H. Lin, F.-Y. Hsieh, C.-S. Tseng, S.-H. Hsu, Preparation and characterization of a biodegradable polyurethane hydrogel and the hybrid gel with soy protein for 3D cell-laden bioprinting, *J. Mater. Chem. B* 4 (2016) 6694–6705.
- [427] V.K. Thakur, M.K. Thakur, Processing and characterization of natural cellulose fibers/thermoset polymer composites, *Carbohydr. Polym.* 109 (2014) 102–117.
- [428] D. Loque, H.V. Scheller, M. Pauly, Engineering of plant cell walls for enhanced biofuel production, *Curr. Opin. Plant Biol.* 25 (2015) 151–161.
- [429] I.M. El-Sherbiny, M.H. Yacoub, Hydrogel scaffolds for tissue engineering: progress and challenges, *Global Cardiol. Sci. Pract.* (2013) 38.
- [430] S. Laurichesse, L. Avérous, Chemical modification of lignins: towards biobased polymers, *Prog. Polym. Sci.* 39 (2014) 1266–1290.
- [431] J.F.A.S. Maior, A.V. Reis, E.C. Muniz, O.A. Cavalcanti, Reaction of pectin and glycidyl methacrylate and ulterior formation of free films by reticulation, *Int. J. Pharm.* 355 (2008) 184–194.
- [432] L.S. Liu, M.L. Fishman, K.B. Hicks, M. Kende, G. Ruthel, Pectin/zein beads for potential colon-specific drug delivery: synthesis and in vitro evaluation, *Drug Deliv.* 13 (2006) 417–423.
- [433] S. Majzoob, F. Atyabi, F. Dorkoosh, K. Kafedjiiski, B. Loretz, A. Bernkop-Schnurch, Pectin-cysteine conjugate: synthesis and in-vitro evaluation of its potential for drug delivery, *J. Pharm. Pharmacol.* 58 (2006) 1601–1610.
- [434] F. Bigucci, B. Luppi, L. Monaco, T. Cerchiara, V. Zecchi, Pectin-based microspheres for colon-specific delivery of vancomycin, *J. Pharm. Pharmacol.* 61 (2009) 41–46.
- [435] M.M. Fares, S.M. Assaf, Y.M. Abul-Haija, Pectin grafted poly(N-vinylpyrrolidone): optimization and in vitro controllable theophylline drug release, *J. Appl. Polym. Sci.* 117 (2010) 1945–1954.
- [436] S. Das, K.Y. Ng, Impact of glutaraldehyde on in vivo colon-specific release of resveratrol from biodegradable pectin-based formulation, *J. Pharm. Sci.* 99 (2010) 4903–4916.
- [437] S. Das, A. Chaudhury, K.Y. Ng, Polyethyleneimine-modified pectin beads for colon-specific drug delivery: In vitro and in vivo implications, *J. Microencapsul.* 28 (2011) 268–279.
- [438] S.M. Assaf, Y.M. Abul-Haija, M.M. Fares, Versatile pectin grafted poly(N-isopropylacrylamide): modulated targeted drug release, *J. Macromol. Sci. A-Pure Appl. Chem.* 48 (2011) 493–502.
- [439] S. Das, A. Chaudhury, K.Y. Ng, Preparation and evaluation of zinc-pectin-chitosan composite particles for drug delivery to the colon: role of chitosan in modifying in vitro and in vivo drug release, *Int. J. Pharm.* 406 (2011) 11–20.
- [440] J.Y. Jung, R.D. Arnold, L. Wicker, Pectin and charge modified pectin hydrogel beads as a colon-targeted drug delivery carrier, *Colloids Surf. B-Biointerfaces* 104 (2013) 116–121.
- [441] X.F. Zheng, Q. Lian, S.T. Song, Chitosan-gelatin-pectin composite films from polyion-complex hydrogels, *Asian J. Chem.* 25 (2013) 5363–5366.
- [442] H.L. Tan, L.S. Tan, Y.Y. Wong, S. Muniyandy, K. Hashim, J. Pushpamalar, Dual crosslinked carboxymethyl sago pulp/pectin hydrogel beads as potential carrier for colon-targeted drug delivery, *J. Appl. Polym. Sci.* 133 (2016).
- [443] H.H. Gadalla, G.M. Soliman, F.A. Mohammed, A.M. El-Sayed, Development and in vitro/in vivo evaluation of Zn-pectinate microparticles reinforced with chitosan for the colonic delivery of progesterone, *Drug Deliv.* 23 (2016) 2541–2554.
- [444] M. Xu, M.-J. Dumont, Evaluation of the stability of pea and canola protein-based hydrogels in simulated gastrointestinal fluids, *J. Food Eng.* 165 (2015) 52–59.
- [445] D. Sathya Seeli, M. Prabakaran, Guar gum oleate-graft-poly (methacrylic acid) hydrogel as a colon-specific controlled drug delivery carrier, *Carbohydr. Polym.* 158 (2017) 51–57.
- [446] M. Mohammadian, A. Madadlou, Cold-set hydrogels made of whey protein nanofibrils with different divalent cations, *Int. J. Biol. Macromol.* 89 (2016) 499–506.
- [447] W. Shi, M.-J. Dumont, E. Babacar Ly, Synthesis and properties of canola protein-based super absorbent hydrogels, *Eur. Polym. J.* 54 (2014) 172–180.
- [448] V.K. Singh, P.M. Pandey, T. Agarwal, D. Kumar, I. Banerjee, A. Anis, K. Pal, Development of soy lecithin based novel self-assembled emulsion hydrogels, *J. Mech. Behav. Biomed. Mater.* 55 (2015) 250–263.
- [449] H. Zand-Rajabi, A. Madadlou, Caffeine-loaded whey protein hydrogels reinforced with gellan and enriched with calcium chloride, *Int. Dairy J.* 56 (2016) 38–44.