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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 has attracted the attention of uncountable researchers. Over the past two decades, hydrogels become smart and sophisticated materials with plenty of applications possibilities. The biomedical research area has demonstrated a particular interest in hydrogels since they can be engineered from different polymers and due to their tunable properties. Moreover, hydrogels engineered from polymers extracted from biorenewable sources have been popularized in biomedical usages, as they are low-toxic, eco-friendly, biocompatible, easily accessible, and inexpensive at the same time. However, the multifaceted challenge is to find an ideal plant green hydrogel in the tissue engineering that can mimic critical properties of human tissues in terms of structure, function, and performance. In addition, these natural polymers are also idealized to be conveniently functionalized so that their chemical and physical behavior can be manipulated for drug delivery and stem cell-guided tissue regeneration. Here, the most recent advances in the synthesis, fabrication and application of plant green hydrogels in biomedical engineering are reviewed. It covers essential and updated information about plant as green sources of biopolymers to be used in hydrogel synthesis, general aspects of hydrogels and plant green hydrogels and a substantive discussion regarding the use of such hydrogels in the biomedical engineering area. Furthermore, this review addresses and detail the present status of the field and, also, answer several important questions about the potential use of plant green hydrogels in advanced biomedical applications including therapeutic, tissue engineering, wound dressing, diagnostic, etc.

Keywords: Hydrogels; green hydrogels; biomaterials; advanced materials; tissue engineering; wound healing.

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1. Introduction

Disease, injury, and trauma are different situations that affect the normal function of tissues and consequently lead to tissue and organ failure. It is necessary to treat the damaged sites to facilitate the process of tissue regeneration. The conventional strategies for tissue repair such as autograft and allograft accompany with several limitations including the multiple surgeries, high infection risk, painful procedures, and lack of a donor. In this regard, there is an increasing demand for alternative strategies to effectively regenerate the damaged tissues [1]. Tissue engineering which applies biomimetic 3D scaffolds seeded by cells seems to be a promising strategy to promote the tissue repair [2-13]. Recently, hydrogels are gained more attraction as tissue engineering scaffolds due to their similar structure to natural extracellular matrix (ECM). Hydrogels mimic a real 3D cell culture environment for cell 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 over the release rate of bioactive molecules [16-17]. Using the delivery vehicles with sustained release rate ease the preserve of the molecules bioactivity while maintaining 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 streo- lithography [19-24]. The physico-chemical properties of polymers along with their surface characteristics define the choice of method for scaffold preparation [25]. However, all the used methods have their own benefits and drawbacks. For instance, solvent casting particulate-leaching is a simple and cost-effective method that faces limited usage due to applying toxic solvents, poor interconnectivity of the ultimate scaffold, and forming skin-like layers when evaporating the solvent. In contrast, freeze-drying is more demanding because it does not use solvents for scaffold fabrication and can control the size of interconnected pores and the porosity of the scaffolds by optimizing different parameters. Scaffolds with high interconnected pores can also be produced by gas-foaming; however, formation of skin layers on the outer layer of the scaffold reduce its mechanical strength which limits the application of this method for fabricating tissue constructs) [8].

From point of materials view, different natural (**Figure 1**) and synthetic polymers have been used for scaffold fabrication. Scaffold materials also have advantages and disadvantages. For instance, natural polymers are excellent candidates for tissue engineering applications due to high biocompatibility and functionality, while synthetic polymers exhibit outstanding

mechanical and physical properties [26-28]. Currently, numerous researches have focused on the structure–function relationship of different plant based-polymers as natural polymers. Plant-polysaccharide based polymers (e.g., cellulose, hemicellulose, lignin, starch, pectin, agar and agarose) 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 with low toxicity [29-30] which are most similar to mammalian ECM components, like glycosaminoglycan molecules. Furthermore, using polymers with plant sources like flavonoid or biflavonoid polyphenolic agents have gained attentions for biomedical applications as antimicrobial agents and antioxidants [31-33]. In different studies, *Stevia rebaudiana* Bertoni leaves-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-regulates the nuclear factor-kappa B (NF-κB) which consequently activated p38 and c-Jun NH2-terminal kinase (JNK) proteins in RAW 264.7 cells [36]. There are a lot of original articles around using plant based-polymers as tissue engineering platforms, while to the best of our knowledge, there are not comprehensive review articles about this issue. In the current paper, we provide an extensive review on recent studies in biomedical applications of plant-based hydrogels.

2. Plants as green sources for advanced biomedical applications

Throughout the centuries, human civilizations have relied on plants for their basic needs such as foodstuffs, fuel, and therapeutics; all obtained directly or indirectly from plant-based materials (bark, leaf, wood, fibre) and storage tissues (seed, fruit, bulb, tuber, root, rhizome) [37-40]. These needs are increasing rapidly due to the growing world population, and urbanization to name a few. There are approximately 300,000 known plant species worldwide, while only ~ 5,000 have been studied for their medicinal applications to this date; therefore, a huge source of natural plant-derived materials are available for medical applications [41-43]. Plants based chemical compounds can be classified as primary and secondary (or specialized) metabolites (phytopharmaceuticals), depends 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. These materials are involved in the primary metabolites which occur in relatively high levels in the plant cells and, then become the foodstuffs of other organisms [47-49]. Apart from being a source of food or food additives, many terrestrial vascular plants produce a high diversity 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) [50-55].

Water soluble compounds, alkaloids, cyanogenic glucosides, glucosinolates, saponins, anthocyanins, flavonoids, cardenolides are usually stored in the vacuole of the plant cell, however, 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, flavors and fragrances, waxes, cosmetics, dyes and colorants, plant protection and production products, pesticides, colchicines and phorbol esters, and so on [61-64].

Botanical excipients are the organic substances originated from different parts of a plant, such as cell walls, trunk exudates, and seaweeds [65]. The primary cell wall of terrestrial higher plants is mainly comprised 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 (**Figure 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-origin therapeutic agents with no synthetic counterpart are including vinblastine (anticancer, from *Catharanthus roseus*), rescinnamine (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 (antispermatogenic, 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 may be defined as water-swollen and cross-linked hydrophilic polymeric networks. They have the capacity to retain large amounts of water whitin their structure, and yet do not dissolve in water. They are of high interest for biomedical applications: their high water content, soft mechanical properties and their structural resemblance to living tissues make them ideal candidates to develop biocompatible materials for in vivo applications [69-70]. Within the denomination "hydrogel", one can find a tremendous diversity based on different criteria, leading to various classifications. These were already summarized in a comprehensive review by Ahmed and co-workers [71]. Most commonly, however, hydrogels are classified according to the type of cross-linking strategy governing the polymer chain interactions. Understanding and having control over the extent and nature of the cross-linking points is of importance, since it defines the network structure and the hydrogel properties. The cross-linking points maintain the integrity of the three- dimensional network, and are related to the mechanical strength of the hydrogel. In terms of characterization, there are essentially three key parameters used to describe the bulk structure of a hydrogel [71-72,69-70]: (i) the polymer chain molecular weight in between two cross-links which is a measure of the cross-linking density; (ii) the volume fraction of the polymer in the swollen state, which is a measure of the amount of water retained by the hydrogel; and (iii) the mesh size which is defined by a structural parameter "ξ" indicating the linear length in between two neighboring cross-links. There are several cross-linking possibilities between the polymeric chains, essentially depending on the nature of the polymer. They may be chosen in order to finely tune the bulk structure of the hydrogel, considering the envisaged biomedical application. Furthermore, **Figure 3** illustrates the classification of the hydrogels based on physical and mechanical properties. In the next sections, we briefly describe the attributes of the two main classes, namely "physical" and "chemical" hydrogels.

3.1. Physical hydrogels

Physical or 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 Walls interactions, or hydrophobic interactions, as well as ionic forces. There are several examples of physical gelation in biopolymers. For instance, calcium alginate gels result from the ionic interactions between negatively charged carboxylic acids and calcium ions (Ca^{2+}), and the self-assembly of various animal gel-forming proteins is driven by hydrophobic interactions and hydrogen bonding [73]. The main advantages of physical cross-linking lie in their ease of processability. The reversibility of the cross-linking points (through the disruption of bonds using external cues such as pH, temperature, ionic strength, or the addition of solutes competing for the cross-linking sites between polymer chains) allows for simple production techniques, such as thermal or solvent casting processes. In addition, chemical modifications (often using toxic crosslinking agents) are avoided, which is an advantage for hydrogels used in biomedical or food applications. However, one of the major disadvantage of physical hydrogels is related to their generally weak mechanical properties when compared to chemical hydrogels.

3.2. Chemical hydrogels

Chemical or irreversible hydrogels are obtained through covalent cross-linking. Covalent bonds between polymer chains can be made 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 that the strategies to cross-link synthetic and bio-polymers may significantly differ. In the case of biopolymers, the limitation arises from the imposed functional groups. Comprehensive reviews on cross-linking strategies for biopolymers have been published by Reddy *et al.,* [74] and Shen *et al.,* [75]. In comparison to physical gels that can be dissolved or degraded easily, chemical hydrogels are more stable and usually demonstrate better mechanical properties. This high durability might also be seen as a disadvantage: the utilizaiton of such gels is indeed limited, since they cannot be reshaped. In addition, gelation kinetics are usually slow, causing solubility issues in the early gel production. Last but not least, the chemical gelation is often accompanied by cytotoxicity, due to residual chemicals used for cross-liking that are difficult to eliminate through purification.

3.3. Composite hydrogels

In many cases, both physical and chemical cross-linking provide higher mechanical properties and stability to hydrogels. However, this is at the expense of the degradation behavior, the

overall availability of functional groups, and significant changes in hydrogel rheology that can affect processability. An alternative is to design hybrid or composite hydrogels, via the incorporation of nanomaterials such as inorganic fillers or nanofibers in the matrix, or by combining polymers using different cross-linking mechanisms (dual gelling hydrogels) [76]. The combination of different materials allows taking advantage of both components, ideally cancelling or limiting their intrinsic disadvantages. The reader is referred to the review 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 one of the most abundant biorenewable materials available on the earth and is expected to become one of the main resources in future [79-81]. This biopolymer is formed by glucose molecules and can be found in plants (in their cells as a structural polymer) and natural fibres [82]. Besides, it can be produced by bacteria through enzymatic reactions [82,81] which presents identical chemical composition compared to plant-based cellulose but with different macromolecular structure and physical properties [83]. The structure of cellulose can be seen in **Figure 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 [84,82]. However, it is important to mention that due to the lack of cellulase enzymes in animals, 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 but it will not be biodegraded by a human/animal body. The main source of cellulose is wood [81]. Considering that this material is a composite containing cellulose and lignin it should be treated in order to extract cellulose [81]. Similarly, in plants the most challenging issue in regard to the widespread usage of plant cellulose is its association with other molecules such as lignin and pectin and need to subsequent purification to eliminate hydroxyl groups[82,89]. Importantly, cellulose properties depend on the source and the extraction/purification methods [84]. In order to improve its properties and produce an easily processable material, cellulose is chemically modified [82]. The main goal of modifications is the esterification of the hydroxyl groups. This type of modifications involves the reaction of the organic species, such as methyl and ethyl units with the hydroxyl groups of

cellulose. As a result, the obtained biopolymers are water soluble. The typical cellulose derivatives are shown in **Figure 4** [79].

A newly emerged class of nanoscale cellulose-based particles and polymers is hairy nanocelluloses, [90-91] with an ability to overcome 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 β β(1 →4) glycosidic linkage, producing nanocrystals of cellulose with a crystalline structure depending on its source; typically, cellulose I as the main constituent of native cellulose, [92] consists of Iα or Iβ structures [98-99]. Assuming a 10 nm by 10 nm crystal packing bearing 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, 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 for a wide range of chemical reactions [103].

Heating dialdehyde functionalized fibrils increases the solubility of amorphous regions, which already bore a higher dialdehyde content than crystalline regions due to better accessibility during periodate oxidation, breaking the fibrils from the amorphous regions. The products of this process are: (i) cellulose nanocrystals sandwiched between protruding dialdehyde-modified amorphous 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 groups to a 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, 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, may accommodate more than one order of magnitude charge groups than conventional

nanaocelluloses [100]. As an example, 4-day periodate oxidation of fibrils followed by one-day chlorite oxidation yields ENCC with more than 5.5 mmol g-1 carboxylic acid per gram of nanoparticles.

Dialdehyde functionalized cellulose fibrils may be partially oxidized by chlorite to result in 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, eliminating post-purification complexities. The one-pot synthesis of bifunctional hydrogels using hairy cellulose nanocrystals provides a robust infrastructure to soft green materials with a broad range of applications. When NHCNC 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 ~ 10 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] (**Figure 5**).

Aerogels synthesized from BHCNC [105] bearing ~ 3 mmol COOH gr-1, and carboxymethylated chitosan (~ 3 mmol COOH gr-1) were able to remove up to ~785 mg methylene blue, a cationic dye, per gram of adsorbent through a time-dependent diffusion-adsorption process at pH ~ 7.5. This aerogel performs 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]. BHNCC may readily be functionalized with a wide range of molecular moieties and polymers, such as aldehyde, amine, carboxylic acid, ionic liquids, surfactants, epoxies, silanes, polycaprolactone, and polyethylene glycol, 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 bonding linked networks easily [79]. The main limitation is to find a proper solvent for cellulose as it is insoluble in the majority of common solvents because of the extremely extended hydrogen-bonded structure [79,75]. Currently, there are a few solvents that have been proven to be able to dissolve native cellulose: N-methyl morpholine N-oxide (NMMO) [106-107], LiCl/dimethylacetamide (DMAc) [108-111], ionic liquids (ILs) [112-115], and thiourea aqueous systems (also known as alkali/urea) [116-118].

When dissolved, 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 gelation into a solid gel with anisotropic structure[75]. When the cellulose concentration increases the number of hydrogen-bonding interactions increases. 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 5-60ºC for a defined period of time (the time scale range from minutes to weeks) [119,75], while the latter is achieved through contacting the cellulose solution with an anti-solvent such as water, ethanol, methanol or H_2SO_4/Na_2SO_4 among others [120,75]. The physical association between the chains is reversible [75].

Nevertheless, there are two scenarios for the resultant 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 ºC). 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 types of gels are transparency and strength. Transparency depends on the parameters selected to form the hydrogel such as the curing temperatures or the coagulation bath [75]. For example, Cai *et al.,* studied the gelation of native cellulose in NaOH/urea and showed an increase in curing temperature led to a decrease in transparency [116]. Higher temperatures caused a higher degree of phase separation leading to hydrogels with more heterogeneity. The other key parameter affecting the transparency is the composition of the coagulant [111]. The transparency is highly dependent on the internal structure of the hydrogel which is directly related to the coagulant and the coagulation conditions.

In addition to transparency, strength is the other 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 the hydrogels [75]. Tensile strength is a function of other factors, such as the biopolymer concentration, particle size, pH environment, and curing conditions [75]. The mechanical strength of native cellulose physical hydrogels can be improved by using a pre-gelation process before performing the coagulation [119]. In this case, by application of a relatively low pre-gelation temperature (~5ºC), the strain and the stress at break of the membranes were 192% and 1.97 MPa, respectively. These values were significantly higher than similar hydrogels prepared through a general solution casting method which the results of strain were between 50-60%, while the stress at break results were between 0.8 and 1 MPa.

An alternative to native cellulose is cellulose nanowhiskers, a product of cellulose acid hydrolysis with lateral dimensions ranging from 3–30 nm [121]. They behave in a similar way as native cellulose and are able to self-organize into solid gels above certain concentrations [122]. Cellulose nanowhisker hydrogels can be obtained through treatment of aqueous nanowhisker suspension with one of the following procedures: ultrasonication [123], or solvent exchange [124]. Ultrasonication provides enough energy to rearrange 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 defined by the thickness of the hydrogel and the density of the whiskers [75]. Furthermore, cellulose nanocrystals may be used to prepare bionanocomposite hydrogels, including injectable systems able to encapsulate cells with improved mechanical properties [125].

Cellulose derivatives can be prepared as physical gels. Cellulose derivatives demonstrate higher water solubility and consequently easier preparation[75]. For example, MC can form physical gels when heated above a critical temperature (depends on MC concentration) [75]. The proposed mechanism for this phenomenon is the reorganization of the solvent. The interactions between the solvent and the cellulose chains changes at higher temperatures leading to the formation of hydrophobic aggregates [126]. HPMC present similar behaviour, but the gelation temperatures are higher [127,75]. 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, physical hydrogels can be 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

This section focuses on the chemical cellulose hydrogels. This type of hydrogels is prepared by the use of chemical crosslinkers [75]. A wide variety of molecules can be 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 the crosslinking reaction all these molecules can be classified as esterifying agents or etherifying agents [75]. The esterifying agents result in the formation of –COOR bonds while the etherifying agents result in the formation of R–O–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 4-dimethylaminopyridine (DMAP) [137,131,138]. 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]. Etherification reactions generally require alkaline environment [75]. To address this issue, the hydroxyl groups of the cellulose can be deprotonated to make nucleophiles and consequently more reactive with the crosslinker (organochlorines, epoxides, and vinyl compounds) [135,134].

Irradiative cross-linking can form chemically crosslinked hydrogels. This process offers several advantages over the previously described methods, including non-toxic and high purity cross-liners hydrogels [75]. This is a critical point for certain applications such as the development of pharmaceutical products. The use of γ-radiation can be used for this purpose [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]. The latter requires a photoinitiator (4-benzoylbenzyl)trimethylammonium chloride [142]. This technique may result in the partial destruction of the cellulose structure due to irradiation with high-energy doses [75].

The combination of cellulose molecules with synthetic or natural polymers is an approach to prepare hybrid hydrogels. The chemical reactions are similar to the ones described before [75]. **Figure 6** illustrates SEM images of cellulose hydrogels obtained after crosslinking cellulose and sodium alginate with epichlorohydrin [133]. The main characteristic parameters of chemically crosslinked cellulose hydrogels are transparency, pore size, strength, and water absorbance [75]. The transparency of chemical hydrogels mainly depends on the crosslinking degree. Higher crosslinking degrees contribute to the formation of a highly hydrophilic and homogeneous 3D network. The use of some crosslinkers can affect transparency as they imbue the hydrogel with a certain colour. Finally, the transparency of the hydrogels depends on the swelling degree [75]. The pore size is an important parameter that affects several properties such as the swelling kinetics and/or the ability to uptake and release a drug molecule [143-144]. It is normally determined by SEM. Based on the preparation process, the hydrogel pore size can vary. HPC hydrogels prepared at temperatures higher than the LCST show microporosity, while the hydrogels synthesized at temperatures higher than the LCST are non-porous [145]. Additionally, the pore size is affected by the drying process. When hydrogels are freeze-dried the average pore size range between 3 to8 μm [134]. However, by controlling the freezing conditions, this range can change [146]. On the other hand, when supercritical drying is applied, the pores normally have smaller size distributions [147].

Another critical parameter is the strength of the hydrogels [148-149]. It depends on the type of cellulose, the concentration of the biopolymer, and the crosslinking density [75]. Of note, the elastic modulus of chemical cellulose hydrogels changes over the water uptake process. At low swelling degrees, it shows the minimum modulus value. After this, it rises steadily with swelling, due to the high intrinsic chain stiffness of the cellulose backbone. Finally, the last governing parameter in cellulose hydrogels is their ability to absorb water [75]. This is a key factor for chemical hydrogels. Due to the weak interactions between chains in physical hydrogels, their capacity for water absorption is limited. The water uptake is influenced by several factors such as the drying process, the molecular weight of the cellulose, the crosslinking degree and the cellulose concentration [75].

4.1.2. Hemicellulose-based hydrogels

After cellulose, hemicellulose is the second most abundant biomass which strengthens the plant cell wall with lignin and cellulose. 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. Given that hemicelluloses are biocompatible, not toxic, and biodegradable, they are the subject of several studies for biomedical applications.

Depending on the source of biomass, the synthesised hemicellulose hydrogels have a different physical property which is due to various struturre, composition and amounts of the hemicellulouse in different biomass. In case of hardwood, Xylose is the most important hemicellulosic monomer which occurs as O-acetyl-4-O-methylglucuronoxlan with degree of polymerisation between 100-400. In soft wood however, 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 study, the hydrogel produced from acetylated galactoglucomannan-rich wood hydrolysate (WH) showed a high swelling ratio of up to 270g/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 of hemicellulose derived from spruce pulp was done with MA resulted in ionic hydrogel matrix for drug release applications. The grafting of monomer on the hemicellulose backbone is initiated by the generation of sulphate anion radicals form the oxidising agent such as ammonium persulfate which forms alkoxy radicals with the hydroxyl group of hemicellulose which initiate the polymerisation 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 provides other interesting advantages such as biodegradability, antioxidant/antimicrobial activity, and availability as a by-product of industrial activity [159-161]. Lignin is composed of phenylpropane units: p-coumaryl, coniferyl, and sinapyl alcohols (**Figure 7, A**) [162]. The structure of lignin is defined mainly by different types of carbon-carbon and carbon-oxygen bonds that link monomer units (**Figure 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, efforts are being made to reuse these waste materials. It is well known that lignin is an imperative aromatic renewable source due to the high presence of aromatic rings in its structure [157,161]. Consequently, 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 [162,165-166,161].

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 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 [167,165,159]. 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 [168,86,169-170,89]. However, several studies investigated the application of these type 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 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 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 Kraft lignin with lignin extracted by ionic liquids for hydrogel formation [87]. Several crosslinking agents were used including epichlorohydrin, polyethylene glycol (PEG), and epoxide-terminated PEG. Additionally, acrylamide was used by other groups to obtain lignin-based hydrogels [173].

El-Zawawy *et al.,* also studied 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 H_2O_2 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 ºC [175]. Consequently, the resulting hydrogels were thermo-responsible. 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.,* to prepare lignin hydrogels with applications as aerogels and cryogels [177]. To prepare 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 CO_2 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 macroprosity. 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 CO_2 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 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 100h 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 ºC for 72 hours. 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 hours 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 hour) [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 [196,192,197]. 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 be able to swell in the slightly alkaline intestinal medium extensively while minimally swell under gastric acidic conditions [198,192]. 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% [203,202]. 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 [212-214,202]. 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 ($–COO^-$) and contribute to chain-chain repulsion and facilitates 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 (**Figure 8**) [215,206]. 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 e 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) [221,220]. 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* gelation of pectin in a 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].

Amidation of LM-pectin improves its gelling ability by reducing the calcium level required for gel formation [225,220]. Indeed, amide groups along the pectin chains favor 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 [233,200]. 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 (–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 produces 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 [234,210]. 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 modification of LM-

pectin with glycidyl methacrylate (GMA) to insert vinylic groups into the polysaccharide backbone (Figure 9) with potentials for e 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 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 has viscoelastic behavior 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].

4.4. 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 plants-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].

4.4.1. 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.

4.4.2. 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].

4.4.3. 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.

4.4.3.1. 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 (-NH_2, -OH, and -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, 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 [295,310,305,311]. Nishinari *et al.,* have comprehensively reviewed the gelation conditions for soy protein [308].

4.4.3.2. 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. To the purpose of application 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 facil 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].

4.4.4. 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 hydrogels mechanical properties such as strength and elasticity (either crosslinking or compositing), the dynamic rheological tests can be conducted to determine the development of storage modulus and loss modulus through exposing and holding the gel to the subsequent heating and cooling conditions at 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 behavior 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 ciprofloxacine [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 ionisable 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-acetylgalactoglucomannan 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 **Figure 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.

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 to 7.4 [346]. Cross-linking, monomer grafting, and degree of polymerization are used to control and adjust the release behavior 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 to 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. Not enough *in vivo* studies are 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 Fe_3O_4) 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 visualised using the iodine test. In another study, the presence of iron oxide (Fe_3O_4) 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 optimised via the retrogradation process. Using the starch retrograded at 4°C for 8 days and gellun 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 to 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 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 behavior [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 favors 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 tumor growth (B16F1 mouse melanoma model). Dox-loaded hydrogels were more effective in suppression of tumor 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-weekpost-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-PaCa-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 behavior. 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 showed pH-dependency and mucoadhesiveness which are critical for localized drug delivery [252,358]. Furthermore, Tragacanth 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-hydroxyethethylmethacrylate and acrylic acid can improve drug release and swelling kinetics of sterculia gum [360]. Guar gum with high molecular weight galactommannans, backbone of D-mannose residues and pendant of D-galactose residues, can control release of therapeutic molecules in drug delivery systems [361,360]. 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 succianate-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 $–NH_2$ 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 behavior 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 addition 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 shoould 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 behavior 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 fibers 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 [315,287-288].

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 behavior 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 behavior 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 fibers [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 (≥ 85%) with pores size ranging from 350-500 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 hydrobels 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, color, 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 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 **Figure 11**, the pore structure of the hydrogel depends on the ratios of starch, acrylic acid, and MBA. 48-hour cell culture on 2mg/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 behavior 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 osteogenetic 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 Ca2+ 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 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 behavior 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 figure 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 relives on the 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 behavior [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 nuduli 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 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 to 48h) 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 nanomaterial 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 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 teams: 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 dialogue bringing together experts from different areas (chemistry, physics, materials and biomedical engineering, pharmaceutics, and so on) in order to look after for the various aspects of these soft-materials as well as their application field. Multidisciplinary teams have more chances to notice and understand the entire process and predict the future of the plant-based hydrogels.

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Figures and their captions

Figure 1

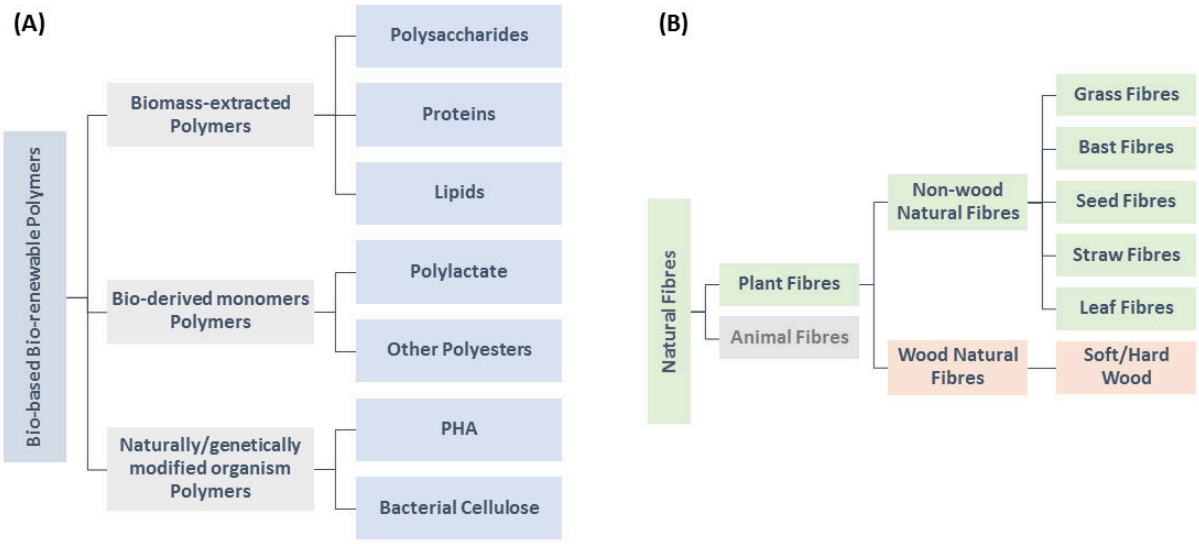


Figure 1. (A) Classification of Bio-based polymers (Reproduced with permission from [427]); (B) Classification of natural fibres (Reproduced with permission from [427]).

Figure 2

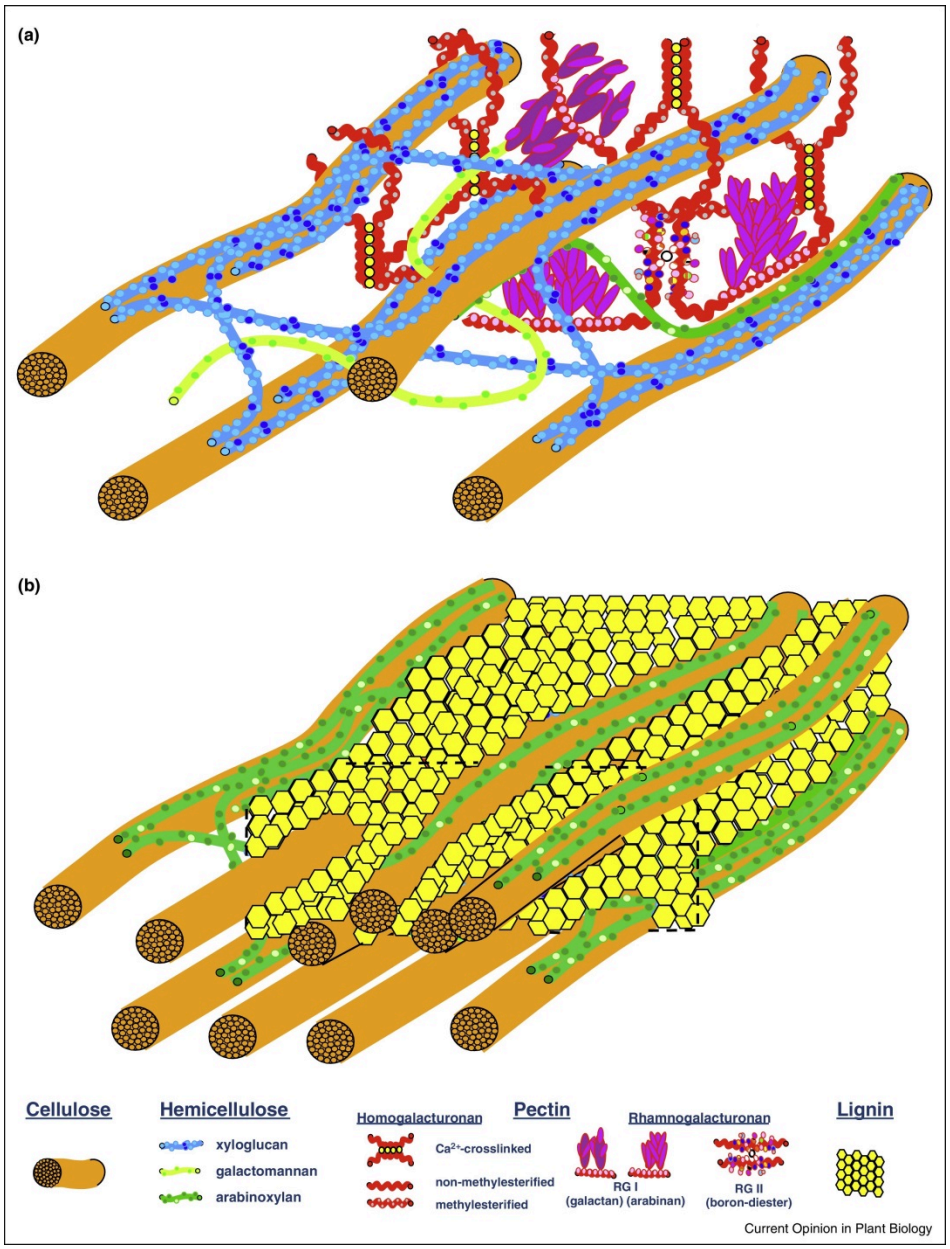


Figure 2. (a) Pectinaceous cell walls in dicots. (b) Lignified cell walls. Reproduced with permission from [428].

Figure 3

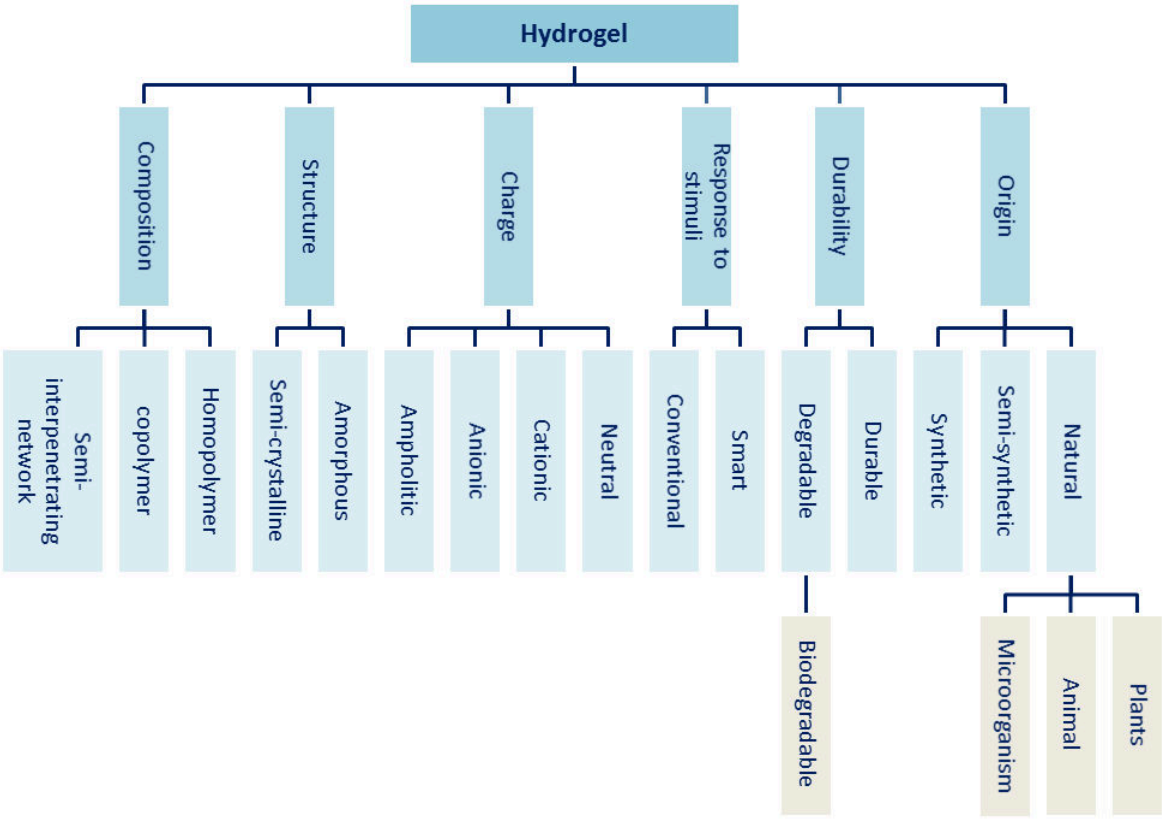


Figure 3. Classification of hydrogels based on physical and mechanical properties. Reproduced with permission from [429].

Figure 4

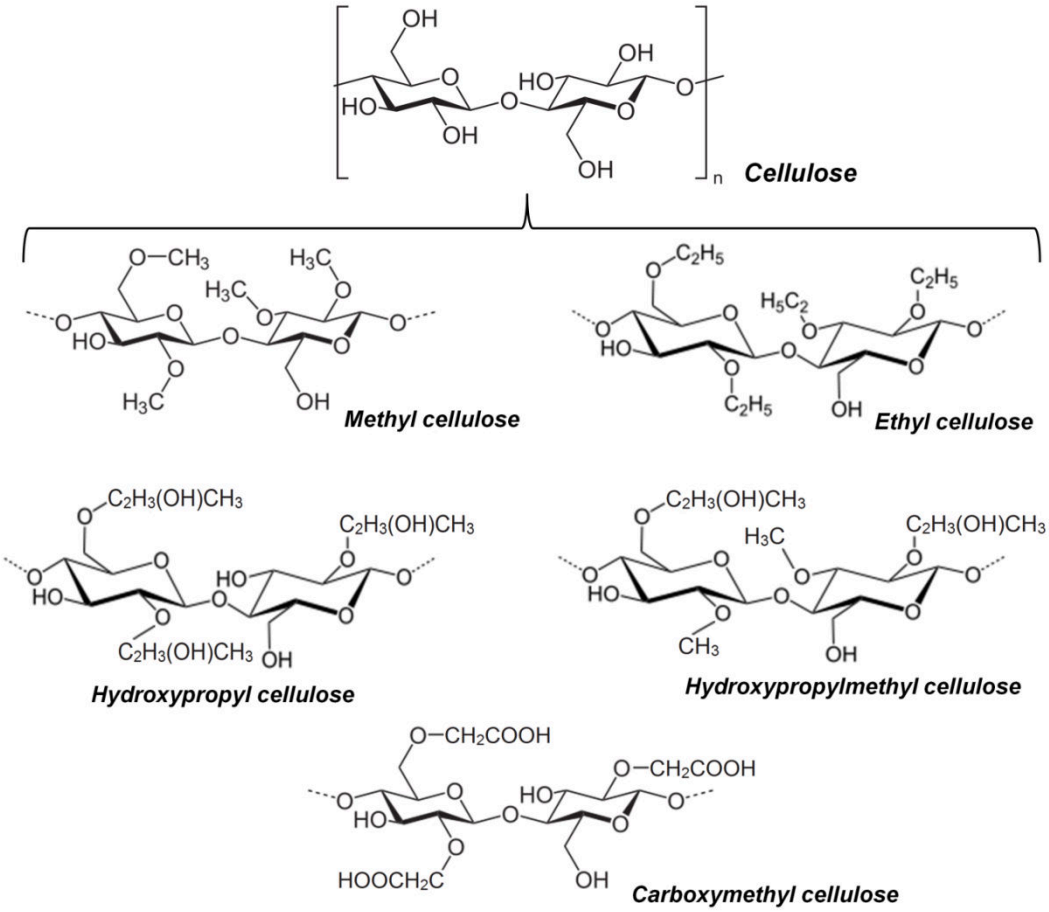


Figure 4. Chemical structure of cellulose and cellulose derivatives.

Figure 5

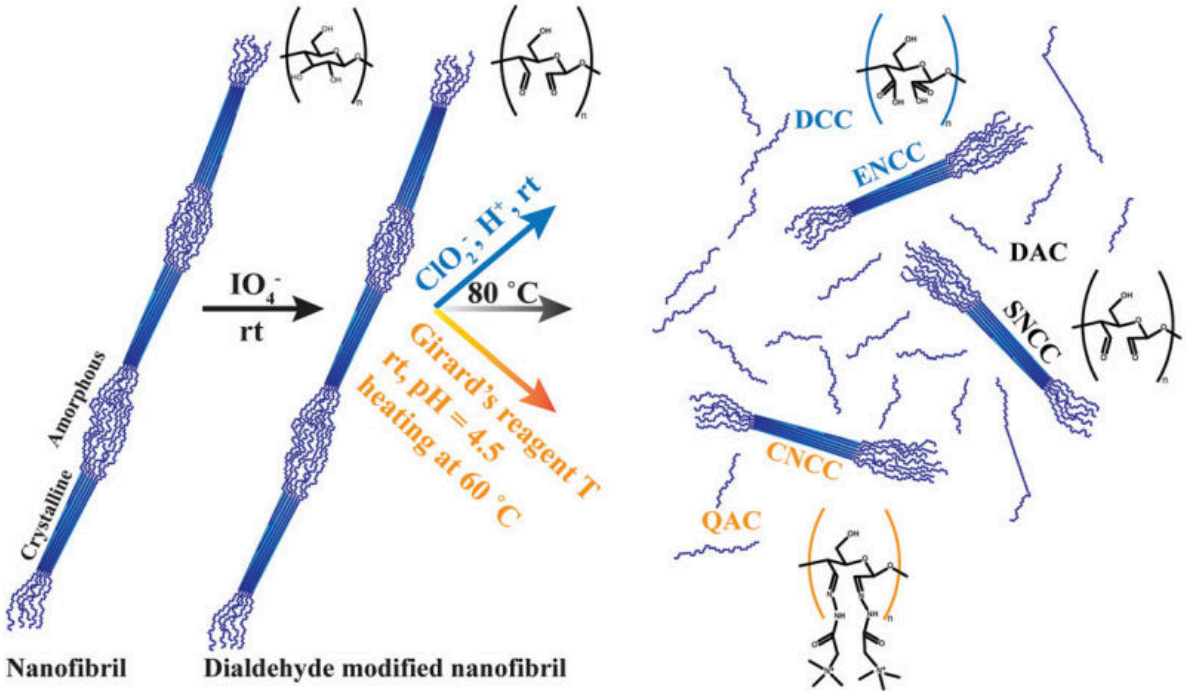


Figure 5. Schematic of hairy nanocellulose synthesis. Cellulose nanofibrils are oxidized using periodate to yield dialdehyde modified fibrils (DAFs). (i) Heating DAFs, (ii) reacting DAFs with chlorite, and (iii) reacting DAFs with Girard's reagent T results in neutral (SNCC: sterically stabilized nanocrystalline 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 [430].

Figure 6

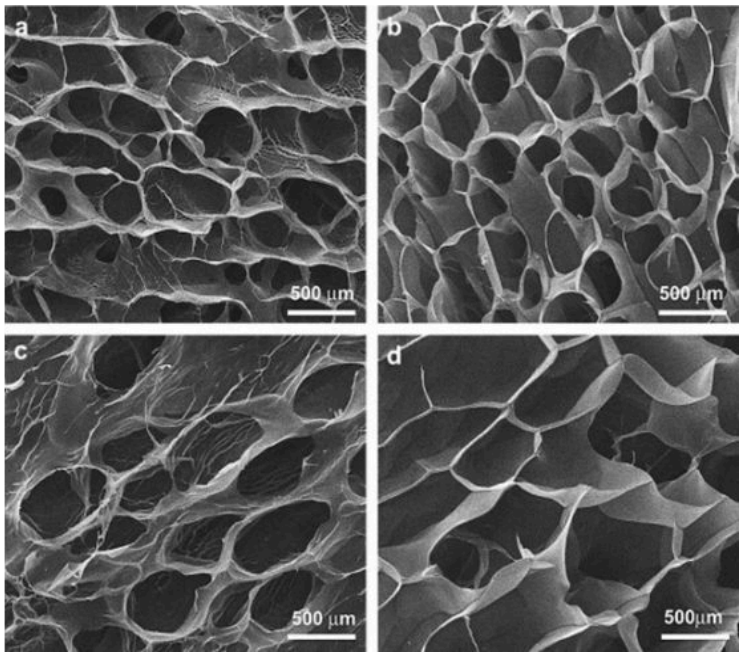


Figure 6. (a-d) SEM images of different cellulose/SA hydrogels. Reproduced with permission from [133].

Figure 7

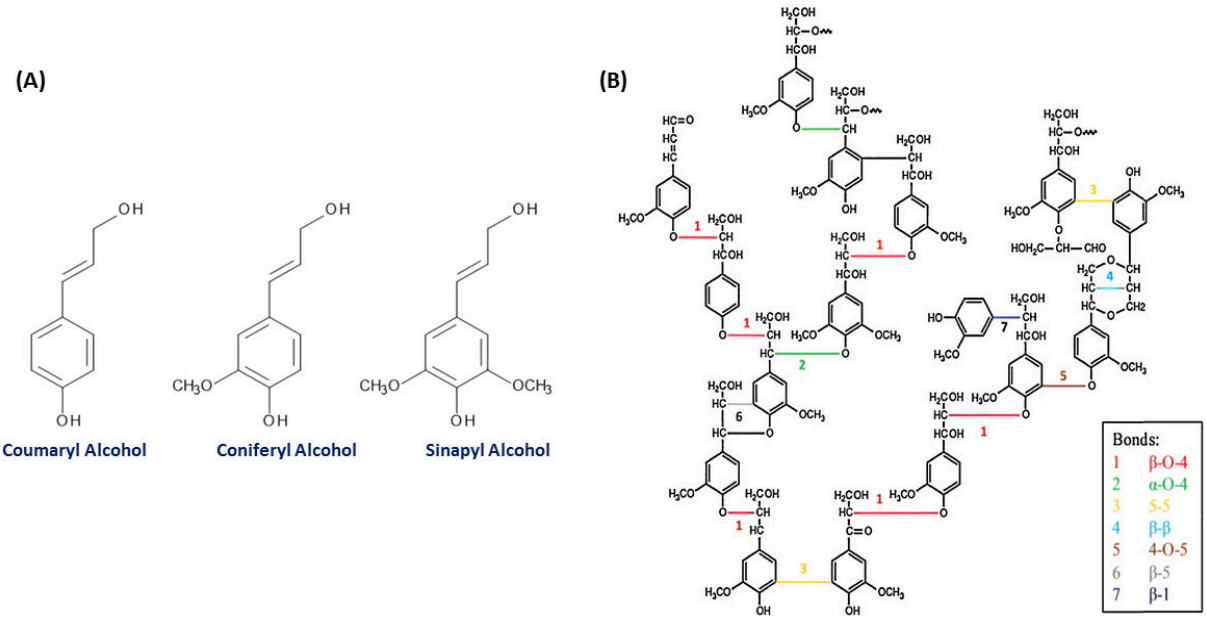


Figure 7. (A) Basic units of lignin; (B) the structure of lignin. Reproduced with permission from [431].

Figure 8

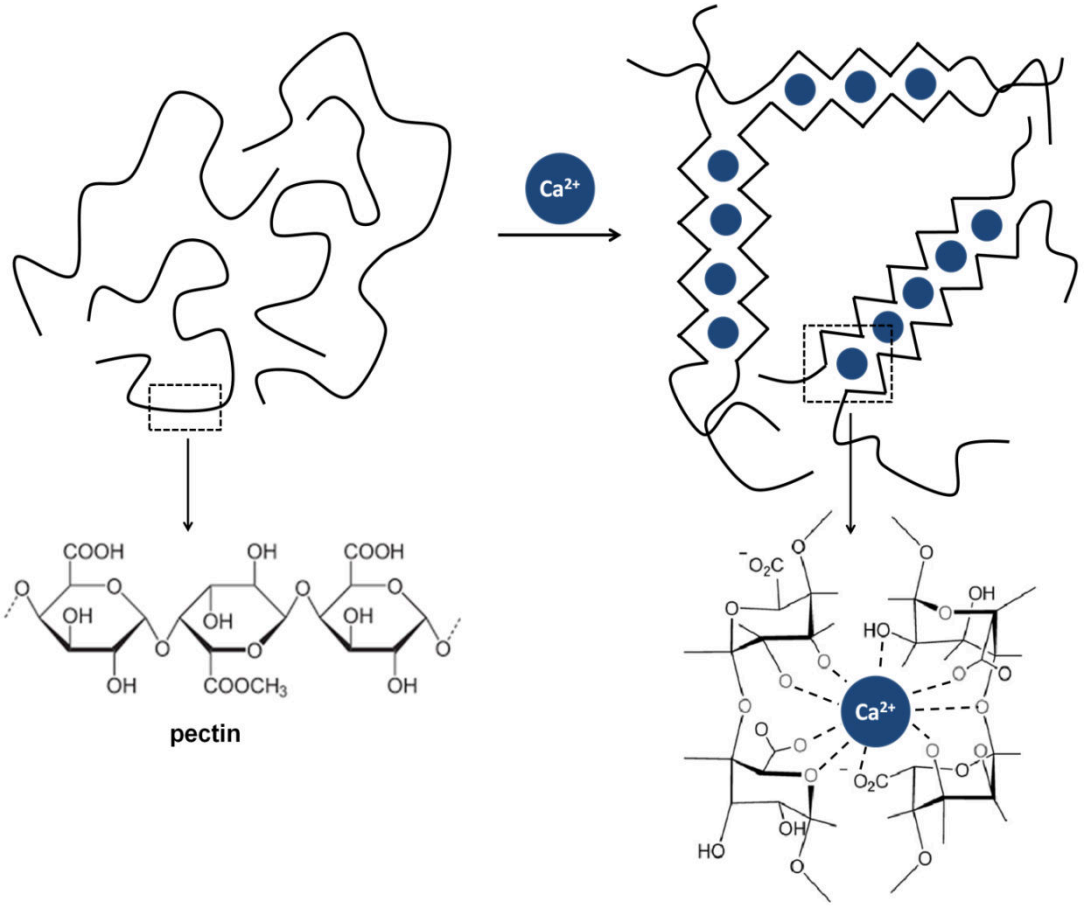


Figure 8. A schematic representing the Ca^{2+} induced gelation of pectin ("egg-box" model). Reproduced with permission from [216].

Figure 9

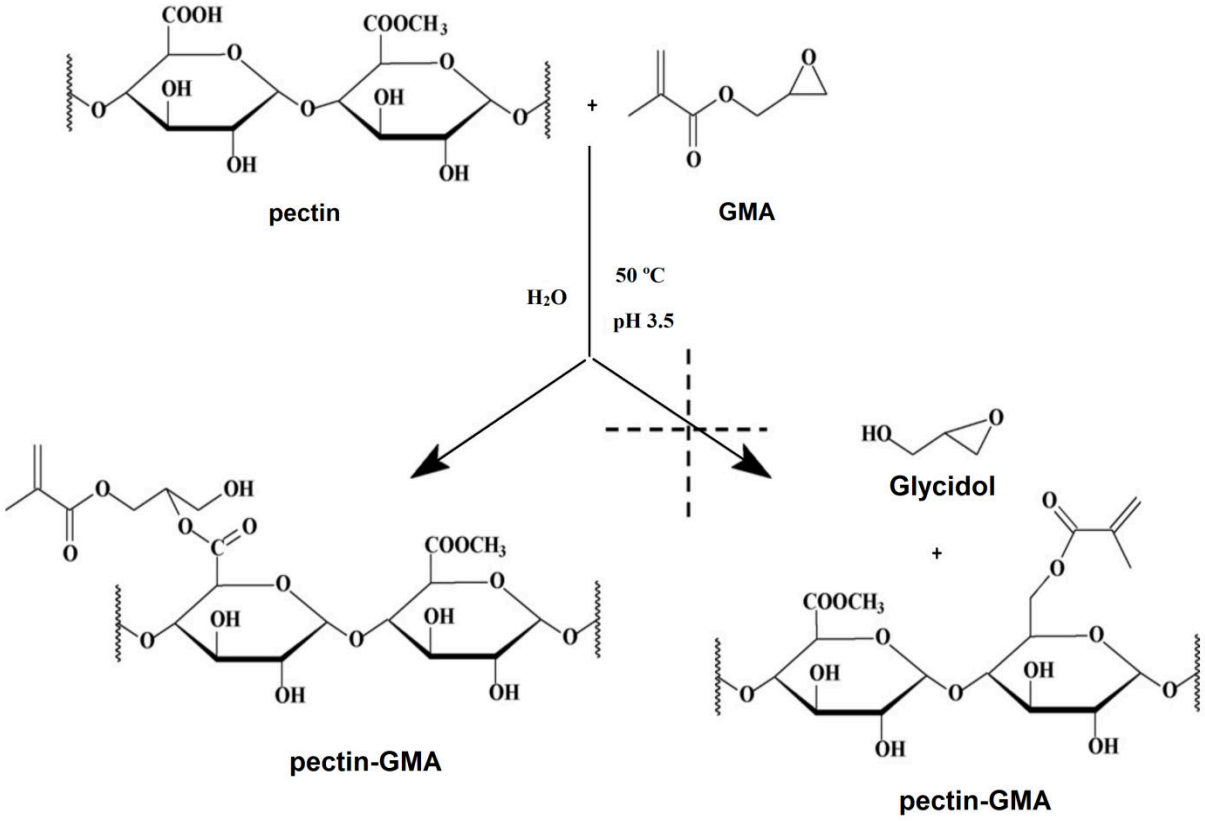


Figure 9. Schematic representation of the reaction between pectin and GMA. Reproduced with permission from [432].

Figure 10

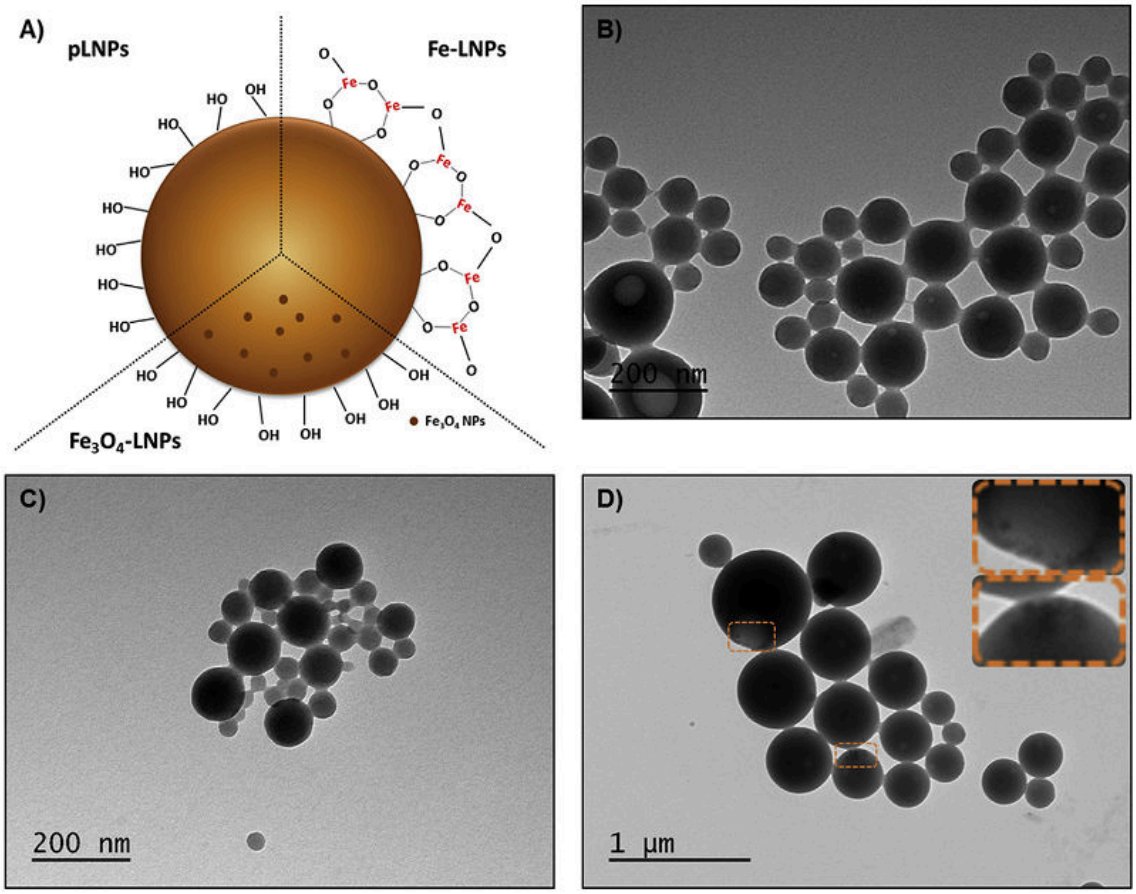


Figure 10. (A) Schematic of three pure, iron(III)-complexed, and infused Fe_3O_4; TEM images of (B) pure; (C) iron(III)-complexed; and (D) infused Fe_3O_4 lignin nanoparticles. Reproduced with permission from [344].

Figure 11

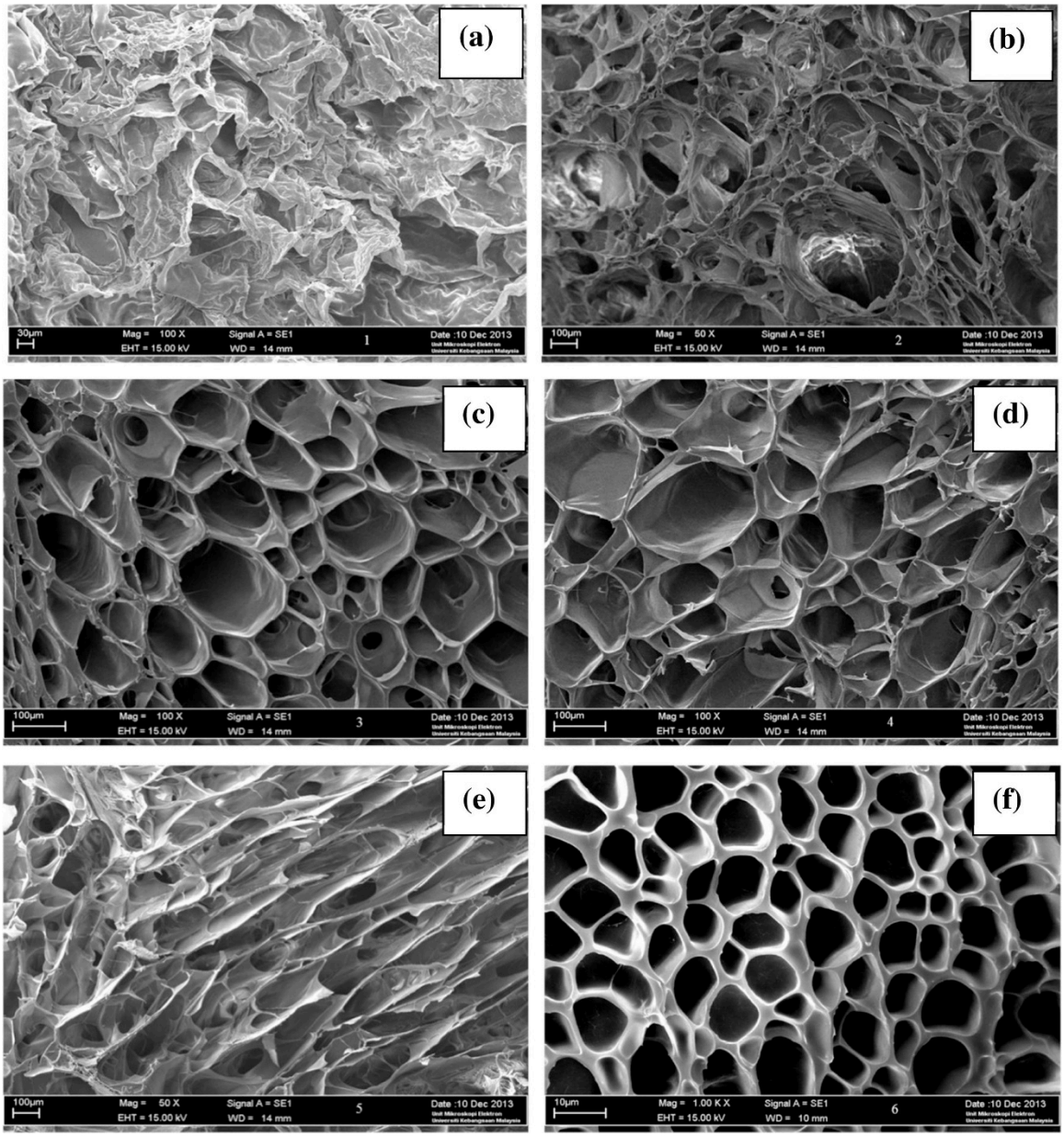


Figure 11. Micrograph images of hydrogels with varying starch-acrylic acid ratio: (A) 1:15; (B) 1:20; (C) 1:30; (D) 0.02 M MBA; (E) 0.1 M MBA; and (F) 0.2 M MBA. Reproduced with permission from [412].

Figure 12

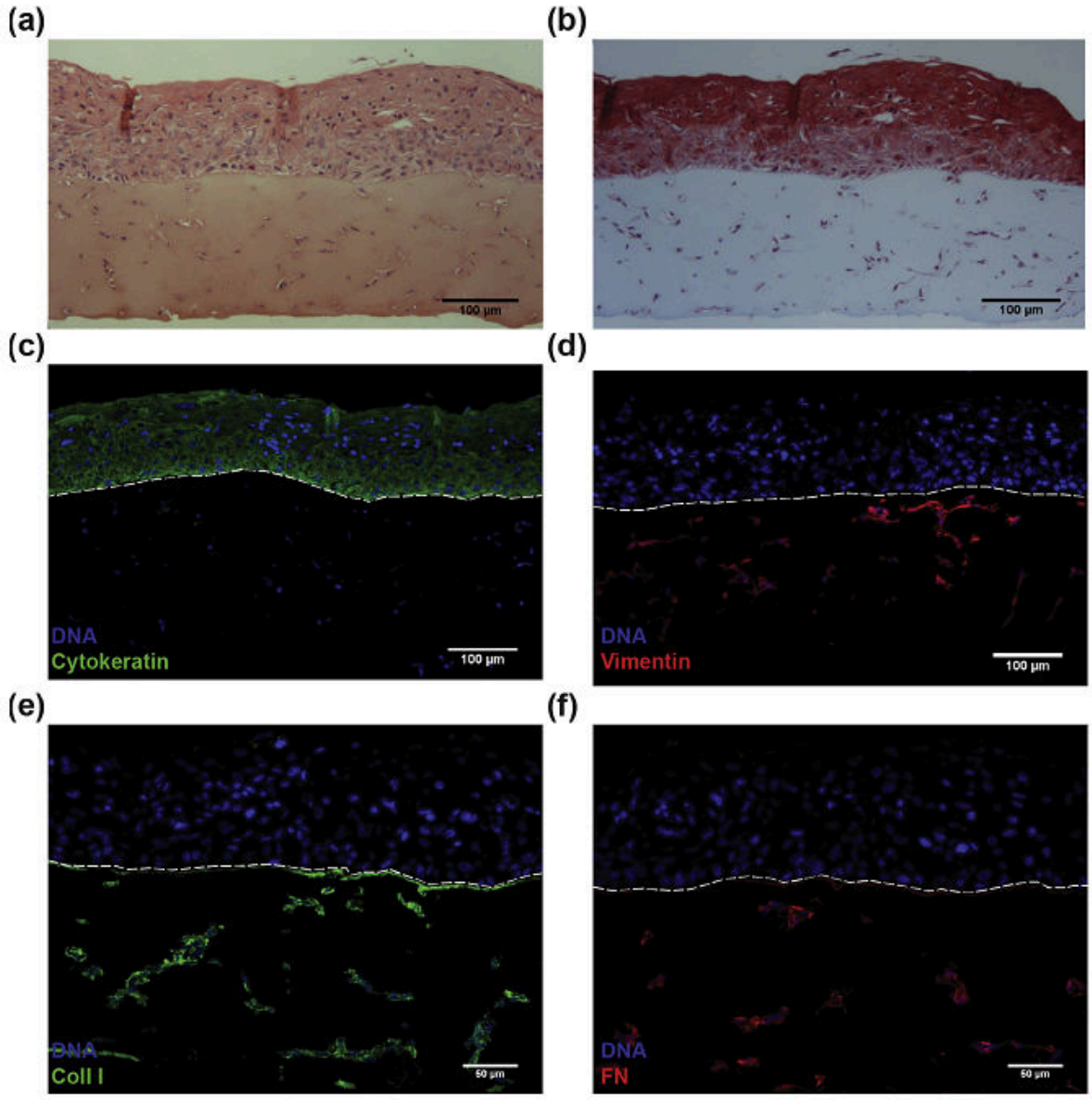


Figure 12. Histological images of pectin hydrogels after 14 days: (A) Hematoxylin & Eosin; (B) Masson trichrome staining; Immunostaining of tissues for (C) cytokeratin; (D) vimentin; (E) collagen I; and (F) fibronectin. Reproduced with permission from [422].

Tables and their captions

Table 1. Molecular weight and percentage of functional groups of lignins. Reproduced with permission from [158]

1 Lignin type	2 Mn (g/mol)	3 COOH (%)	4 OH phenolic (%)	5 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

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 polyelectrolyte complex	microspheres	vancomycin	[435]
pectin-*g*-poly(vinylpyrrolidone)	macro gels	theophylline	[436]
pectin crosslinked by glutaraldehyde	microspheres	resveratrol	[437]
poly(ethyleneimine)-modified pectin ionicallycrosslinked by Ca^{2+} ions	beads	resveratrol	[438]
pectin-*g*-poly(*N*-isopropylacrylamide)	macro gels	theophylline	[439]
pectin/chitosan ionically crosslinked by Zn^{2+} ions	microparticles	resveratrol	[440]
pectin methylesterase-modified pectin ionically crosslinked by Ca^{2+} ions	beads	indomethacin	[441]
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 ionicallycrosslinked by Zn^{2+}/Al^{3+} ions	microspheres	progesterone	[20]
pectin/chitosan ionicallycrosslinked by Zn^{2+} ions	microparticles	progesterone	[444]

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 8C, 24 hours; 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 8C, 24 hours	Can protect riboflavin from gastric conditions and release in intestinal conditions	[371]
Tableted Cold set soyprotein hydrogel	8% swelling at 25 8C; 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 hours	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 8C, 6 hours	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, 6h, 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, 6h, 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 behavior 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, 4h 55%, pH=7.4, 7h 95%, pH=6.8, 30h	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 behavior The maximum swelling behavior in pH 7; minimum swelling behavior in pH 7	**The cargo release has not investigated**	A good swelling behavior confer them as smart materials for controlled and slow delivery of drugs and agricultural products	[448]

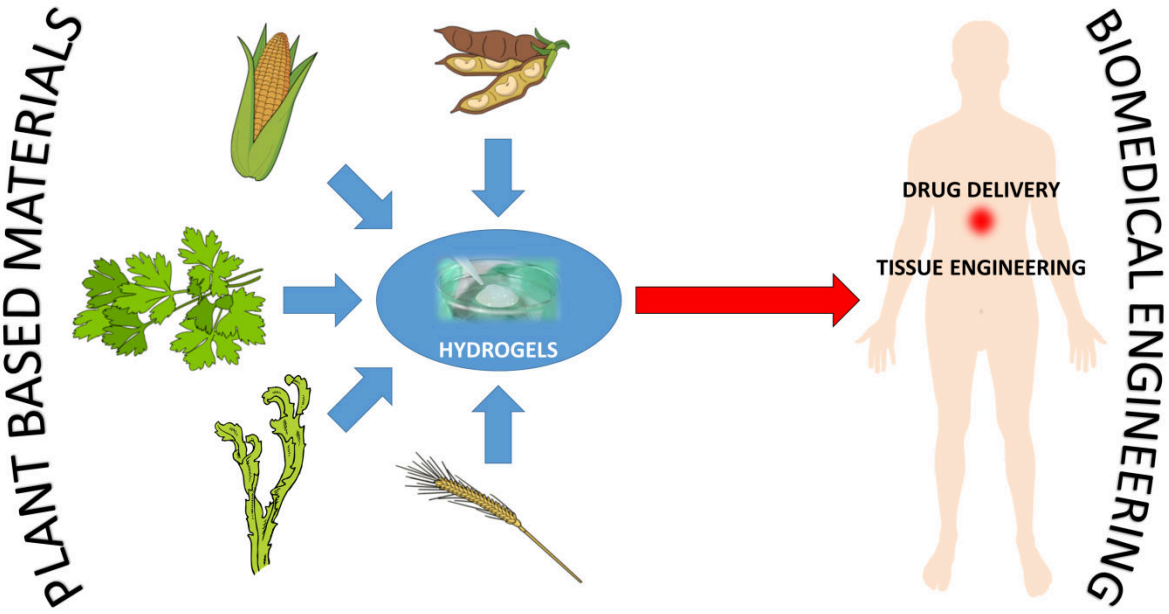
Soy lecithin self-assembled emulsion hydrogels.	Emulsion hydrogel formed at lecithin conc. 40 w/w %; Amorphous network; Viscoelastic nature; Biocompatible toward HaCaT cells (human keratinocytes)	100% in vitro release of metronidazole at 24 h.	The mechanism of drug release was predicted using Kor-smeyer–Peppas model; The drug loaded emulsion gels showed a good antimicrobial activity; Release behavior 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 behavior: gellan enriched, 6.45±0.05, pH=30, 30h; 9.94±0.09, pH=7, 30h Partial hydrogel disintegration Gellan/$CaCl_2$-enriched at pH 3 and 5	Gellan/$CaCl_2$-enriched, ~65% release in pH=3, 270min; Gellan (0.5 mg mL^{-1})-enriched, ~ 45% release in in pH=3, 270min	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]

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

Highlights

- Hydrogels are very important materials for biomedical applications.
- Plants based green hydrogels are briefly discussed.
- Synthesis of plant based green hydrogels is summarized in detail
- Biomedical applications of plant based green hydrogels are highlighted
- State-of-art applications of some of the green hydrogels are briefly presented and discussed.

Graphical Abstract





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

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