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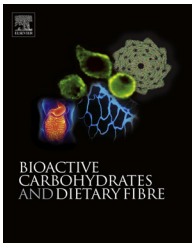

A review of bioactive plant polysaccharides: Biological activities, functionalization, and biomedical applications

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ABSTRACT

Natural polysaccharides from different sources have long been studied and widely used in different areas, such as food and feed, medicine and pharmaceutics, and in papermaking. In recent decades, there has been an increased interest in the utilization of polysaccharides, particularly bioactive ones, for various novel applications owing to their biocompatibility, biodegradability, non-toxicity, and some specific therapeutic activities. The main goal of this paper was to review the sources, natively biological activities, isolation, characterization, and the structural features of natively bioactive polysaccharides. Moreover, the article has also been forcused on the chemical/chemo-enzymatic functionalizations that may create novel opportunities to maximally exploit the various valuable properties of polysaccharides, particularly from wood species, in previously unperceived applications especially for biomedical applications, such as tissue engineering, wound healing, and drug delivery. This article was to review novel strategies to tailor functional materials with above mentioned application potentials for the polysaccharides from wood species.

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1. Introduction

Polysaccharides along with oligosaccharides, the most abundant group of biopolymers, have been found to participate in many biological processes, such as cell–cell communication, embryonic development, infection of bacteria and/or virus, and humoral and cellular immunity (Cooke, An, Kim, Solnick, & Lebrilla, 2007; Dube & Bertozzi, 2005; Varki, 1993). Therefore, polysaccharides together with polynucleotides, proteins, and lipids constitute the most important four biomacromolecules in life science. In this review, the bioactive polysaccharides refer to those polysaccharides that show biological effects on organisms and those polysaccharides that can be produced by living organisms or functionalized from sugar-based materials. Additionally, the biological effects that polysaccharides can exert are limited to therapeutic activities for diseases of humans and animals, and toxic activity responsible for causing human and animal disease (Colegate & Molyneux, 2008).

Although polysaccharides have been used for decades in various industrial applications, e.g. pharmaceuticals, biomaterials, food stuff and nutrition, and biofuels, growing understanding and deeper investigations of the importance of polysaccharides in life science are driving the development of polysaccharides for novel (biomolecular) applications (Alonso-Sande, Teijeiro-Osorio, Remunan-Lopez, & Alonso, 2009; Crini, 2005; García-González, Alnaief, & Smirnova, 2011; Kamerling & Boons, 2007; Pitarresi, Calabrese, Palumbo, Licciardi, & Giammona, 2009; Spizzirri et al. 2010; Suh & Matthew, 2000). The biological activities of polysaccharides are strongly affected by their chemical structure and chain conformations. However, the macromolecular structures of plant cell wall polysaccharides, especially hetero-polysaccharides or so-called hemicelluloses, are extremely complex due to the presence of different monosaccharides as building blocks, which usually are isobaric stereoisomers, variations in sequence, linkage, branching, and distribution of side chains (An & Lebrilla, 2011; Cancilla, Penn, & Lebrilla, 1998; Mäki-Arvela, Salmi, Holmbom, Willför, & Murzin, 2011). Besides, the polysaccharides in microorganisms (fungi, yeasts, and bacteria), algae, plants, and animals are always physically and/or chemically tangled together with other biomolecules, e.g. proteins, polynucleotides, lipids, lignin, and some inorganic mineral substances (Yang & Zhang, 2009). Therefore, comprehensive understanding the important roles of the bioactive polysaccharides in life science and exploring their application call for the multidisciplinary collaboration from experts on plant and microbial polysaccharides, glycochemistry, glycobiology, glycomedicine, phytology, and zoology (Colegate & Molyneux, 2008).

The aim of this article was to review the state-of-art in identification, isolation, functionalization, characterization, and application of bioactive polysaccharides derived from natural sources. Exploration of biomedical applications such as tissue engineering, wound healing, and drug delivery for polysaccharides were emphasized. The goal was to seek novel strategies to tailor functional materials with above mentioned application potentials for the polysaccharides from plants.

2. Sources and biological activities of bioactive polysaccharides

Polysaccharides can be classified in many possible ways, such as on the basis of structure, chemical composition, solubility, sources, and applications. With regard to the chemical composition, the polysaccharides are classified into two types, i.e. homo-polysaccharides or homoglycans, which are made up of a single type of monosaccharide, for example, cellulose and glycogen consist of glucose; hetero-polysaccharides or heteroglycans, which consist of more than one type of monosaccharide, such as heparin which consists of, α-L-idopyranosyluronic acid 2-sulfate and 2-deoxy-2-sulfoamino-α-D-glucopyranose 6-sulfate (Xiao et al., 2011). According to the glycosides linked onto the glycan, polysaccharides can also be classified as proteoglycans and glycoproteins, glycolipids, and glycoconjugates (Berg, Tymoczko, & Stryer, 2012; Gatti, Casu, Hamer, & Perlin, 1979). Based on the origins, bioactive polysaccharides from plant (dietary fibers, herbs and wood plants), algae and lichen, and other bioactive polysaccharides which are derived from animals (e.g. heparin, chondroitin sulfate, and hyaluronan)

and possess similar structural features (e.g. sulfate) as certain plant ones are reviewed in this paper. Specifically, the sources, chemical composition, molecular structure, and biological activities of naturally bioactive polysaccharides are reviewed below based on their original sources, to understand their presence and biological function.

2.1. Bioactive polysaccharides in dietary fibers

The dietary fiber was defined by the Food and Agriculture Organization (FAO) as a variety of indigestible plant polysaccharides including cellulose, hemicelluloses, pectins, oligosaccharides, gums, and various lignified compounds. Polysaccharides in the dietary fibers may be active in their native form or after chemical/enzymatic treatments. For example, the cellulose and hemicellulose can directly stimulate the bowel movement, while the inulin needs to be fermented into short-chain fatty-acids by microflora so as to prevent numerous gastrointestinal disorders (Pool-Zobel, 2005). Among the constituent in dietary fibers, polysaccharides play an important role in disease prevention. For example, pectins, inulin, and gums are able to slow the movement of food in the digestive tract, to reduce the blood cholesterol level, and to slow the speed of sugar absorption from the food into the blood, avoiding sudden hyperglycemia after food intake. Cellulose, hemicellulose and lignin constitute the insoluble fibers of dietary fibers which are able to stimulate the movement of bowel, speeding up the passage of waste through digestive tract, and to prevent constipation, diverticulosis, and hemorrhoids (Chawla & Patil, 2010; Tungland & Meyer, 2002). Numerous convincing epidemiological and clinical studies suggest that moderate or higher intakes of dietary fiber can effectively lower risks for developing diseases like diabetes (Weng, Lee, Yeh, Ho, & Pan, 2012), cardiovascular diseases including stroke (Casiglia et al., 2013), coronary heart disease and hypertension (Viuda-Martos et al., 2010; Whelton et al., 2005), hypercholesterolemia, hyperlipidemia (Chau, Huang, & Lin, 2004; Kendall, Esfahani, & Jenkins, 2010), obesity, and gastrointestinal (colorectal) cancer (Lunn & Buttriss, 2007). Generally, dietary fiber intake provides many benefits, including a decrease in intestinal transit time and an increase in stools bulk, and decreases in blood total cholesterol, and postprandial blood glucose, and/or insulin levels (Anderson et al., 2009; Brown, Rosner, Willett, & Sacks, 1999; Lunn & Buttriss, 2007).

Considering the importance of dietary fibers to human health and its specific working mechanism, we included the dietary fibers as a source of bioactive polysaccharides. The main sources, structure, composition, and biological effects of dietary fiber polysaccharides from follow-up investigations, intervention trials, and/or randomized-controlled trials are summarized in Table 1.

2.2. Bioactive polysaccharides in herbs

In traditional medicines of many countries, such as the traditional Chinese medicines, Japanese Kampo medicines, Indian Ayurveda, and Phyto-medicines in western countries, herbs have been used to treat various types of illnesses. Modern pharmacological experiments have identified that the main or key components of herbal medicines generally include low-molar-mass compounds, such as alkaloids (e.g. phenanthridine alkaloid in *Lycoris radiata* herb, protoberberine alkaloids in *Rhizoma coptidis*), terpenoids (e.g. *Rabdosia* diterpenes and quassinoids), flavonoids (e.g. *scutellaria* flavones), saponins; and high-molar-mass proteins, tannins, and most importantly polysaccharides (Tang, Hemm, & Bertram, 2003a,b). Of these fractions in herbal medicines, polysaccharides have been identified as one of the major active ingredients responsible for various pharmacological activities, such as immunostimulatory activity, antiviral activity, antioxidant activity, antitumor activity, radioprotection effect, hepatoprotection effect, and antifatigue effect. (Harlev, Nevo, Lansky, Ofir, & Bishayee, 2012; Jin, Huang, Zhao, & Shang, 2013; Li & Peng, 2013; Thakur et al., 2012; Tian, Zhao, Guo, & Yang, 2011). Polysaccharides in various herbs are believed to be active in their native form to stimulate human immune systems, to inhibit viral replication, to scavenge free radicals, and to inhibit lipid oxidation (Harhaji Trajkovic et al., 2009; Ke et al. 2011; Li & Peng, 2013). A brief summary of the recent advances in the study and application of bioactive polysaccharides from herbal medicines for disease control and treatment is presented in Table 1.

2.3. Bioactive polysaccharides in algae and lichens

The polysaccharides in algae and lichens have attracted an increasing interest due to their excellent physical properties, such as thickening, gelling, and stabilizing ability, and also due to their beneficial biological activities, such as anticoagulant, antithrombotic, antioxidative, antiviral, anti-inflammation, antitumour, and immunomodulating activity. (Kim & Li, 2011; Olafsdottir & Ingólfsdottir, 2001).

The sulfated polysaccharides are one group of the most interesting and attractive components in the marine algae, such as fucoidans and laminarans in brown algae (*Phaeophyceae*), carrageenans in red algae (*Rhodophyceae*), and ulvans in green algae (*Chlorophyceae*) (Wijesekara, Pangestuti, & Kim, 2011). Anticoagulant activity could be the most attractive property of the sulfated polysaccharides. For example, the sulfated galactans (carrageenan) from red algae and the sulfated fucoidans from brown algae have been identified with high anticoagulant activity. Sulfated polysaccharides from algae were reported to possess similar or even stronger activity than those of heparin (Maeda, Uehara, Harada, Sekiguchi, & Hiraoka, 1991). There are several other beneficial biological activities of sulfated polysaccharides from algae that have also been intensively studied. For example, (1) the highest antioxidant activity expressed as protection of the human body against damage from reactive oxygen species was found in fucoidan (followed by alginate and laminaran); (2) the anticancer activity of the algae was found to originate from its free-radical scavenging and antioxidant activity (Chattopadhyay et al., 2010); (3) the antiviral activity of carrageenans, fucoidans, and sulfated rhamnogalactans was proved by exerting inhibitory effects on the entry of herpes and HIV viruses into cells (Wijesekara et al., 2011); (4) immunomodulatory activity of algae-derived polysaccharides was shown by enhancing the phagocytic and secretory activity of

Table 1 – A brief summary of bioactive polysaccharides from different sources.

Type	Name	Composition	Sources	Physiological effects	Ref.
Dietary fiber	Cellulose	β-(1→4) linked-D-glucopyranose, linear and homopolysaccharides	Grains, fruit, vegetables, nuts	Increase stool bulk and help to regulate bowel movement	Viuda-Martos et al. (2010)
	Hemicelluloses	Four classes of structurally different cell-wall polysaccharides including xylans, mannans, β-glucans with mixed linkages and xyloglucans	Vegetative and storage tissues of annual and perennial plants, fruit, legumes, and nuts	Immunomodulating activity, antithrombotic activity, free radicals eliminating activity, antioxidant activity, bowel movements regulating and cholesterol lowering effect	Doliška et al. (2012), Ebringerová et al. (2008), Heinze (2005), Mudgil and Barak (2013), Wu and Chen (2011)
	Pectins	α-(1→4)-D-Galacturonic acid and rhamnose backbone, arabinose, galactose, xylose side chains, partially O-methyl/acetylated	Plant primary cell wall, soft tissues of fruit and vegetable	Intestinal immune system modulating activity, cholesterol lowering effect, decrease gastric emptying and small intestine transit time	Mudgil and Barak (2013), Suh et al. (2013), Yu, Kiyohara, Matsumoto, Yang, and Yamada (2001)
	β-Glucans	β-(1→4)-D-Glucose and β-(1→3)-D-glucose	Oats, barley grains	Cholesterol lowering effect, control of blood glucose level and lipids; reduction of hypertension, stimulation of immune system	Charlton et al. (2012), Chen and Raymond (2008), Marques, Dhont, Sorgeloos, and Bossier (2006), Wolever et al. (2011)
	Resistant starch	α-(1→4) and/or (1→6) linked D-glucopyranosyl	Cooked and cooled potatoes, rice, green bananas, legumes, food containing modified starch	Prevention of colonic cancer, hypoglycemic and hypocholesterolemic effects, role as prebiotic, inhibition of fat accumulation, enhance the absorption of minerals	Bird, Conlon, Christophersen, and Topping (2010), Fuentes-Zaragoza, Riquelme-Navarrete, Sánchez-Zapata, and Pérez-Álvarez (2010)
	Gums	Galactan, xylan, xyloglucan, glucuronic mannan, galacturonic rhamnosan type	Locust bean gum, gum arabic, and guar gum which are exudates of trees or isolated from seeds	Hypocholesterolemic and hypotriglyceridemic effects, influence on postprandial glycemia, lipemia, and lipoprotein composition, gel-forming to increase satiety, slow gastric emptying	Chawla and Patil (2010), Whistler and BeMiller (1993)
	Inulin	β-(1→2)-D-Fructofuranosyl	Chicory root, wheat, onion, garlic	Hypolipidemic effects, prebiotic properties which influence gut microbiota, stimulate mineral (calcium, magnesium) absorption	Capriles and Areas (2013), Cherbut (2002), Russo et al. (2012)
	Konjac glucomannan	β-(1→4)-Linked D-glucose and β-(1→4)-linked D-mannose	Amorphophallus konjac plant	Cholesterol lowering, bulking for weight reduction, reduces the risk of constipation	Al-Ghazzewi et al. (2007)
Herbs	Ginseng polysaccharides	(1→4)-Linked homogalacturonan backbone. (1→2(3))-Linked rhamnose on position 4 as a part	Ginseng, the root of *Panax ginseng*	Antirotavirus activity	Baek etb al. (2010)

Table 1 (*continued*)

Type	Name	Composition	Sources	Physiological effects	Ref.
		of backbone or ramified regions. (1→5(2))-Linked arabinose with branch points at position 3. (1→3(4))-Linked terminal galactose			
	Astragalus polysaccharides	α-(1→4)-D-Glucan with α-(1→6)-branches	*Astragalus* roots	Immunemodulating activity, antiviral activity	Li et al. (2011), Li and Peng (2013)
	Acanthopanax senticosu polysaccharides	Seven monosaccharides including rhamnose, xylose, glucose, mannose, arabinose, galactose, and glucuronic acid in a molar ratio of 7.45:18.63:25.15:0.93:8.35:2.79:5.69	*Acanthopanax senticosus* leaves	Antioxidant and immunobiological activity	Chen et al. (2011)
	Polygonum multiflorum Thunb polysaccharides	Mainly glucose	*Polygonum multiflorum* Thunb root	Antioxidant activity and antiglycation	Lv, Cheng, Zheng, Li and, Zhai (2014)
	Platycodon grandiflorum polysaccharides	(1→4(6))-Linked galactopyranosyl residues, with branches attached to O_3 of (1→6)-linked galactose residues. Arabinose and galactose in the molar ratio of 1.42:1.0	*Platycodon grandiflorum* root	Antiangiogenic activity	Xu, Dong, Qiu, Cong, and Ding (2010)
Algae and lichens	Green algae sulfated polysaccharides	(1→3(6))-Linked galactose, (1→3(4))-linked arabinose, (1→4)-linked glucose and terminal, (1→4)-linked xylose residues. Sulfations occur on O_6 of galactose and O_3 of arabinose. Sulfate ester content: 9%	Green algae, *Caulerpa racemosa*	Antiviral activity (herpes simplex virus type 1 and 2)	(Ghosh et al., 2004)
	Brown algae sulfated polysaccharides	Fucan: (1→3)-linked α-L-fucopyranosyl backbone, mostly sulfated at C_4, and branched at C_2 with non-sulfated fucofuranosyl and fucopyranosyl units, and 2-sulfated fucopyranosyl units. Galactan: D-galactopyranose units linked on C_3 and C_6, and sulfation mostly on C_4. Sulfate ester content: 30–34%/21–24%	Brown algae, *Adenocystis utricularis*	Antiviral activity (herpes simplex virus type 1 and 2), Antiretroviral activity (HIV-1)	Ponce, Pujol, Damonte, Flores, and Stortz (2003), Trinchero et al. (2009)
	Red algae sulfated polysaccharides (porphyran)	Backbone of alternating β-(1→3)-linked D-galactosyl units and α-(1→4)-linked L-galactosyl, (1→6)-sulfate or 3,6-anhydro-α-L-galactosyl units. Sulfate ester content: 17%	Red algae, *Porphyra haitanensis*	Antioxidant activities, anticoagulant activities	Zhang et al. (2010)
	Green algae sulfated rhamnan	(1→2)-Linked L-rhamnose residues with sulfate groups substituted at positions of C_3 and/or C_4. Sulfate ester content: 23%/25%	Green algae, *Monostroma latissimum*	Anticoagulant activity	Li et al. (2012a), Mao et al. (2009)
	Algal fucoidan	Fucose, galactose. Sulfations occur on position-2 and -3. Sulfate ester content: 41–92%	Brown algae, *Ecklonia cava*	Anti-inflammatory activity	Kang et al. (2011)
	Brown algae sulfated polysaccharides	Mainly composed of fucose (82%), galactose (14%), and small amounts of xylose and mannose Sulfate ester content: 92%	Brown algae, *Ecklonia cava*	Antiproliferative activity, anticancer activity	Athukorala et al. (2009)
		Galactofuranomannans, β-glucan lichenan			
		Galactofuranomannans, β-glucan	Lichen *Thamnolia vermicularis var. subuliformis*	Immunomodulating activity	Omarsdottir, Freysdottir, and Olafsdottir (2007)

Table 1 (*continued*)

Type	Name	Composition	Sources	Physiological effects	Ref.
β-Glucans lichenan	Lichenan: β-(1→3(4))-linked glucan Isolichenan: α-(1→3(4))-linked glucan Pustulan: β-(1→6)-linked glucan partially acetylated at O_3 Heteroglycan	Lichens, *Cetraria islandica/ Umbilicaria proboscidea/Thamnolia vermicularis var. subuliformis/ Peltigera canina*		Immunomodulating activity	Omarsdottir, Olafsdottir, and Freysdottir (2006)
Other sources (derived from animal)	Heparan sulfate/ heparin	(1→4) Linked glucuronic/ iduronic acid and *N*-acetylglucosamine disaccharide unites with variable 2/3/6-*O*-sulfonation	Animal granules of mast cell (heparin); Animal tissues, e.g. porcine intestine, bovine lung	Anticoagulant activity	Linhardt (2003), Schedin-Weiss et al. (2008)
	Chondroitin sulfate/dermatan sulfate	(1→3) linked glucuronic/iduronic acid and (1→4) linked *N*-acetylgalactosamine disaccharide unites with variable 2/3/6-*O*-sulfonation	Animal cartilaginous tissue, e.g. bovine trachea, and shark cartilage	Modulating cellular growth and signaling, maintaining the extracellular matrix integrity	Barnhill et al. (2006), Hitchcock, Costello, and Zaia (2006), Takegawa et al. (2011)

macrophages and by inducing the production of reactive oxygen species, nitric oxide, and cytokines (Schepetkin & Quinn, 2006).

Polysaccharides isolated from lichens are primarily linear or scarcely substituted α- and/or β-glucans. Such glucans from lichens have been reported to possess a variety of biological activities like antitumour activity, immunomodulating effect, and antiviral activity (Olafsdottir & Ingólfsdottir, 2001; Omarsdottir, Freysdottir, & Olafsdottir, 2007; Zambare & Christopher, 2012). The β-glucans from lichens and lichenan showed the immunomodulating activity by stimulating a wide range of immune responses such as cytokine release, generation of reactive oxygen species and nitric oxide, and release of arachidonic acid metabolites (Schepetkin & Quinn, 2006). Lichenan with a galactoglucomannan structure showing anticoagulant and antithrombotic activity was also reported (Martinichen-Herrero, Carbonero, Sassaki, Gorin, & Iacomini, 2005).

Biological activities of the sulfated polysaccharides from both algae and lichens highly depend on their structural features, such as the sulfate content and distribution of sulfate groups on the main chain, molar mass, and stereochemistry. Therefore, modification of the native sulfate polysaccharides to obtain the bioactive polysaccharides with desired molecular size and functional property for application is needed (Ngo & Kim, 2013; Wijesekara et al., 2011). A brief summary of recent research advance is listed in Table 1.

2.4. *Bioactive polysaccharides in wood*

Polysaccharides from wood mainly include cellulose and a few primary groups of hemicelluloses, i.e. xylans, glucomannans, arabinans, galactans, and glucans (Fraser-Reid, Tatsuta, & Thiem, 2008; Gatenholm & Tenkanen, 2004; Heinze, 2005). Galactoglucomannans and pectins from wood have been reported to show immunostimulating activities and radical-scavenging activities (Ebringerová et al., 2008; Le Normand et al., 2014). Xylans or Xylooligosaccharides from hardwood, softwood, and dietary fibers have also been found to possess great prebiotic potential for application in both medical and nutrition research (Aachary & Prapulla, 2011). However, most polysaccharides do not show biological activity unless some modifications are carried out. Cellulose derivatives, such as methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, and hydroxylpropylmethylcellulose, have found promising applications in various fields such as food, medical, pharmaceutical, and cosmetics (Li & Mei, 2006). Therefore, further review of wood polysaccharides will be presented in the later functionalization/modification section. There, the strategies to functionalize wood polysaccharides towards bioactive applications will be discussed in detail.

2.5. *Bioactive polysaccharides from other sources*

The sulfated glycosaminoglycans such as the heparan sulfate (HS), chondroitin sulfate (CS), dermatan sulfate (DS), and keratin sulfate represent another group of bioactive polysaccharides that are mainly derived from animals. HS chains are made up of variably sulfated and *N*-acetylated repeating disaccharide unites, i.e. glucuronic/iduronic acid and glucosamine (Chappell & Liu, 2013; Linhardt, 2003; Sakiyama-Elbert, 2014). Heparin, the most highly sulfacted heparan sulfate, has been widely used as the most effective clinical anticoagulant. Anticoagulant activity of the heparin highly relies on its specific structure sequence, within which the binding site of an important protein (antithrombin III) is crucial for heparin to prevent the generation of a fibrin clot which is formed by the action of thrombin (Schedin-Weiss, Richard, Hjelm, & Olson, 2008). Understanding of this structure–activity relationship of heparin offers the opportunity to develop drugs with higher specificity and better regulation of coagulation and to explore other therapeutic applications such as infection, inflammation, cancer and wound-healing treatment (Linhardt, 2003; Rajangam et al., 2006; Sakiyama-Elbert, 2014; Zhang et al., 2013a; Zhang, Wardwell, & Bader, 2013b). CS/DS chains are composed variably sulfated *N*-acetylgalactosamine and glucuronic acid or its epimeride iduronic acid disaccharides repeating units (Silbert & Sugumaran, 2002; Takegawa et al., 2011). Growing research evidence reveals the previously less or

unperceived functions of CS/DS (Sugahara et al., 2003), for example being a key molecule of the brain extracellular matrix (Kwok, Warren, & Fawcett, 2012), regulating the cell adhesion, proliferation and migration during wound healing (Zou et al., 2004), signaling of growth factor in skeleton (Alliston, 2010).

Hyaluronic acid (HA), which is mainly drived from animal and plant tissues, is a linear non-sulfated glycosaminoglycan with repeating disaccharide units of β-(1→4)-D-glucuronic acid and β-(1→3)-*N*-acetyl-D-glucosamine. HA is an essential component of the extracellular matrix, mediating cellular signaling, wound repair, morphogenesis, and matrix organization and thus HA and its derivatives have been clinically used for medical applications, such as viscosupplementation, eye surgery, and drug delivery for decades (Balazs, 2009; Gaffney, Matou-Nasri, Grau-Olivares, & Slevin, 2010; Prestwich, 2011).

Chitin, the second most abundant polymer after cellulose, is a co-polymer of β-(1→4)-linked N-acetyl-glucosamine (acetylated unit) and *N*-glucosamine (deacetylated unit) which randomly distributed along the chain (Khan & Ahmad, 2013). Chitin can primarily be found in the exoskeleton of arthropods (e.g., shells of crabs and shrimp) and in the cuticles of insects, however it have been identified and extracted in the cell walls of fungi and yeast (Bartnicki-Garcia, 1968; Logesh, Thillaimaharani, Sharmila, Kalaiselvam, & Raffi, 2012). So the chitin and chitosan will be also reviewed in this paper even if there are not belonging to the plant kingdom. Partial deacetylation of chitin under alkaline conditions or by chitin deacetylase yields the most important derivative of chitin, i.e. chitosan. Generally, when the number of *N*-glucosamine units is higher than 50%, the term chitosan is used (Fig. 4) (Khor & Lim, 2003). Oligomers from partial acid hydrolysis of chitin and chitosan were recognized for their bioactivity, including hemostatic action, anti-inflammatory effect, antitumoral, antibacterial, and fungicidal properties, eliciting chitinase, and regulating plant growth (Rinaudo, 2008).

3. Isolation of bioactive polysaccharides

Generally, (bioactive) polysaccharides are present together with various other components such as proteins, polynucleotides, lipids, extractives, lignin, and some inorganic mineral substances. However, the desired biological activities of the naturally bioactive polysaccharides may be undermined by other compounds, which may even cause antagonistic effects or undesirable toxicity. In other words, pure bioactive polysaccharides could enable the safe, reproducible and accurate dosage for experimental or therapeutic applications, and also enable the investigation of structure/activity relationship, facilitating the development of new compounds with similar or higher desirable bioactivities (Colegate & Molyneux, 2008). Thus, the isolation of natural polysaccharides that have biological activities toward organisms from various sources plays an important role in the investigation and application of bioactive polysaccharides.

Generally, bioactivities of polysaccharides are highly dependent on their structural information, such as molar mass, extent of side chains/groups or substitution and their distribution on the backbone. Thus, how to isolate the polysaccharides from the complex matrix networks, meanwhile minimizing any loss of the desired bioactivity, is one of the most important tasks to deal with.

In recent years, novel and effective extraction methods, such as supercritical fluid extraction, microwave-assisted extraction, and the most promising hot-water extraction, have gained increasing attention due to their environmentally friendly process, higher extraction efficiency, cost effectiveness, and structure-preservation ability (Chao, Ri-fu, & Tai-qiu, 2013; Le Normand et al., 2014; Song, Pranovich & Holmbom, 2013). For example, Cheng et al. (2013) compared hot-water, ultrasonic assisted, enzyme, and microwave-assisted extractions to isolate bioactive polysaccharides and discovered that the yielded four polysaccharides had similar physicochemical properties, however, the antioxidant activity of the polysaccharides obtained by hot-water extraction was stronger than those isolated with other methods. Hot-water extraction combined with some novel assistant methods, such as microwave, ultrasonic, and enzymatic pretreatment, increases the extraction efficiency and yield of products. For example, enzymatic pretreatment of the raw material before extraction normally results in a reduction in extraction time, lowers energy consumption, minimizes the usage of solvents, increases the yield, and maximally preserves biological activities of the product when compared to non-enzymatic methods (Chen et al., 2014; Dong, Wang, & Wang, 2011; Jia et al., 2013; Lazaridou, Chornick, Biliaderis, & Izydorczyk, 2008; Puri, Sharma, & Barrow, 2012). Recently, ionic liquids have also been developed to extract polysaccharides at low temperature and short time (Abe, Fukaya, & Ohno, 2010).

Further purification of bioactive polysaccharides from crude extracts is of high importance, which ensures understanding of the relationship between structures and the safety of the furture biomedical, pharmaceutical, and food applications. This can be done with a combination of several techniques, such as ethanol precipitation, fractional precipitation, ion-exchange chromatography, gel filtration, and affinity chromatography by taking advantages of particular properties of the desired compound such as acidity, polarity, and molecular size (Jin et al., 2013).

4. Functionalization of polysaccharides

The naturally bioactive polysaccharides from different sources could offer numerous bioactive properties and benefit humanity in health care, as reviewed above. It is known that the structural features of the polysaccharides, such as degree and steric configuration of substitutions, linkages of monosaccharides and substitutes, and molar mass and its distribution play a critical role on their physicochemical (e.g. solubility and fluid capability) and bioactive properties (Ngo & Kim, 2013). Therefore, the modification of natively bioactive polysaccharides to extend their applications in both traditional and newly explored biomedical areas, such as tissue engineering, controlled drug delivery and release, and wound healing/dressing, is of high importance. Besides, the functionalization of those polysaccharides that do not possess innate bioactivity to introduce bioactivity by designing cost-effective approaches is also attracting increasing attention. This section will focus on the functionalization of polysaccharides, mainly including plant derived polysaccharides, i.e. cellulose and hemicelluloses, and starch as summarized in Table 2. Other non-plant derived polysaccharides such as chitin and chitosan, alginate,

Table 2 – Summary of polysaccharide modification and applications of the functionalized derivatives.

Polysaccharides	Modification approaches	Description of reactions or products	Potential applications	Ref.
Cellulose	Etherification	Methyl-/carboxymethyl-/ethyl-/hydroxyethyl-/hydroxypropyl-/hydroxypropylmethyl-/cyanoethyl-cellulose	Pharmacy	Kalia, Kaith, and Inderjeet (2011), Li and Mei (2006)
	Selective oxidation	TEMPO mediated oxidation, periodate oxidized 2,3-dialdehyde cellulose	Drug delivery system, wound healing, regulation of postprandial glucose and insulin level	Lacin (2014), Shimotoyodome et al. (2011), Valo et al. (2013), Zhu et al. (2001)
	Graft copolymerization	Chemical redox initiation or irradiation methods to introduce different monomers, e.g. acrylic acid, acrylamide, acrylonitrile, methyl methacrylate, ethyl acrylate etc.	Stimuli-responsive drug delivery	Mohd Amin et al. (2013), Thakur, Thakur, and Gupta, (2013b)
Chitin/chitosan	Etherification	*O*-carboxymethyl and *N*-carboxymethyl derivatives obtained when the carboxymethylation takes place at carboxyl groups and free amino groups respectively.	Target drug delivery, hemostatic dressings	Zhang et al. (2010)
	Quaternization (etherification)	Trimethyl chitosan chloride, *N*-propyl-*N*,*N*-dimethyl chitosan, *N*-furfuryl-*N*,*N*-dimethyl chitosan, *N*-diethylmethylamino chitosan. Different degree of quaternization (methylation) of amino groups in chitosan can be achieved with methyl iodide in alkaline solution of *N*-methyl pyrrolidinone	Absorption enhancer for test drugs, gene carriers, controlled drug releaser, antibacterial agents	Mourya and Inamdar (2008)
	Graft copolymerization	Initiated by free radicals initiator systems, irradiation methods, or grafting via enzymatic methods (e.g. tyrosinase)	Wound-dressing materials, drug delivery, tissue engineering, antimicrobial agents	Alves and Mano (2008), Ito et al. (2013)
Alginate	Esterification	Propylene glycol alginate, synthesized by reaction with propyleneoxide. Dodecyl alginate, prepared by reaction of tetrabutylammonium salts of alginic acid with dodecyl bromide	Amorphous solid dispersion of drugs	d'Ayala et al. (2008); Pawar and Edgar (2013)
	Oxidation	Selectively breaks the vicinal glycols and introduces new reactive groups, i.e. two aldehyde groups	Tissue engineering	Bouhadir et al. (2001), Kim et al. (2012)
	Graft copolymerization	Chemical redox initiation, microwave initiated synthesis, or microwave assisted synthesis to introduce different monomers (vinyl or acrylic compounds, e.g. poly(*N*-isopropylacrylamide))	Temperature and pH responsive hydrogel for delivery of proteins or drugs, wound healing dressing	Gao, Liu, Chen, Jin, and Chen (2009), Isiklan and Kucukbalci (2012), Pawar and Edgar (2012), Wong (2011), Xu et al. (2013)
	Layer-by-layer self-assembly	Repeated deposition of oppositely charged polymers (e.g. negative charged alginate and positive charged chitosan in acid conditions) on material surfaces as polyelectrolyte multilayers	Cell adhesion and spreading, drug and DNA delivery	Caridade et al. (2013), Hu and Tsou (2014), Liu, Liu, Liu, Li, and Liu (2013), Silva et al. (2013a)
Starch	Esterification			Tupa et al. (2013)

Table 2 (*continued*)

Polysaccharides	Modification approaches	Description of reactions or products	Potential applications	Ref.
		Prepared by reaction of starch with fatty acid chlorides/vinyl esters/anhydride/carboxylic acids as reactants. E.g. Starch acetates, starch butyrates	Used as superdisintegrant and matrix former in capsules and tablet formulations, controlled release, maintaining human colonic function	
	Etherification	Methyl/hydroxypropylmethyl/ hydroxyethyl/ hydroxyethylmethyl starch	Pharmaceutical application	BeMiller and Whistler (2009), Tharanathan (2005)
Hyaluronic acid (HA)	Esterification	Esterification of HA by alkylation using akyl halides (chlorides, iodides, bromide), by using diazomethane, and by using epoxides	Cell carrier for skin wounds, drug carrier	Benedetti et al. (1993), Schanté et al. (2011)
	Amidation	Amidation of HA in water or of HA's TBA salt in organic solvent with coupling agents, e.g. EDC, NHS	HA–drug conjugates for controlling release, target specific delivery of biomolecules	Oh et al. (2010) Bulpitt and Aeschlimann (1999), Kong, Oh, Chae, Lee & Hahn (2010)
	Ugi condensation	Formation of diamide linkage between polysaccharides chains by using formaldehyde, cyclohexyl isocyanide and diamine	Controlled drug delivery	Crescenzi et al. (2003), Maleki, Kjoniksen, and Nystrom (2007)
Xylans	Graft-copolymerization	Free radical graft copolymerization of xylan-rich hemicelluloses with acrylic acid yielded ionic xylan-rich hydrogels	Adsorption, separation, and drug release applications.	Peng et al. (2011)
	Amidation & Enzymatic modification	Conjugating of tyramine with spruce arabinoglucuronoxylan by EDAC/NHS first then cross-linking using horseradish peroxidase and H_2O_2	Cell culture, tissue engineering.	Kuzmenko et al.
(Galacto) glucomannans	Hydrolysis	Partial hydrolysis of Konjac glucomannan by acid or enzymes	Food ingredient and prebiotic	Al-Ghazzewi et al. (2007)
	Esterification	Methacrylated galactoglucomannan cross-linked hydrogel	Drug delivery	Edgar, Heinze, and Buchanan, (2009)
	Oxidation	TEMPO-mediated oxidation	Further functionalization platform, e.g. functional biocomposites	Leppänen et al. (2013)
	Enzymatic modification	Selectively oxidize the primary hydroxyl groups of galactosyl to aldehyde functionalities using galactose oxidase	Potential platforms for further functionalizations, e.g. development of new anticoagulant and antithrombotic drugs	(Gatenholm and Tenkanen (2004), Leppänen et al. (2014), Parikka et al. (2012), Parikka et al. (2009), Xu et al. (2012)
Xyloglucan	Chemo-enzymatic modification	Incorporation of different chemically reactive groups or functional moieties, such as biotin into the xyloglucan by xyloglucan endotransglycosylase. Regioselectively oxidize the primary alcohols of galactosyl to aldehydes using galactose oxidase	Potential platforms for further functionalizations, e.g. functional biocomposites, *in vitro* diagnostics, biomolecular capture or detection	(Brumer et al. (2004), Xu et al. (2012)
Pectins	Graft copolymerization	Grafting with poly(N-vinylpyrrolidone) to prepare hydrogel copolymer	Colon-targeted dug delivery	Fares, Assaf, and Abul-Haija (2010)
	Cross-linking	Cross-linking *via* calcium or prepare composites with other polymers such as ethylcellulose and hydroxypropylmethyl cellulose	Controlled drug delivery	Liu et al. (2003)

and hyaluronic acid are also subjected to review. The aims of modification or functionalization include, but are not limited to, the improvement and/or introduction of bioactivity, biocompatibility, control of biodegradability, as well as manufacturing and shaping for biomedical, pharmaceutical, and food applications (Cumpstey, 2013; d'Ayala, Malinconico, & Laurienzo, 2008). When considering the application of the modified or functionalized polysaccharides, safe and green approaches such as enzymatic methods are preferred because of their selectivity and non-toxic solvent medium.

4.1. *Cellulose*

Cellulose is the most abundant polysaccharide in nature. Its value has been recognized in numerous traditional industries, such as construction, pulp and papermaking, and textile industries. For upgrading the value of cellulose, various value-added cellulose derivatives after chemical transformation or functionalization have been developed and utilized in other industries such as food, cosmetic, (bio)medical, and pharmaceutical. However, the application of cellulosic material is limited due to the difficulty in processing, for example, the high crystallinity degree and rigid intra/intermolecular hydrogen bonds which result in its insolubility in most solvents (Tashiro & Kobayashi, 1991).

Generally, the hydroxyl group is the most targeted reactive group on the cellulose chain. Chemical functionalizations of cellulose based on hydroxyl group include esterification, etherification, selective oxidation, graft copolymerization, and intermolecular crosslinking reaction (Pérez & Samain, 2010) as summarized in Table 2. However, the primary and secondary hydroxyl groups show different reactivity in different conditions. For example, the reactivity order of these hydroxyl groups during etherification reactions in alkaline condition is C_2–OH > C_6–OH > C_3–OH, while the reactive order of cellulose acetylation in LiCl/acetic acid dimethylamide (DMAc) shows as C_6–OH > C_3–OH > C_2–OH, but when the reaction takes place in LiCl/1,3-dimethyl-2-imidazolidinone, the corresponding order is C_6–OH > C_2–OH > C_3–OH (Heinze, 2005). In addition to the inherent reactivity difference of hydroxyl groups, regioselective control of the substitution of desired hydroxyls with functional groups can be achieved *via* various protecting and activating approaches as shown in Fig. 1. The difference in accessibility, reactivity, and regioselective control of hydroxyl groups provides the possibility to prepare cellulose derivatives with specific molecular structures for various applications.

Oxidation of cellulose is one of the most important modification methods to prepare value-added cellulose derivatives for further applications. For example, oxidized cellulose and regenerated cellulose are widely used as excellent hemostatic materials in various surgical operations and postsurgical adhesion prevention layers (Wu, He, Huang, Wang, & Tang, 2012). Selective oxidation of cellulose by converting the primary alcohol groups into carboxyl groups is of significance and has been studied intensively, especially for the preparation of nanofibrillated cellulose in recent years (Isogai, Saito, & Fukuzumi, 2011). Selective oxidation of cellulose primary hydroxyl groups into carboxyl and/or aldehyde groups can be achieved through two oxidation systems (Fig. 1): (1) 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and its derivatives; (2) *N*-hydroxyphthalimide (NHPI), *N*-hydroxybenzotriazole (HBT), and violuric acid (VA). (Biliuta et al., 2013; Coseri et al., 2009). Lately, oral administration of TEMPO-oxidized cellulose with glucose and glyceryl trioleate to mice was found to exhibit characteristic biological activities in reducing postprandial blood glucose, plasma insulin, glucose-dependent insulinotropic polypeptide, and triglyceride concentrations. This finding may suggest potential applications of TEMPO-oxidized cellulose in biomedical fields for human health (Shimotoyodome, Suzuki, Kumamoto, Hase, & Isogai, 2011). The carboxyl groups introduced by these approaches can be utilized for further functionalization. For example, by grafting amine-terminated polyethylene glycol chains (PEG) onto carboxylic sites of the TEMPO-oxidized cellulose, a better steric stabilization and salt tolerance property can be achieved (Araki, Wada, & Kuga, 2000). Besides, topological modification of films prepared from oxidized cellulose *via* 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC)/*N*-hydroxysuccinimide (NHS) chemical activation to produce non-porous, water-resistant substrates for immunoassays and diagnostics application, or to introduce linking biomolecular onto cellulose for immobilizing antibodies and other functionalities for medical and biological application have also been studied recently (Fig. 1) (Arola, Tammelin, Setälä, Tullila, & Linder, 2012; Orelma et al., 2012a; Orelma, Johansson, Filpponen, Rojas, & Laine, 2012b). Ascribed to the gelling properties, biodegradability, biocompatibility, and bioactivity of TEMPO oxidized NFC, its structured hydrogel and aerogel materials have been used for biomedical applications such as scaffold for wound-healing and 3-D cell culture, and drug carrier and controlled release, cosmetic applications such as thickeners and water-retaining agents, and other applications (Bhattacharya et al., 2012; Dong, Snyder, Tran, & Leadore, 2013; Sehaqui, Zhou, & Berglund, 2011; Shimotoyodome et al., 2011; Valo et al., 2013).

Another selective oxidation approach is the periodate oxidation (Fig. 1), which selectively oxidizes the adjacent hydroxyl groups (C_2–OH and C_3–OH) of cellulose yielding a sugar ring opened product with two aldehyde groups in the C_2 and C_3 position of the glucopyranose units (Calvini, Gorassini, Luciano, & Franceschi, 2006). This opens up untapped possibilities for further functionalization and application. For example, sulfonation of the periodate oxidized 2,3-dialdehyde cellulose with sodium bisulfite yields the corresponding $C_{2/3}$ sulfonates possessing stronger water retention ability (Zhang, Jiang, Dang, Elder, & Ragauskas, 2008).

Other oxidant systems, such as N_2O_4/CCl_4, NO_2/CCl_4, and HNO_3/H_3PO_4–$NaNO_2$ have also been developed to selectively oxidize cellulose (Fig. 1) (Coseri et al., 2009; Kumar & Yang, 2002; Wu et al., 2012). Oxidized cellulose has shown anti-tumor, immunostimulant, wound healing, and adhesion-prevention properties (Novotna et al., 2013; Zimnitsky, Yurkshtovich, & Bychkovsky, 2004). For example, the calcium/sodium salts of oxidized cellulose prepared from nitrogen oxides in nitric acid have shown immunomodulatory effects in both *in vitro* and *in vivo* tests (Jelinkova, Briestensky, Santar & Rihova, 2002). The carboxyl groups of the HNO_3/H_3PO_4–$NaNO_2$ oxidized cellulose open up possibilities for immobilization of drugs, the products of which have found

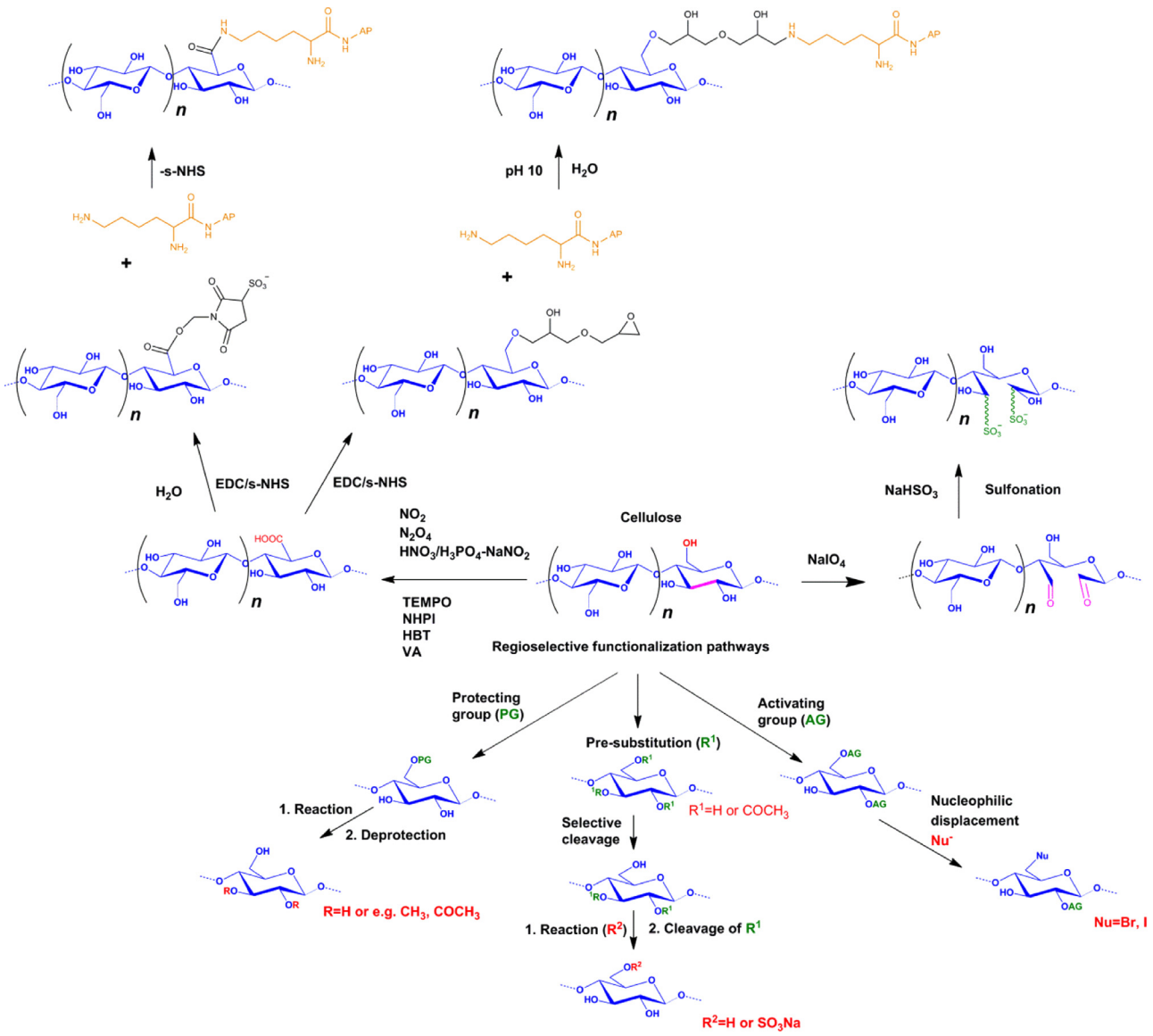

Fig. 1 – Selected pathways for regioselective functionalization of cellulose (adapted from Arola et al., 2012; Biliuta et al., 2013; Coseri et al., 2009; Koschella, Fenn, Illy, & Heinze, 2006; Wu et al., 2012; Zhang et al., 2008).

potential applications as biodegradable macromolecules used in drug delivery systems (Zhu, Kumar, & Banker, 2001).

Graft copolymerization is another approach for cellulose modification *via* chemical redox initiation methods (ceric ammonium nitrate or ferrous ammonium sulfate–potassium persulfate) or irradiation methods (UV, microwave, and γ-rays). Intensive studies have been carried out on the graft copolymerization of cellulosic polymers with suitable hydrophobic monomers to introduce desired functionalities into the cellulosic backbone, so as to overcome the sensitivity of cellulosic fibers towards water/moisture absorption and poor chemical resistance and thus to improve the existing physicochemical properties of the cellulosic polymers (Bashar, Khan, & Idriss Ali, 1995; Kaur, Kumar, & Sharma, 2010; Rattan, Maitra, Misra, & Kaur, 2008; Thakur, Thakur, & Gupta, 2013a). A biocide cellulose carbamate with antimicrobial properties was prepared by impregnating the fibers in aqueous thiourea solution and subsequently grafting with acrylonitrile (Dahou, Ghemati, Oudia, & Aliouche, 2010). Stimuli-responsive bacterial cellulose-*g*-poly(acrylic acid-*co*-acrylamide) hydrogels as drug delivery carriers have been synthesized by graft copolymerization of the monomers onto bacterial cellulose fibers using microwave irradiation. The grafted cellulose hydrogels demonstrated a pH-responsive swelling behavior (reaching maximum swelling at pH 7), suggesting a suitable controlled release in the lower gastrointestinal tract (Mohd Amin, Ahmad, Pandey, & Jue Xin, 2013).

4.2. *Hemicelluloses*

Hemicelluloses are a type of heterogeneous polysaccharides and are widely distributed in biomass. Hemicelluloses mainly include xylans, glucomannans, arabinans, galactans, and glucans. The diversity of hemicelluloses originates from: (a) sugar constituents, which mainly include glucose, xylose, mannose, galactose, arabinose, fucose, (4-*O*-methyl)glucuronic acid, and

galacturonic acid; (b) glycosidic linkages position and conformation between monosaccharides, e.g. , arabnformation, 1→2,3,4,5,6 linkages; and (c) side group/chain types, distribution, and linkages. Such structural and compositional complexities result in previously unperceived applications. However, as a group of important biopolymers, hemicelluloes have found a broad spectrum of applications both in native and in their modified forms. Generally similar to other polysaccharides, chemical modifications of hemicelluloses mainly include partial hydrolysis, graft polymerization, (regioselective) oxidation, reduction, etherification, esterification, and cross-linking. The modifications bring in new functionality and therefore create novel opportunities to exploit them for various applications such as in food, cosmetic, biomedical, and pharmaceuticals.

4.2.1. *Xylans*

Xylans are a diverse group of polysaccharides with the common feature of a backbone of β-(1→4)-linked xylopyranosyl units. Substitution or side groups/chains are varying according to different sources and methods of isolation. For example, *O*-acetyl-4-*O*-methylglucuronoxylans with (1→2) linked 4-*O*-methyl-α-D-glucuronic acid side groups and *O*-acetyl group at C_2 or C_3 are the major hemicelluloses in hardwoods and account for 15–30% of the dry wood. Xylans in softwood account only for 5–10% of the dry wood, and mainly exist as arabino-4-*O*-methylglucuronoxylans, which have 1→3) linked α-L-arabinofuranose and (1→2) linked 4-*O*-methyl-α-D-glucuronic acid side groups (Teleman, Tenkanen, Jacobs, & Dahlman, 2002; Viikari, Poutanen, Tenkanen, & Tolan, 2002).

Recently, xylans have gained increasing attention as basis for new functional biopolymeric materials by chemical modifications. Various functional groups can be introduced to xylans by esterification, etherification, and cross-linking for different applications, such as drug delivery, wound dressing, and antimicrobial agents. (Ebringerová & Heinze, 2000; Petzold-Welcke, Schwikal, Daus, & Heinze, 2014; Pohjanlehto, Setälä, Kammiovirta, & Harlin, 2011). For example, introduction of antioxidant activity to xylans for biomedical applications could be achieved by esterification with ferulic acid and sinapic acid (Wrigstedt et al., 2010). Pentosan polysulfate, an FDA-approved oral medicine, was prepared by sulfation of beechwood xylan. It has been known for its anticoagulant properties, anti-inflammatory and anticancer effects, and for lowering cholesterol and triglyceride levels (Doctor & Sauls, 1983; Schuchman et al., 2013). Product derived from xylan and chitosan *via* the Maillard reaction was found to exert antioxidant and antimicrobial activity (Wu et al., 2014). Peng, Ren, Zhong, Peng, and Sun (2011) reported ionic xylan-rich hydrogels with rapid and multiple responses to pH, ions, and organic solvents, which may allow the use in drug release systems. An *in situ* forming spruce xylan-based hydrogel was synthesized chemo-enzymatically for stem cell culture application (Kuzmenko, Hägg, Toriz, & Gatenholm). This xylan-based hydrogel showed mechanical integrity, interconnected porous structure, high degree of swelling, and supporting the differentiation of mesenchymal stem cells inside the gel, which is worthful for further evaluation for tissue engineering purposes. Other typical modifications to prepare xylan derivatives, such as cationic, ionic, and non-ionic xylan derivatives have been previously reviewed (Heinze, Koschella, & Ebringerová, 2003; Petzold-Welcke et al., 2014).

4.2.2. *Galactomannans, glucomannans, and galactoglucomannans*

The galactomannans and glucomannans belong to the mannan-type polysaccharides, but with different structures. Typical seed (carob, guar, locust bean, tara, etc.) galactomannans contain a β-(1→4)-linked D-mannan backbone to which is attached single α-D-galactose at the C_6 position of D-mannose (Srivastava & Kapoor, 2005). The glucomannans consist of random distrubtion of β-(1→4)-linked D-glucose and β-(1→4)-linked D-mannose in the main chain. In softwoods, there are additionally side chains of α-D-galactose linked to the mannan backbone, i.e. galactoglucomannans (GGMs). GGMs from wood, such as spruce, are partially substituted with *O*-acetyl groups at hydroxyl groups of C_2 and C_3, yielding *O*-acetyl-galactoglucomannans (Willför et al., 2003).

Chemical modifications of galactomannans by esterification, etherification, oxidation, and hydroxypylation could lead to derivatives such as carboxymethyl, hydroxylpropyl, and carboxymethylhydroxypropyl galactomannans (Kamerling & Boons, 2007). Cationic, anionic, and nonionic GGM have been synthesized and reported in our group as summarized in Fig. 2.

GGM from wood, e.g. spruce, represents the main hemicellulose component of softwoods and as such have been reported to show immunomodulating and radical-scavenging activities in native as potential additives with immune-potentiating and antioxidant properties in food products and pharmaceutical formulations (Ebringerová et al., 2008; Laine et al., 2010). Chemical modifications of GGM from forestry sources have also been extensively studied (Kisonen et al., 2012, 2014; Leppänen et al., 2013). For example, methacrylation reaction has been taken to prepare cross-linked GGM hydrogel for drug delivery (Lindblad, Dahlman, Sjöberg, & Albertsson, 2009). Sulfation and carboxymethylation of GGM have been studied by Doliška et al. (2012) to increase their antithrombotic properties, and the synergistic effect of carboxymethylation and sulfation was found to play the most important role in the antithrombotic effect.

Enzymatic modification with different enzymes provides alternative environmentally friendly and specific approaches (Tenkanen, 2003). Regioselective oxidation of galactose-containing polysaccharides, e.g. GGM from spruce and guar gum (galactomannan) from the seed of leguminous shrub *Cyamopsis tetragonoloba*, can be achieved by using galactose oxidase which selectively oxidizes the primary hydroxyl groups of the galactosyl to aldehyde functionalities (Fig. 2). The oxidized galactose-containing polysaccharides can be further tailored at the selectively introduced aldehyde groups towards further functionalizations, e.g. development of new anticoagulant and antithrombotic drugs applications (Hartmans et al., 2003; Leppänen et al., 2014; Parikka et al., 2012; Xu, Spadiut, Araújo, Nakhai, & Brumer, 2012).

Partially acidic or enzymatic hydrolysis have been applied to degrade native konjac glucomannan for food ingredient and prebiotic applications, the resultant konjac glucomannan with low molecular mass has been reported to show some attractive biological activities, such as cholesterol lowering, bulking for weight reduction, and to reduce the risk of constipation (Al-Ghazzewi, Khanna, Tester, & Piggott, 2007).

4.2.3. *Xyloglucans*

Xyloglucans are the major hemicelluloses in the primary cell walls of higher plants, they have a common structure of

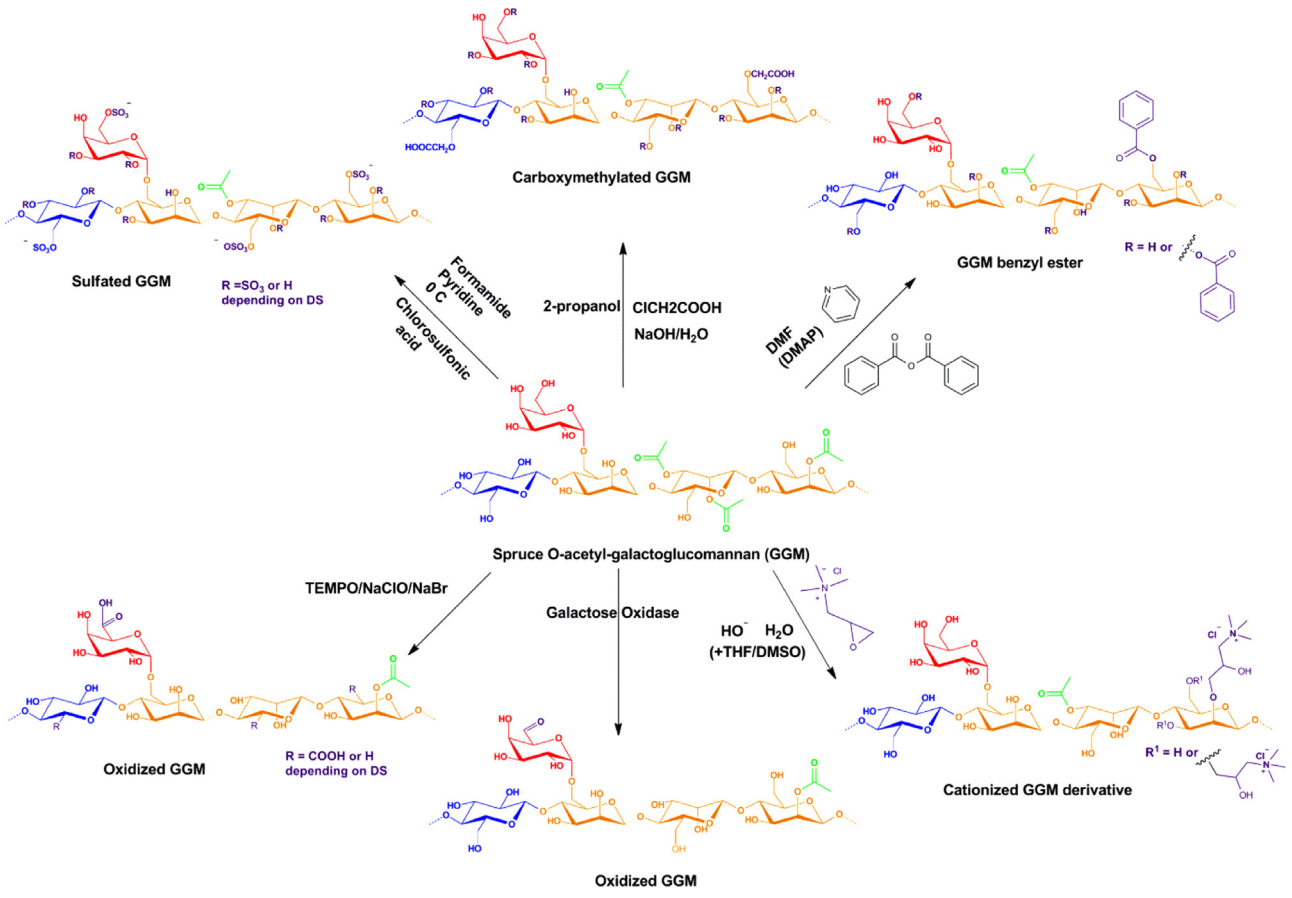

Fig. 2 – Chemical modifications of spruce galactoglucomannan to prepare anionic/cationic/nonionic derivatives (adapted from Doliška et al., 2012; Kisonen et al., 2012, 2014; Leppänen et al., 2013, 2014; Xu et al., 2011).

β-(1→4)-linked D-glucan, and three out of four glucose residues are substituted with α-D-(1→6) xylose. Depending on the source of the xyloglucans, further substituted residues of xylose is β-(1→2)-linked D-galactose, which in turn is sometimes substituted with α-fucosyl residures (Gidley et al., 1991; Kochumalayil, Zhou, Kasai, & Berglund, 2013).

Xyloglucans provide stronger bioavailability of drug and longer residence times, and therefore, has been used as skin patches, oral or rectal drug delivery, and for intraperitoneal injections (Coviello, Matricardi, & Alhaique, 2006). Chemical or chemo-enzymatic modifications to prepare various xyloglucan derivatives can be performed for medical and other applications. For example, sulfated xyloglucan and its selenious ester have been reported to show antioxidant activity and antitumor activity (Cao & Ikeda, 2009).

Chemo-enzymatic modifications of xyloglucan have also been intensively studied. Xyloglucan endotransglycosylase (XET), which transfers glycosyl moieties to carbohydrate acceptors, readily accepts not only xyloglucan polymers, but also xyloglucan oligosaccharides, even after chemical modifications. Thereby, various functional moieties, such as biotin, aminoalditol and its derivatives, can be introduced to xyloglucan. By taking advantage of the high affinity between xyloglucan and cellulose, the functionalized xyloglucan can be bound to different cellulosic surfaces to prepare functional materials as shown in Fig. 3 (Brumer, Zhou, Baumann, Carlsson, & Teeri, 2004).

Another important chemo-enzymatic approach is to regioselectively oxidize the primary hydroxyl groups of galactose on the side chains of xyloglucan to aldehydes by using galactose oxidase (Parikka et al., 2009). Judicious choices of the functional group allow further *in situ* surface modification. For example, Xu et al. (2012) attached propargylamino groups to yield multialkynylated conjugates, which are clickable by "click chemistry" for desired applications, such as *in vitro* diagnostics, (bio) molecular capture, and detection as illustrated in Fig. 3.

4.3. *Pectins*

Pectins are heterogeneous polysaccharides with three main domains: α-(1→4)-linked linear homo-galacturonic backbone (HG) alternating with two types of highly branched rhamnogalacturonans regions designated as RG-I and RG-II. RG-I is substituted with side chains of arabinose and galactose units. RG-II has a highly conserved structure, consisting of a HG backbone branched with eleven different monosaccharides, including some rare sugars such as 2-*O*-methylxylose, 2-*O*-methylfucose, apiose, aceric acid, 2-keto-3-deoxy-*d*-manno-octulosonic acid, and 3-deoxy-*d*-lyxo-2-heptulosaric acid (Le Normand et al., 2014; Ridley, O'Neill, & Mohnen, 2001). In all natural pectins, some of the carboxyl groups exist in the methyl ester form.

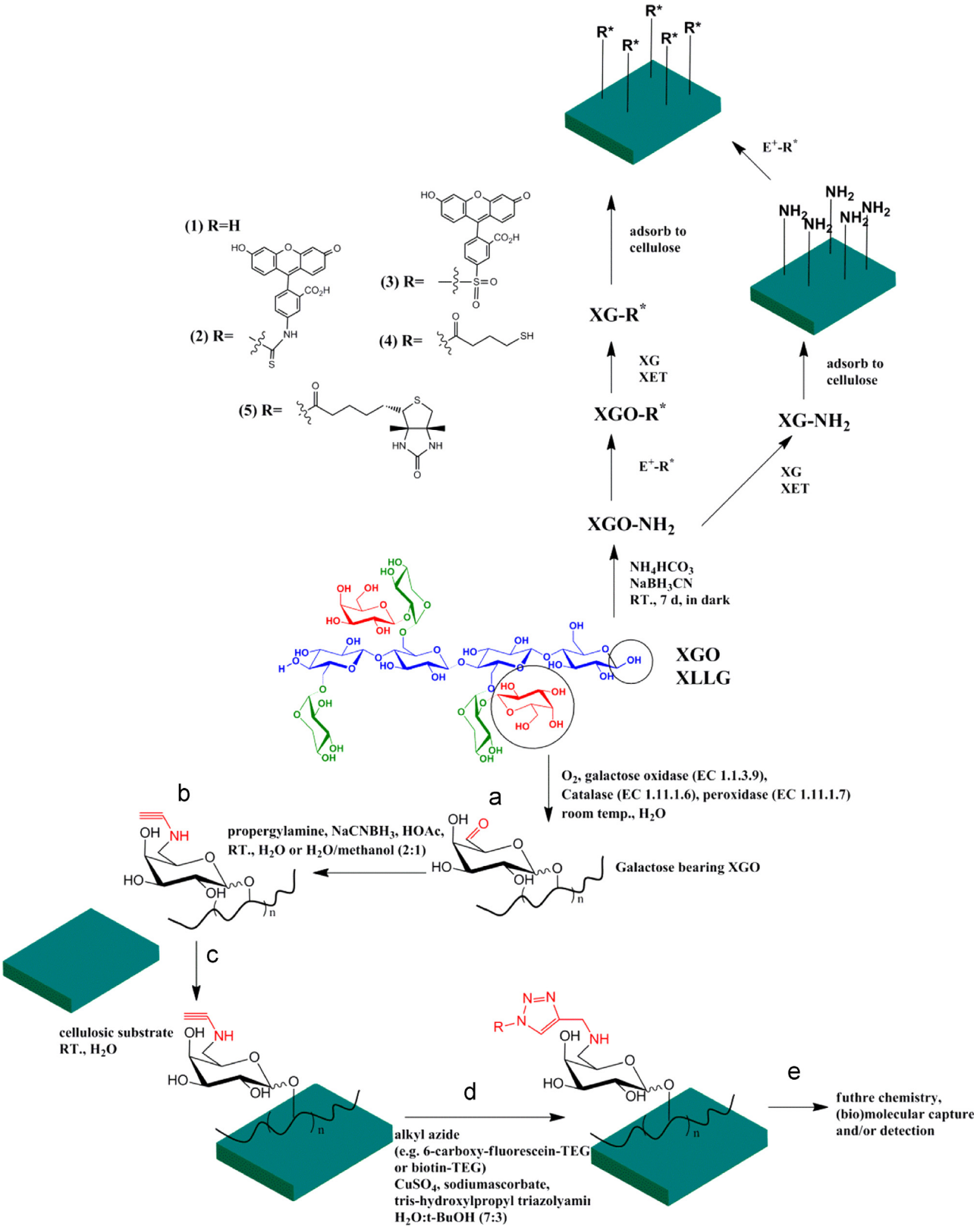

Fig. 3 – Chemo-enzymatic modifications of xyloglucan *via* XET techniques and regioselectively oxidization plus click chemistry. (pathway up) adapted with permission from (Brumer et al., 2004). Copyright (2004) American Chemical Society. (pathway below) adapted with permission from (Xu et al., 2012). Copyright (2012) Wiley.

Pectins, mainly from citrus peel and apple pomace, are widely used in the food industry as gelling or thickening agents and in the pharmaceutical industry as an excipient due to its non-toxicity, low production costs, and gelling activity properties. Because pectin is intact in the upper gastrointestinal tract and degraded by colonic microflora, pectin-derived drug carriers provide promising potential for colon-specific drug delivery. Gelation of pectin, calcium cross-linked pectinate, composites of pectin and other polymers such as ethylcellulose and hydroxypropylmethylcellulose have been examined and tested for controlled drug delivery (Liu, Fishman, Kost, & Hicks, 2003). Modification of pectin *via* grafting with poly(*N*-vinylpyrrolidone) (PVP) has also been reported to form an effective hydrogel that can make effective colon-targeted drug delivery (Fares, Assaf, & Abul-Haija, 2010). In addition to food and pharmaceutical applications, a recent study reported that pectins (rhamnogalacturonan RG-I domain ramified with highly-branched arabinans) extracted from spruce bark showed immunomodulating activities, which suggested a potential application as immunostimulant (Le Normand et al., 2014). The hydrogel of pectin has been explored in tissue engineering applications for bone cells culture and promoting the nucleation of minerals, and in wound healing applications for binding active drugs or growth factors and protecting against bacterials (Munarin, Tanzi, & Petrini, 2012).

4.4. *Starch*

Starch is a biopolymer synthesized in a granular form by green plants and consists of two major components, i.e. linear amylose with α-(1→4)-D-glucopyranose, and branched amylopectin with α-(1→4)-D glucopyranose backbone and 5–6% of α-(1→6)-branch linkages (Pérez & Bertoft, 2010). Minor constituents such as lipids, proteins, and minerals are present in starch and the levels vary with the origin (Waterschoot, Gomand, Fierens, & Delcour, 2014). Starch is an excellent material for industrial uses due to its non-toxic, renewable and biodegradable properties. However, the intrinsic properties such as thermal, mechanical, and biological properties and poor processability of starch have limited its direct applications (Khan & Ahmad, 2013). Thus, various chemical, physical, and enzymatic modifications or blending with other materials have provided solutions to achieve more desirable properties.

Similar to the cellulose, conventional chemical modifications of starch based on the primary and secondary hydroxyl groups include esterification, etherification, oxidation, and graft copolymerization (Table 2).

Starch esters are generally prepared by reacting with fatty acid chlorides, fatty acid vinyl esters, carboxylic acids, and fatty acid methyl ester in organic solvents such as pyridine, toluene, DMSO, and DMAc/LiCl (Grote & Heinze, 2005; Xie & Wang, 2011). Starch esters have been developed for pharmaceutical applications, e.g. used as superdisintegrant and matrix former in capsules and tablet formulations; and for medical application to maintaining human colonic function and preventing colonic disease (Tupa, Maldonado, Vazquez, & Foresti, 2013).

Quaternary ammonium cationic starches, the major commercial starch ethers, are commonly prepared by the reaction of an aqueous alkaline solution of 2,3-epoxypropyltrimethyl ammonium chloride or 3-chloro-2-hydroxypropyltrimethyl ammonium chloride (Pigorsch, 2009). The quaternary ammonium-substituted cationic starches may form nanoparticles with anionic sodium tripolyphosphate. The nanoparticles could entrap hydrophobic molecules, providing a great potential as nanosized carrier in health care and environmental sciences (Rutkaite, Bendoraitiene, Klimaviciute, & Zemaitaitis, 2012).

Hydroxyethyl starch is semisynthetic starch ether by reacting with ethylene oxide in alkaline medium, and it has been used as a plasma volume expander and cryoprotectant in medicine. Further functionalization by esterification with lauric, palmitic, and stearic acid using dicyclohexyl carbodiimide and dimethylaminopyridine has been used to prepare a fully biodegradable amphiphilic polymer for drug carrier application (Besheer, Hause, Kressler, & Mader, 2007). Lately, a nanocarrier based on hydroxyethyl starch for active receptor-mediated targeting was synthesized (Baier et al., 2012). The hydroxyethyl starch folic acid conjugate nanocarriers could be of high interest for the development of receptor mediated targeting using polymeric nanocapsules to deliver and accumulate their encapsulated molecules to the targeted area.

Selective oxidation of starch with N_2O_4 or a TEMPO/NaClO/NaBr system can exclusively yield carboxylates on the primary hydroxyl groups. Such oxidation approaches can also be applied to selectively oxidize starch derivatives, which bear another oxidation candidate primary hydroxyl group (e.g. hydroxyethyl starch) (BeMiller & Whistler, 2009). Dialdehyde starch can be prepared by oxidation of vicinal alcohol groups to aldehyde groups at the C_2 and C_3 by using periodic acid or periodate. The yielded aldehyde groups may react with alcohols, amines, hydrazines, and hydrazides to provide additional functionialized products and applications (Haaksman, Besemer, Jetten, Timmermans, & Slaghek, 2006).

4.5. *Chitin and chitosan*

Application of chitin/chitosan has been extensively developed, e.g. in oral administration for lowering serum cholesterol concentration and hypertension and in ophthalmic preparations for improving the retention and biodistribution of drugs applied topically onto the eyes (Muzzarelli & Muzzarelli, 2005). However, due to the semi-crystalline structure of chitin with extensive hydrogen bonds, the chitin is insoluble in common solvents, and this has limited the development and processing of chitin for practical applications. The chitosan is normally insoluble in aqueous solution above pH 7, but its free amine groups can be protonated in dilute acids (pH 6) and the chitosan molecule becomes soluble. Such pH-dependent solubility might provide potential applications as sensors. Nevertheless, it also poses challenges, especially for biological applications that require neutralized environment. Therefore, further modification of chitin and chitosan to introduce desired physicochemical and biochemical properties without any changes in their fundamental skeleton is of significance for a breakthrough in utilization of their unique features and activities (Oliveira & Reis, 2011).

The active groups or the possible reaction sites of both chitin and chitosan mainly include the free amino groups, primary and secondary hydroxyl groups, and acetamido groups. As summarized in Fig. 4, chemical reactions targeted at the hydroxyl groups, such as etherification, esterification, cross-linking, graft copolymerization, and *O*-acetylation, can be used for modification. Chemical reactions targeting the amino groups of chitin and chitosan include acetylation, quaternization, Schiff base reaction (reactions with aldehydes and ketones), and grafting (Jain et al., 2013; Pillai, Paul, & Sharma, 2009). Modification of chitosan with sugars onto the amino groups (Fig. 4, method (A), method (B)) provides a promising approach to introduce desired sugars for various applications in specific drug, DNA, and antibody carriers by incorporation of cell-specific sugars that are specifically recognized by cells, viruses, and bacteria (Kim, 2013; Yao, 2012).

Carboxymethylation can take place at hydroxyl groups of chitin and chitosan to yield *O*-carboxymethyl derivatives, and can also take place at the free amino groups of chitosan to yield *N*-carboxymethyl derivatives (Fig. 4). Derivatization of chitosan by introducing alkyl or carboxymethyl groups onto the C_3 and/or C_6 hydroxyl groups to prepare e.g. *O*-carboxymethyl chitosan can significantly increase the solubility at neutral and even alkaline conditions at the same time maintaining the cationic properties. Such *O*-carboxymethyl chitosan was used to enhance the biocompatibility of polylactic acid film surfaces, which had higher cell adhesion and proliferation than that of the unmodified one (Alves & Mano, 2008; Cai, Yao, Li, Yang, & Li, 2001). Carboxymethyl chitin, a water-soluble anionic polymer was selectively modified to prepare antitumour drug conjugates (Rinaudo, 2008). A microsphere of 6-*O*-carboxymethyl chitin was reported as a potential vehicle for targeted drug delivery to the liver due to its preferentially located and long retainment in the liver and spleen after *i.v.* injection (Hata, Onishi, & Machida, 2000). An amphiprotic ether derivative that contains both carboxyl groups and amino groups can be prepared when the substitution moieties bear carboxyl groups (Alves & Mano, 2008). Simultaneous incorporation of substituents, for example carboxymethyl groups, onto some of the amino and primary hydroxyl sites of the glucosamine units can also be achieved by using chitosan, sodium hydroxide, isopropanol with chloroacetic acid as solvent (Khan & Ahmad, 2013).

Graft copolymerization is an important approach for modification of the chitin and chitosan towards medical and pharmaceutical applications, such as in orthopedic/periodontal materials, wound-dressing materials, tissue engineering, and controlled drug/gene delivery (Ito, Yoshida, & Murakami, 2013). Graft copolymerization of chitin and chitosan can be initiated by chemical (free radicals) initiator systems, by radiation methods and by enzymatic grafting methods (Alves & Mano, 2008). Graft copolymerization of chitosan with "presynthesized" polymers instead of their monomers can help to control the side-chain molar mass and avoid the absence of residual monomers. For example, Lu, Xu, Zhang, Cheng, and Zhuo (2008), prepared a chitosan-based copolymer, which had a good potential as efficient nonviral gene vectors, through grafting polyethylenimine (800 Da) to *N*-maleated chitosans. Kumar et al. (2012) utilized polyacrylamide, instead of normal acrylamide monomer, for grafting onto chitosan with high grafting efficiency (GE=92%) and grafting ratio (GR=263%). The resulting macroporous polyacrylamide-grafted-chitosan exhibited superior neuronal

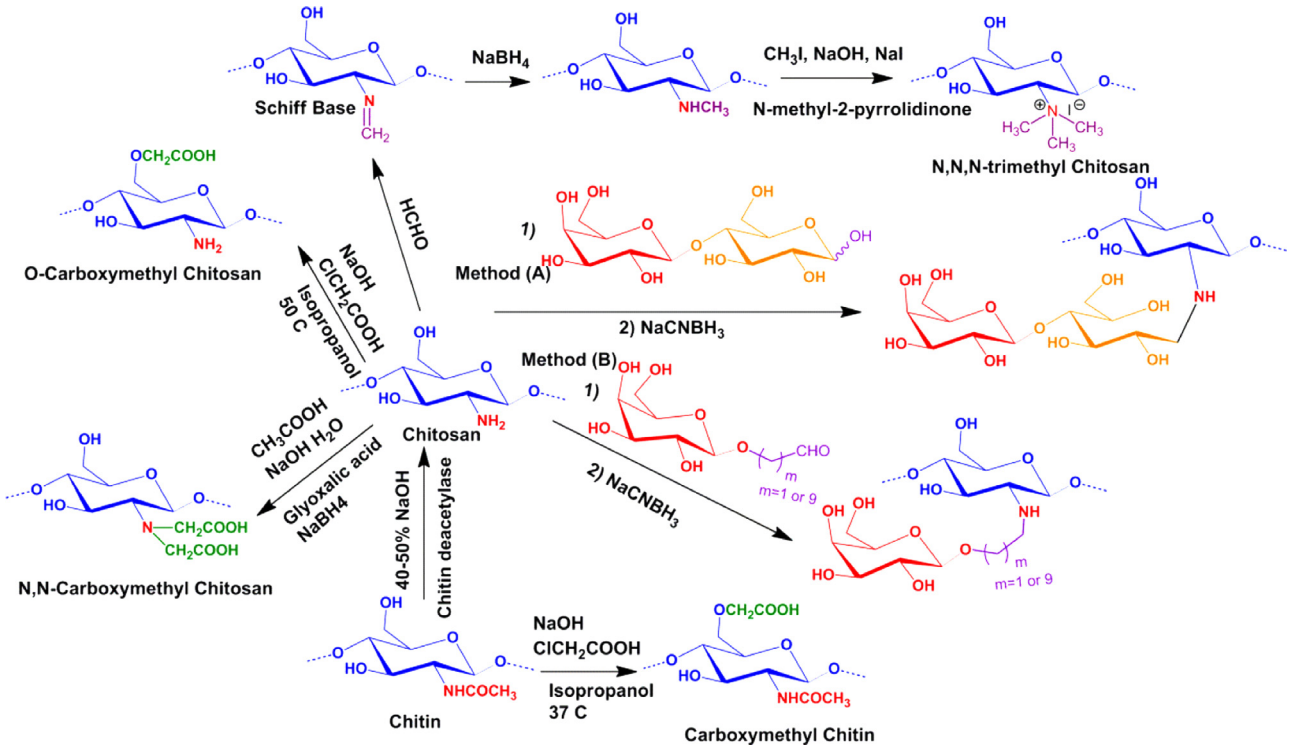

Fig. 4 – Chemical modification of chitin/chitosan (adapted from Kean, Roth, & Thanou, 2005; Khan & Ahmad, 2013; Kim, 2013; Nemtsev, Gamzazade, Rogozhin, Bykova, & Bykov, 2002).

cell infiltration owing to the anisotropic porous architecture, high-molar-mass mediated robustness, and superior hydrophilicity, as well as surface charge due to the acrylic chains and the substrate could act as a potential neural cell carrier applied in scaffolds for neural tissue engineering.

Based on graft copolymerization and a molecular imprinting technique, chitosan has been used to prepare recognition materials, such as metal ions, dyes, and proteins, and therefore, could be used for special absorption of template molecules mimicking natural recognition materials such as antibodies for diagnostics (Kyzas, Lazaridis, & Bikiaris, 2013; Monier & El-Mekabaty, 2013). For example, Dan et al. (2013), prepared a molecular imprinted chitosan gel to recognize the template ovalbumin. Their resulting gels showed notable adsorption capacities and high special selectivity to the template protein. Similarly, Fu, Zhao, Yu, Liu, and He (2007) synthesized a molecularly imprinted polymer (MIP) gel using bovine serum albumin (BSA) as a template and based on copolymerization of acrylamide with *N,N′*-methylenebisacrylamide on chitosan in aqueous medium. The resultant MIP gels were found not only to show significantly higher imprinting efficiency and specificity for BSA, but also much better stability in rebinding of the imprint molecules after adsorption–regeneration cycles.

Blends or composites of chitin or chitosan with synthetic or natural polymers, such as polyethylene glycol, polylactic acid, polypyrrole, collagen, starch, and with inoraganic materials such as bioactive glass and ceramics, for drug delivery systems, tissue-engineering, and other medical applications have recently been intensively studied (Jayakumar et al., 2011; Kumar, Muzzarelli, Muzzarelli, Sashiwa, & Domb, 2004; Nakamatsu, Torres, Troncoso, Min-Lin, & Boccaccini, 2006; Rinaudo, 2008). Furthermore, similar to alginate as listed in Table 2, layer-by-layer or multilayer coating techniques have been developed to prepare chitosan-based polyelectrolyte complexes with 2D and 3D structures such as freestanding films, capsules, and porous scaffolds. Hyaluronic acid, alginate, chondroitin sulfate, and hydroxyapatite have also been applied with chitosan to prepare multilayer-structured biomaterials based on the layer-by-layer technique for tissue-engineering applications (Miranda, Silva, Reis, & Mano, 2011; Rinaudo, 2008; Santo, Gomes, Mano, & Reis, 2012; Schneider, Richert, Francius, Voegel, & Picart, 2007; Silva et al., 2013a; Silva et al., 2013b).

4.6. *Alginate*

Seaweed polysaccharides from the marine plants represent the most abundant polysaccharides in the sea, and alginate is one of the most widely explored seaweed polysaccharides (Wang, Wang, & Guan, 2012). It's a linear block copolymer which composed of β-(1→4)-linked D-mannuronic acid (M block) and α-L-guluronic acid (G block) units arranged with varying proportion of GG, MG, and GM blocks (Fig. 5) (d'Ayala et al., 2008; Khan & Ahmad, 2013; Rehm, 2009). In the tissue-engineering and cell immobilization fields, the use of alginate for cartilage regeneration is well known due to its gelling and stabilizing properties, in which the G-blocks serve to introduce a steric hindrance and to provide folded and rigid structural conformation (Khan & Ahmad, 2013; Rinaudo, 2008; Spiller, Maher, & Lowman, 2011). However, the drawbacks of inadequate mechanical properties, uncontrollable degradation profiles, and lack of cell recognition signals have limited its medical application. Notably, carboxyl groups and hydroxyl groups along the backbone of the alginate enable various modification approaches to enhance or tailor the properties such as physicochemical, biological, mechanical, and other desired properties (Oliveira & Reis, 2011).

Conventional chemical modification of alginate mainly include graft copolymerization, oxidation, crosslinking with polyvalent cations and/or cationic polymers, sulfation, and esterification targeting the hydroxyl groups and carboxyl groups, and also aldehyde groups after rupture of C_2 and C_3 carbon-carbon bond as reviewed previously (Khan & Ahmad, 2013; Yang, Xie, & He, 2011) and summarized in Fig. 5.

Esterification as a simple method to introduce alkyl groups onto the backbone of the alginate was successfully commercialized decades ago; and the propylene glycol alginate (PGA, Fig. 5) is currently the most representative commercial product (d'Ayala et al., 2008). Esterification of alginate to introduce long alkyl chains can be achieved by reaction with alkyl halides, but the alginate needs to be converted into its tetrabutylammonium salt (TBA) at first. For example, dodecyl alginate was prepared by the reaction of the TBA salt of alginic acid with dodecyl bromide in DMSO (Pawar & Edgar, 2013). However, the partial or total substitution of carboxyl groups after esterification might result in a reduced gelling capacity, which is the most attractive feature of alginate.

The periodate oxidation that selectively cleaves the vicinal glycols (C_2–OH, C_3–OH) and introduces new reactive groups is an alternative approach to modify the alginate while maintaining the gelling properties. Due to the slow degradation rate of alginate, partial periodate oxidation has been reported to accelerate the biodegradation rate of the oxidized alginate and this has found application in tissue engineering (Bouhadir et al., 2001; Rinaudo, 2008). For example, partially periodate oxidized injectable alginate hydrogels have been developed to provide a suitable delivery vehicle for stem cells to engineer adipose tissue (Kim et al., 2012). Actually, such selective oxidation is a classical pre-modification method due to the obtained new reactive groups with larger rotational freedom. Various graft copolymerizations or reductive amination can be further carried out based on such pre-modified intermediate product as shown in Fig. 5 (Yang et al. 2011). For example, low-molar-mass polyethylene glycol (mono-carboxyl terminated), a highly biocompatible polymer, was grafted onto a sodium alginate, which was first modified by inserting a given amount of amine functionalities. The retained gelation characteristics and increased biocompatibility and pore dimension of the alginate-PEG copolymers are requirements for gel entrapment devices and microencapsulation techniques (Laurienzo, Malinconico, Motta, & Vicinanza, 2005). By controlling the degree of alginate oxidation, a crosslinked bio-adhesive alginate-PEG system with controllable mechanical properties, swelling, and degradation rates have been developed (Jeon, Samorezov, & Alsberg, 2014). The oxidized alginate itself is also promising material with improved biodegradability due to the presence of more reactive groups, which

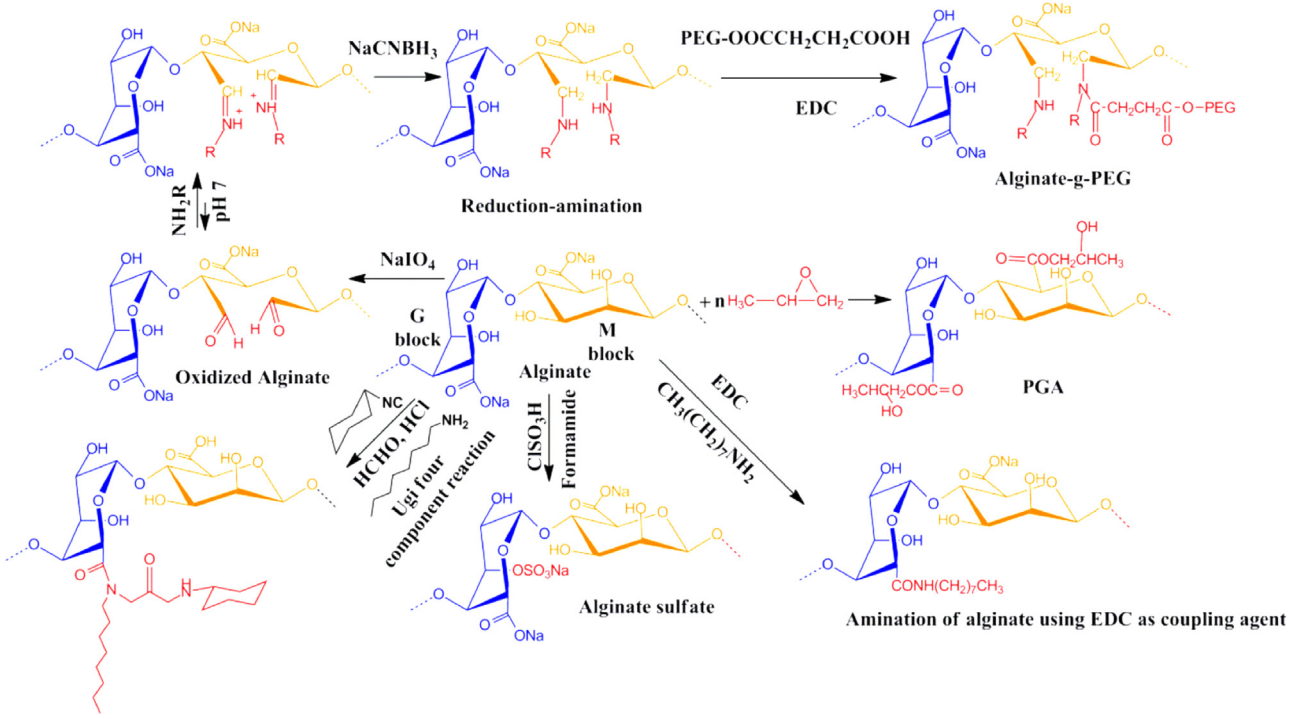

Fig. 5 – Chemical modification of alginate (adapted from d'Ayala et al., 2008; Yang et al., 2011).

contribute to faster degradation when applied in a controlled drug delivery system (Yang et al., 2011).

Ugi reaction has been applied to modify the alginate to form a bis-amine (Fig. 5). Amidation reaction (Fig. 5) has been applied to form amide linkage between amine bearing molecules (e.g. EDC, NHS, 2-chloro-1-methylpyridinium iodide (CMPI), etc.) and the carboxylate moieties on the alginate (Yang et al., 2011).

Grafted alginate copolymers have recently been developed for biomedical applications. An alginate-based pH- and temperature-responsive hydrogel was synthesized by grafting of poly (*N*-isopropylacrylamide) to the alginate backbone using EDC/NHS as coupling agents (Kim, Lee, Kim, & Lee, 2002). The product might be useful in a rapid stimuli-responsive drug delivery system or as a biomimetic actuator in biomedical fields. Similarly, grafting of *N*-isopropylacrylamide onto sodium alginate with microwave radiation in aqueous environment was carried out to prepare novel pH- and temperature-responsive beads for colon-specific drug delivery (Isiklan & Kucukbalci, 2012).

In addition to the conventional chemical modification approaches to tailor the alginate derivatives, a self-assembly approach has been explored to develop functional multilayer alginate capsules with core-shell structure, which are useful in biomedical applications such as drug delivery, bionanoreactors, nanofiltration, and biosensors (Srivastava & McShane, 2005; Zhu, Srivastava, & McShane, 2005). Partial protonation of the carboxylate groups in alginate chains followed by the cross-linking reaction with cross-linker 2,2′-(ethylenedioxy)-bis(ethylamine) yielded a pH-dependent structure, which could change between a coreshell to a hollow structure depending on the pH change of the medium (Cao et al., 2005). Layer-by-layer self-assembly has been used to prepare microporous alginate hydrogels containing a variety of encapsulates (Roberts, Ritter, & McShane, 2013). In this approach, a variety of functional materials including sensing element, bioactive agents, and various types of nanoparticles may be encapsulated. A similar multilayer self-assembly approach by coating or depositing with oppositely charged polyelectrolytes bearing complementary amine and acetoacetate reactive groups has also been used to strengthen the alginate microcapsules by internally and externally cross-linked networks, which could become resistant to chemical and mechanical stress while remaining cyto-compatible. The resulting microcapsules are promising materials for cell encapsulation in cell-based therapies (Mazumder, Burke, Shen, Potter, & Stover, 2009; Mazumder, Shen, Burke, Potter, & Stover, 2008; Srivastava & McShane, 2005). Moreover, multilayers could also be built from negatively charged alginate and positively charged chitosan in acid conditions and be used for cell adhesion in tissue engineering applications (Silva et al., 2013a). Other polyelectrolytes such as proteins (β-lactoglobulin or gelatin), poly(L-lysin), and poly(L-ornithine) may also be utilized to form such multilayer structures (Rinaudo, 2008).

4.7. *Hyaluronic acid*

For diverse biological applications, further chemical modification of HA to introduce desirable properties (e.g. the hydrophobicity and biological activity of resultant materials) is often necessary. In HA, there are three targeting sites per repeating unit available for chemical modifications: carboxylic acid groups; primary and secondary hydroxyl groups; *N*-acetyl groups. Generally, chemical modifications targeting carboxylic groups include amidation, Ugi condensation, and esterification (Table 2). Carboxylic groups of HA can react either as electrophiles or nucleophiles to form esters (Cumpstey, 2013).

Esterifications of HA by alkylation using akyl halides (chlorides, iodides, and bromides), by using diazomethane, and by using epoxides have been intensively studied and reviewed previously (Schanté, Zuber, Herlin, & Vandamme, 2011). For example, benzyl ester formation has been used to increase the hydrophobic properties of HA for production of different commercial biocompatibable and biodegradable materials (HYAFF®) (Benedetti et al., 1993).

Functionalization targeted at the carboxylic group is similar as that of the alginate and the TEMPO oxidized cellulose modification as described above (Fig. 1 and Fig. 5). Recently Wang, Oommen, Yan, and Varghese (2013) reported a mild and efficient strategy for aldehyde modification of HA by conjugating the amino-glycerol moiety onto the carboxylate residue of HA, which allowed selective cleavage of pendent diol groups without opening of the sugar ring structure of HA during periodate oxidation. This site-selective aldehyde modification could minimize the change of the native structure of HA and preserve its unique physiochemical and biochemical properties. The aldehyde-bearing HA was developed to tailor extracellular matrix injectable hydrogel for growth factor release.

Chemical modifications of HA on the hydroxyl groups (both primary and secondary) mainly include etherification, esterification, hemiacetal crosslinking, carbamate formation, and selective oxidation (Khan & Ahmad, 2013; Schanté et al., 2011).

Modification of the *N*-acetylglucosamine is difficult to carry out directly, thus deacetylation is often taken to recover the reactive amino groups which are able to conduct amidation or reductive amidation with aldehydes.

When developing HA derivatives for medical and pharmaceutical applications, HA derivatives are categorized as "monolithic", which are "terminally modified" forms of HA that do not form new chemical bonds in the presence of added cells or molecules, and "living" which can form new covalent bonds in the presence of cells, tissues, and small or large molecules (Prestwich & Kuo, 2008). Living HA crosslinked hydrogels (e.g. crosslinked with poly(ethylene glycol) diacrylate) act as an extracellular matrix and permit incorporation of cells and a wide variety of small molecules, large molecules, nanoparticles, and microparticles, which have broad applications, e.g. targeting specific and long-acting delivery, wound repair, drug evaluation, stem cell niche engineering, and regenerative medicine (Oh et al., 2010; Prestwich, 2007, 2011).

5. Structural analysis

Generally, bioactivities of polysaccharides are highly dependent on their structural features. For example, the anticoagulant activity of seaweed fucans was shown to depend on their molar mass, the extent of sulfation, and the distribution of sulfate groups in the repeating units (Jiao, Yu, Zhang, & Ewart, 2011). Thus, accurately determining and establishing structure–function relationship is the prerequisite and fundament for their applications. Structures of polysaccharides, especially those of heteropolysaccharides or hemicelluloses are complicated by the presence of different monosaccharides used as building blocks, which are usually isobaric stereoisomers, variations in sequence, linkage, branching, and distribution of side chains (Bauer, 2012). Structural elucidation of polysaccharides involves obtaining data from numerous analytical approaches, each of which gives some structural information, and the assimilation/integration of these data into a chemical structure that rigorously and uniquely fits all the available structural information (Kamerling & Boons, 2007). Thus, several different analytical strategies should be taken for analysis to reach final and accurate conclusions of the polysaccharide structure. Nowadays, the improvements in analytic techniques such as nuclear magnetic resonance (NMR) spectroscopy, high-pressure liquid chromatograph (HPLC), capillary electrophoresis (CE), and mass spectrometry (MS), together with the development of suitable microchemical degradation and derivatization protocols, and the incorporation of exo- and endo-glycosidase digestions, are all greatly contributing to the structural analysis of polysaccharides. Different methodologies available for structural elucidation of polysaccharides have been previously summarized by Kamerling and Boons (2007).

For building the detailed structure of polysaccharides, the primary structural analysis should be carried out to understand the nature and number of the monosaccharides building blocks. This is generally done by hydrolysis and methanolysis followed by gas chromatograph and liquid chromatograph analysis. The absolute configuration (D or L) of the monosaccharides can be determined by separation of enantiomers using gas-liquid chromatograph directly on a chiral stationary phase, or on a nonchiral stationary phase after conversion of the enantiomers into diastereomers using chiral reagent. Linkages between monosaccharides and branch pattern can be analyzed by firstly using methylation analysis, which involves methylation of the free hydroxyl groups, hydrolysis of the methylated glycan, and reduction with $NaBH_4$ or $NaBD_4$ and acetylation with acetic anhydride in pyridine, followed by gas-liquid chromatograph separation in combination with mass spectrometric profiling. The following monosaccharides identification can be done by using different mass spectrometry and NMR spectroscopy. Sometimes, modification or degradation (e.g. smith degradation, uronic acid reduction or degradation, enzymatic and/or partial acid/alkaline hydrolysis, acetolysis, labeling with radioactive or fluorophoric compounds etc.) of polysaccharides are beneficial for constructing the ultimate structures (Kamerling & Boons, 2007; Varki, 2009).

The introduction of soft-ionization techniques in mass spectrometry provides new possibilities for the analysis of polysaccharides. Fast-atom-bombardment MS (FAB MS), matrix-assisted laser-desorption-ionization time-of-flight MS (MALDI TOF MS), and electrospray ionization MS (ESI MS) have become key techniques for identification and molecular mass profiling of polysaccharides present in complex mixtures. Tandem mass (MS/MS) or even MS^n spectrometry can give more detailed structural information including sugar constituents, sequence and interresidue linkage positions, and some information on stereochemistry (Mischnick, 2012). To reduce the complexity of the analyte, isolation and profiling of analyte mixtures and even isobaric analytes can be achieved by coupling techniques. For example, conjunction of mass analyzers with different isolation methods, such as reverse-phase, normalphase (NP), porous graphitized carbon, size exclusion, ion exchange, or high performance anion-exchange, liquid chromatographic (LC) or capillary electrophoretic separation methods are all possible

(Maslen, Goubet, Adam, Dupree, & Stephens, 2007; Ungewiß et al., 2005).

However, due to the structural complexity of polysaccharides, no single analytical method alone is able to give the detailed structural information. Collecting structural information from different available techniques such as ultraviolet (UV)/visible (vis) and infrared (IR) absorption spectroscopies, NMR and MS is of significance for accurate elucidation of polysaccharide fine structures.

6. Biomedical applications

Polysaccharides and their derivatives hold advantages over the synthetic polymers, because they are non-toxic, biodegradable, biocompatible, and less expensive compared to their synthetic counterparts. All these merits endow polysaccharides and their derivatives a broad spectrum of applications in different areas, such as in biomedical or pharmaceutical, food, and cosmetic applications. Nowadays, polysaccharides play important roles in traditional disease control and health care (such as those originating from herbs and dietary fibers as reviewed above), meanwhile many new application areas are also explored such as in tissue engineering, in drug delivery, in wound treatment (both internal and external), in cancer prevention, diagnosis, and therapy, and in treatment of bacterial and viral diseases as already mentioned in the previous section for each polysaccharide and their derivatives following functionalization (Khan & Ahmad, 2013; Lindblad, Sjöberg, Albertsson, & Hartman, 2007; Sandra, 2009). Thus, here in this section we emphasize the development of bioactive polysaccharides for such biomedical applications as tissue engineering, wound dressing/healing, and drug delivery applications, which are the three major topics of the most recent research activities.

6.1. *Tissue engineering*

Exploitation of polysaccharides and their derivatives for tissue engineering applications, such as biological signaling, cell adhesion, cell proliferation, cell differentiation, cell responsive degradation, and re-modeling, is attracting a great deal of interest in medical research for guiding and promoting new tissue regeneration or to define the shape and structure of cell growth (Khan & Ahmad, 2013). A variety of polysaccharides, such as alginate, chitin, chitosan, hyaluronic acid, cellulose, chondroitin sulfate, starch and their derivatives, have been developed as biomaterials for tissue engineering applications as reviewed above and previously elsewhere (Oliveira & Reis, 2011). Application of polysaccharides as scaffolds in tissue engineering needs to fulfill the requirements like biocompatibility and nontoxicity, biodegradability with controllable degradation rate, appropriate porosity, and structural integrity (Khan & Ahmad, 2013).

Chitin and chitosan possess the requisite properties to act as scaffolds for tissue engineering, with respect to their degradability, immunogenicity, and mechanical strength, and therefore have been developed for tissue engineering applications in the form of 3D hydrogels or porous sponges, fibrous scaffolds or free-standing films, within which the appropriate cell types are seeded for *in vitro* or *in vivo* culture and evaluation (Wan & Tai, 2013). Design of 3D chitin/chitosan hydrogel and sponge scaffolds, or 2D scaffolds and free-stand films to support cartilage regeneration, to chemically interact with apatite for bone and tendon regeneration, to encapsulate stem cells and support their growth and differentiation for different stem cell therapy, and their utility in regenerative medicine have been recently reported and reviewed elsewhere (Croisier & Jérôme, 2013; Lu et al., 2012; Lu et al., 2012; Suh & Matthew, 2000; Wu & Hochedlinger, 2011). Moreover, composites of chitosan with hydroxyapatite and grafted chitosan with carbon nanotubes have been developed as potential materials for artificial bone and bone regeneration in tissue engineering (Venkatesan & Kim, 2010). Other polysaccharide-based materials, such as, hyaluronic acid, starch, and cellulose, have also been explored for bone, cartilage, and/or skin tissue engineering applications (Rinaudo, 2008).

6.2. *Wound healing and wound dressing*

Due to their inherent biocompatibility, low toxicity, and pharmaceutical biomedical activity, various polysaccharides, such as chitin, chitosan, cellulose, hyaluronan, and alginate, have been widely used to prepare wound healing materials (Barud Hda et al., 2013; Czaja, Krystynowicz, Bielecki, & Brown, 2006; Czaja, Young, Kawecki, & Brown, 2007; Hrynyk, Martins-Green, Barron, & Neufeld, 2012). For example, hyaluronan, a major extracellular component with unique hygroscopic, rheological, and viscoelastic properties, has been extensively developed for tissue repair purposes due to its physicochemical properties and specific interactions with cells and extracellular matrix. It is generally accepted that hyaluronan plays multifaceted roles in the mediation of the tissue repair process and is involved in all the stages of wound healing, i.e. inflammation, granulation tissue formation, reepithelialization, and remodeling. Derivatives of hyaluronan, such as cross-linked, esterified or other chemically modified products have also been developed for tissue repair or wound healing purposes (Anilkumar et al., 2011; Chen & Abatangelo, 1999). Notably, wound healing-promoting activity of the materials is also important in the designing of materials for tissue engineering.

All-natural composite wound dressing films prepared by dispersion and encapsulation of essential oils (elicriso italic, chamomile blue, cinnamon, lavender, tea tree, peppermint, eucalyptus, lemongrass, and lemon oils) in sodium alginate matrices have been reported to show remarkable antimicrobial and antifungal properties and may find application as disposable wound dressings (Liakos et al., 2013). Chitosan/silk fibroin blending membranes crosslinked with dialdehyde alginate have been developed for wound dressing and the membranes were found to promote the cell attachment and proliferation, which suggests a promising candidate for wound healing applications (Gu, Xie, Huang, Li, & Yu, 2013). Blending aqueous dispersions of sodium alginate and povidone iodine (PVPI) complex was prepared as freestanding NaAlg films or as Ca^{2+}-cross-linked alginate beads. These products were demonstrated to show antibacterial and antifungal activity and controlled release of PVPI into open wounds when the composite films and beads were brought into direct contact with water or with moist media (Liakos

et al., 2013). This proved that they could be suitable for therapeutic applications such as wound dressings. *In situ* injectable nano-composite hydrogels composed of curcumin, *N,O*-carboxymethyl chitosan, and oxidized alginate as a novel wound dressing was successfully developed for dermal wound repair application (Li et al., 2012b). *In vitro* release, *in vivo* wound healing, and histological studies all suggested that the developed nano-curcumin/*N,O*-carboxymethyl chitosan/oxidized alginate hydrogel as a promising wound dressing might have a potential application in the wound healing. Silver nanoparticles containing polyvinyl pyrrolidone and alginate hydrogels were synthesized using gamma radiation and showed the ability of preventing fluid accumulation in exudating wound (Singh & Singh, 2012). The incorporation of nanosilver particles provided a strong antimicrobial effect and therefore made such polyvinyl pyrrolidone/alginate hydrogels suitable for use as wound dressing. Except the alginate and its various derivatives, other natural polysaccharides such as cellulose, chitin, chitosan, and hyaluronic acid have also been explored for wound dressing or wound healing applications (Anisha, Biswas, Chennazhi, & Jayakumar, 2013; Kondo, Niiyama, Yu, & Kuroyanagi, 2011; Matsumoto & Kuroyanagi, 2010).

6.3. *Drug delivery and controlled release*

Polysaccharides hold their promising potential in drug delivery and controlled release applications due to their advantages such as biocompatibility, low immunogenicity, and minimal cytotoxicity. Numerous polysaccharide-based drug delivery systems have been developed for specific targeting delivery or controlling release, for protection of drugs from premature degradation, for improving intracellular penetration and transporation, for enhancing stability and bioavailability of drugs, or for the delivery of biomolecules such as genes, antigens, and small interfering RNA (Csaba, Koping-Hoggard, & Alonso, 2009; Mao, Sun, & Kissel, 2010; Mizrahy & Peer, 2012; Valo et al., 2011). These delivery systems are generally prepared in the form of 3-D cross-linking network (covalently or ionically crosslinking), the polyelectrolyte structures (polyelectrolyste complexes or layer-by-layer assembly), self-assembly, and the polysaccharides-drug conjugate (Mizrahy & Peer, 2012). The release of the entrapped drugs or certain molecules can be triggered by the change of pH, ions, electrical or magnetic field, light, temperature, redox potential, or certain molecules (Alvarez-Lorenzo, Blanco-Fernandez, Puga, & Concheiro, 2013). Cellulose, chitin or chitosan, and alginate, representing the three most abundant polysaccharide types, are discussed more in detail below.

Pharmaceutical utilization of cellulose and its derivatives range from excipients through carriers and protecting agents to active substances themselves. Oral drug delivery is one of those applications, in which the polysaccharide excipients are used to increase the solubility and bioavailability of the active drugs, to achieve a certain release profile from the final formulation, and to enhance the stability of the final drug products (Marchessault, Ravenelle, & Zhu, 2006; Reddy, Mohan, Satla, & Gaikwad, 2011). Nowadays, cellulose (e.g. microcrystalline cellulose) and starch (e.g. corn and rice starch) are widely used as glidants, tablet disintegrants and binders, and capsule diluents (Marchessault et al., 2006). Numerous cellulose derivatives such as methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, and hydroxylpropylmethyl cellulose, which often possess specific respond or even better physicochemical properties than cellulose have been applied in pharmaceutical applications (Francis, Piredda, & Winnik, 2006; Jain et al., 2014; Li & Mei, 2006; Marchessault et al., 2006). For example, phthalated hydroxypropylmethyl cellulose has excellent pH-dependent solubility, namely, stability in acidic conditions (at stomach) but soluble in mildly acidic to slightly alkaline solution and, therefore, has been developed for controlled intestinal targeting drug release systems (Kim, Park, Cheong, & Kim, 2003; Xu, Gao, Xu, Wu, & Sun, 2009). Recently, drug delivery systems based on nanocellulose which including cellulose nanocrystals (CNCs), nanofibrilated cellulose (NFC), and bacterial cellulose (BC) have been explored extensively (Plackett, Letchford, JacksonJohn, & Burt, 2014). For example, antimicrobials (doxorubicin hydrochloride and tetracycline hydrochloride) binding to and release from CNCs have been tested based on the ionically crosslinking delivery system, in which negatively charged sulfate groups on the CNCs form reversible ionic crosslinking with the positively charged drugs (Jackson et al., 2011). Similarly, NFC film networks have been studied to entrap drugs and used for long lasting drug release, for example the entrapped poorly water soluble drugs in the NFC film networks can sustainably release over weeks (e.g. indomethacin, 1–2 weeks) or even monthes (e.g. beclamethasone dipropionate and itraconazole, 3 monthes) (Kolakovic, Peltonen, Laukkanen, Hirvonen, & Laaksonen, 2012). Highly porous nanocellulose aerogels (ε=90–99%) with large surface areas (S_a=70–680 m^2/g) prepared by freeze-drying may provide new possiblilities for enhancing drug bioavailability and drug loading capacity (García-González et al., 2011). For example aerogels of BC (Valo et al., 2013) or NFC (Valo et al., 2011) have been studied for stabilizing and release of insoluble drugs within nanoparticle formulations in a controlled manner.

Exploring the use of chitin or chitosan as biomolecular delivery vector is of increasing interest in drug delivery for therapeutic application, such as genes (Csaba et al., 2009), antigens (Chen, Huang, Lai, & Ling, 2013), small interfering RNA carrier (siRNA) (Mao, Sun, & Kissel, 2010), and cells and proteins (Shelke, James, Laurencin, & Kumbar, 2014). Application of chitosan-based siRNA carrier for efficient delivery of siRNA *in vivo* has shown great promise as a therapeutic tool for gene expression implicated disease (Ragelle, Vandermeulen, & Preat, 2013). For example the chitosan (Ji et al., 2009) has been directly used to prepare chitosan/siRNA nanoparticles which showed knockdown human colorectal cancer gene expression. Alternative, Katas and Alpar (2006) found that the chitosan/siRNA nanoparticles which were prepared by ionic gelation with sodium tripolyphosphate showed much higher target gene silencing effect due to the higher binding and loading efficiency. Tahara, Yamamoto, Hirashima, and Kawashima (2010) proved that the chitosan coating of the nanocapsules can protect the encapsulated siRNA from the degradation by nucleases meanwhile avoid the burst release of siRNA. Extended delivery of encapsulated antigens or intradermal vaccines to the skin *via* a chitosan microneedle transdermal delivery system has been reported to provide sustained immune stimulation (Chen, Huang, Lai & Ling, 2013).

Cross-linking of alginate with di- and tri-valent ions (Ca, Ba, Sr, Al) to form the reversible "egg-box" array has been exploited to prepare pH-responsive network for intestinal target drug delivery (Alvarez-Lorenzo et al., 2013). Such pH-responsive is based on the limited swelling in the acidic environment (pH 1.2) in stomach and erosion of the network in the neutral environment (pH 7–7.4) in intestine. However, such pH sensitivity can also result in the stability problem of the delivery system (Mizrahy & Peer, 2012). Alternatively, various alginate and hyaluronic acid (semi-) interpenetrating polymer networks ((semi-)IPNs) have been developed for the application in drug delivery systems as reviewed by Matricardi, Di Meo, Coviello, Hennink, and Alhaique (2013). In addition to the pH-responsive network, the temperature-responsive alginate (semi-)IPNs delivery system has been explored by incorporation of poly(N-isopropylacrylamide); by physically or chemically crosslinking *via* the addition of Ca^{2+} and *N,N′*-methylenebisacrylamide respectively; and by photopolymerization *via* incorporation of photoinitiator, such as 2-hydroxy-1-[4-(2-hydroxyethoxy)phenyl]-2-methyl-1-propanone (Matricardi et al., 2013).

Several other polysaccharides such as pectin, chitin, chitosan, guar gum, xanthan gum, gellan gum, dextran, and chondroitin have also been developed for drug delivery or controlled drug release, which were reviewed in the functionalization of polysaccharides section in this paper and somewhere else by others (Liu, Jiao, Wang, Zhou, & Zhang, 2008; Luo & Wang, 2013; Morris, Kok, Harding, & Adams, 2010; Pachuau & Mazumder, 2013; Reddy et al., 2011; Tonnesen & Karlsen, 2002; Zhang et al., 2013b).

7. Concluding remarks and outlook

Polysaccharides have received considerable attention as functional biomaterials for novel and highly value-added applications, such as pharmaceutical, biomedical, and cosmetic applications owing to their non-toxic, biocompatible, and biodegradable properties. Proper isolation of native bioactive polysaccharides from various sources and determination of their structural features enable a clear understanding of the mechanism of biological action and structure–activity relationships. These in turn will facilitate the biomimic structural modification or functionalization of non-bioactive polysaccharides towards similar or more desirable bioactivities. However, how to isolate the bioactive polysaccharides with high purity and in large amount, meanwhile preserving their native structure remains a demanding and important task for future research. Various chemical modification approaches, such as partial hydrolysis, oxidation, reduction, etherification, esterification, and cross-linking, are available for tailoring the polysaccharides with desired properties. However, the presence of different monosaccharides used as building blocks, which usually are isobaric stereoisomers, variations in sequence, linkage, branching, and distribution of side chains, and functional groups after modifications result in a wide structural diversity of polysaccharides. This not only leads to the uncertainty or less specificity of the chemical modification to some extent, but also brings challenges to determine and establish the structure–function relationships that are the prerequisite and foundation for their applications. Enzymatic modifications are valuable tools for targeted functionalization of polysaccharides with high specificity; therefore, combining enzymatic and chemical approaches may offer an excellent alternative to engineer the properties of polysaccharides in a controlled manner. Proper isolation and purification of the chemically functionalized or natively bioactive polysaccharides is of crucial importance for applications in the biomedical area, as there is a need to avoid the undesirable side reactions of by-products, remainants of solvents and impurits in the products, and thus to enable the safe, reproducible and accurate dosage for experimental or therapeutic applications. Accumulating data from different modern structural analysis techniques, such as ultraviolet and infrared absorption spectroscopic, mass spectrometry, nuclear magnetic resonance spectroscopy, and some hyphenated approaches (HPLC–MS, HPLC–NMR, HPLC–DAD–MS–NMR, HPLC–TOF–MS^n, etc.) may enable a clear determination of structural features of the functionalized polysaccharides. The successful outcome of exploitation of polysaccharides in biomedical applications will require multidisciplinary expertise in plant biology, organic chemistry, material science and engineering, medical, health care and beyond.

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