Biologically Active Polysaccharides in Medicinal Plants†

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Abstract

Biologically active polysaccharides from medicinal plants have been studied for many years. In addition to immuno-modulating effects, human clinical studies have shown that some polysaccharides have certain benefits for human health. Most studies have focused on the side chains of pectic rhamnogalacturonan I (RG-I), particularly the Type II arabinogalactans, which have been isolated and shown to have anti-complementary and other immuno-activities. These studies have provided valuable information about how carbohydrate moieties induce certain biological events.

Keywords: cell wall polysaccharides; glucomannans; heteroxylans; medicinal plant; pectins, rhamnogalacturonan I; xyloglucans.

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Introduction

Polysaccharides are major components of plant cell walls and some of the most abundant biomaterials on earth. Cell wall polysaccharides are vital to human nutrition and health, and are sold commercially as dietary fibres and as health supplements (Paulsen, 2001; Tungland & Meyer, 2002; Harris & Smith, 2006). Many polysaccharides extracted from medicinal plants are recognised as having therapeutic potential as anti-cancer, anti-inflammatory, anti-bacterial, anti-viral, and immunodulatory agents (Darshan & Doreswamy, 2004). Some polysaccharides have been subjected to clinical trails and significant improvements in certain disease states have been reported (Guess et al., 2003). However, how polysaccharides induce complex cellular events in the human body remains largely unknown.

Nevertheless, it is likely that they act by regulating receptor mechanisms. If this is so, then it is essential to know the structures of specific polysaccharides and how they interact with the different receptors that lead to their biological effects. Such studies form the basis of glycobiology.

To determine the detailed structures of complex polysaccharides is a tedious task which often requires multiple strategies and requires enormous effort. Polysaccharides range in their structures from homopolymers to complex heteropolymers with different monomers, ring sizes, anomeric configurations, glycosidic linkages, and non-carbohydrate substituents. Their structures vary...
Biologically active cell wall polysaccharides

Pectins

Pectins are the major non-cellulosic components in the primary cell walls of medicinal plants belonging to eudicotyledons and non-commelinid monocotyledons (Harris, 2005). Examples of sources for commercial preparations are the dried peels of lemons (*Citrus limon* (L.) Burm.f.) and limes (*Citrus aurantiifolia* (Christm.) Swingle) (Harris & Smith, 2006). Pectins have complex structures and are classified according to their botanical origin and on the organ and cell type from which they were extracted, making it hard to evaluate which part of the structure contributes to its pharmaceutical activity. This review provides an overview of the structures of biologically active cell wall polysaccharides and related polysaccharides in medicinal plants.

*Angelica acutiloba* (Siebold & Zucc.) Kitag. has been shown to induce anti-complementary activity (Kiyohara et al., 1988). This preparation was composed of 90% α-0-GalpA residues with some α-L-Rhap residues, and neutral polysaccharide side chains attached to O-4 of the α-L-Rhap residues. Treatment of this anti-complementary pectin with *endo*-α-(1→4)-polygalacturonanase hydrolysed the HG domains, but the RG-I domains, rich in neutral polysaccharide side chains, were enzyme resistant. Although the oligogalacturonides derived from enzyme-sensitive HG had weak or negligible activity, the RG-I domains had potent anti-complementary activity (Kiyohara et al., 1988).

Similar studies have also been carried out on the neutral polysaccharide side chains of RG-I from leaves of *Panax ginseng* C.A.Mey (Gao et al., 1988; Gao et al., 1990), roots of *A. acutiloba* (Yamada et al., 1985a) and leaves of *Plantago major* L. (Samuelsen et al., 1996). An arabinogalactan Type II with a β-(1→3)-galactan backbone and α-1-arabinofuranosyl (α-1-Araf) residues linked at O-6 was shown to have the greatest effect on the complement system by neutralising the immune complement; it, therefore, has potent anti-complementary activity (Samuelsen et al., 1996). Some of the analyses of these active fractions showed a high proportion of (1→6)-linked β-D-Galp residues. The α-(1→5)-arabinans from fruits of *Zizyphus jujube* Lam. and roots of *Bupleurum falcatum* L. have also been shown to activate the complement system through both the alternative pathway and classical pathway, initiated by antibody and formation of antigen-antibody complexes, respectively (Yamada et al., 1985b; Yamada et al., 1988).

Immunomodulatory activities have also been reported for pectins with RG-I domains bearing arabinogalactan Type I and II side chains. For example, the GOA2-I fraction of the Malian medicinal plant (*Ginisus oppositifolius* (L.) Aug. DC.) was found to induce B-cell proliferation and upregulate the expression of the gene IL-1B and IFN-γ (Inngjerdingen et al., 2007). Clinical studies showed that oral administration of modified citrus pectin lengthened the doubling time of prostate specific antigen (PSA) in prostate cancer patients, thus slower cancer progression (Guess et al., 2003). In addition, Jackson et al. (2007) reported that citrus pectin that had been treated by heating to 123 °C induced apoptosis in human prostate cancer cells. However, it remains unclear what structural or physical changes occurred on heating the pectin and it appears that not all citrus pectins are effective against prostate cancer cells.

Studies on medically related biological activities of pectins have focused mostly on the RG-I domain. This domain has been shown to be associated with modulating the immune system including anti-complementary activity, B-cell proliferation and up-regulation of immune cytokines (Kiyohara et al., 1988; Samuelsen et al., 1996; Sakurai et al., 1999; Inngjerdingen et al., 2007).

The complement system plays an important role in host defence by mediating the lysis of erythrocytes and invading bacteria, the inflammatory response, the opsonisation of antigens and viral neutralisation. Overstimulation of the complement system can have negative effects such the development of aschronic hemolytic anemia caused by the excess lysis of host erythrocytes. Interestingly, a preparation containing RG-I and HG isolated from *Angelica acutiloba* (Siebold & Zucc.) Kitag. has been shown to induce anti-complementary activity (Kiyohara et al., 1988).
FIGURE 1: Structures of pectins from plant cell walls (modified from Harris, 2005 and Harris & Stone, 2008).

**Pectins**

**Homogalacturonan**

\[ \rightarrow 4\)-α- GalpA\( \rightarrow 4\)-α- GalpA\( \rightarrow 4\)-α- GalpA\( \rightarrow 4\)-α- GalpA\( \rightarrow 4\)-α- GalpA\( \rightarrow 4\)-α- GalpA\]

**Rhamnogalacturonan I**

\[ \rightarrow 4\)-α- L-Rhap\( \rightarrow 4\)-α- GalpA\( \rightarrow 4\)-α- L-Rhap\( \rightarrow 4\)-α- GalpA\( \rightarrow 4\)-α- L-Rhap\]

**Rhamnogalacturonan II**

**Arabinan**

**Arabinogalactan Type I**

**Arabinogalactan Type II**

**Side chain A**

\[ β-β- Galp \]

**Side chain B**

\[ α-L- AcefA \]

**Side chain C**

\[ \rightarrow 3\)-α- L-Rhap \]

**Side chain D**

\[ \rightarrow 2\)-α- L-Araf \]

\[ \rightarrow 3\)-β- D-Araf \]

\[ \rightarrow 3\)-β- D-Araf \]

\[ \rightarrow 3\)-β- D-Araf \]
FIGURE 2: Structures of heteroxylans, xyloglucans, and heteromannans from plant cell walls (modified from Harris, 2005 and Harris & Stone, 2008).

**Heteroxylans**

**Glucuronarabinoxylan (GAX)**

\[
\rightarrow 4)\beta-O-\text{Xylp}(1\rightarrow 4)\beta-O-\text{Xylp}(1\rightarrow 4)\beta-O-\text{Xylp}(1\rightarrow 4)\beta-O-\text{Xylp}(1\rightarrow 4)\beta-O-\text{Xylp}(1\rightarrow 2)\alpha-O-\text{GlcA} \downarrow \alpha-L-\text{Araf}
\]

**4-O-methyl glucuronarabinoxylans**

\[
\rightarrow 4)\beta-O-\text{Xylp}(1\rightarrow 4)\beta-O-\text{Xylp}(1\rightarrow 4)\beta-O-\text{Xylp}(1\rightarrow 4)\beta-O-\text{Xylp}(1\rightarrow 4)\beta-O-\text{Xylp}(1\rightarrow 2)\alpha-O-\text{GlcA} \downarrow \alpha-L-\text{Araf}
\]

**Feruloylated glucuronarabinoxylans**

\[
\rightarrow 4)\beta-O-\text{Xylp}(1\rightarrow 4)\beta-O-\text{Xylp}(1\rightarrow 4)\beta-O-\text{Xylp}(1\rightarrow 4)\beta-O-\text{Xylp}(1\rightarrow 4)\beta-O-\text{Xylp}(1\rightarrow 2)\alpha-O-\text{GlcA} \downarrow \alpha-L-\text{Araf}
\]

**Ferulic acid**

**Xyloglucans**

\[
\rightarrow 4)\beta-O-\text{Glc}(1\rightarrow 4)\beta-O-\text{Glc}(1\rightarrow 4)\beta-O-\text{Glc}(1\rightarrow 4)\beta-O-\text{Glc}(1\rightarrow 2)\alpha-O-\text{Xylp} \downarrow \alpha-O-\text{Xylp}
\]

**Heteromannans**

**Mannan**

\[
\rightarrow 4)\beta-O-\text{Manp}(1\rightarrow 4)\beta-O-\text{Manp}(1\rightarrow 4)\beta-O-\text{Manp}(1\rightarrow 4)\beta-O-\text{Manp}(1\rightarrow 4)\beta-O-\text{Manp}(1\rightarrow 1)
\]

**Glucomannan**

\[
\rightarrow 4)\beta-O-\text{Glc}(1\rightarrow 4)\beta-O-\text{Glc}(1\rightarrow 4)\beta-O-\text{Manp}(1\rightarrow 4)\beta-O-\text{Manp}(1\rightarrow 4)\beta-O-\text{Manp}(1\rightarrow 1)
\]
Heteroxylans

There are only a few reports on the biological activities of heteroxylans because it is challenging to extract these polysaccharides from cell wall preparations. To gain quantitative yields, strong alkalies, such as 4 M potassium hydroxide or 6 M sodium hydroxide, are required to break hydrogen-bonds that link these molecules to cellulose microfibrils. Heteroxylans have linear backbones of β-D-Xylp residues, some of which are substituted with single α-D-glucuronopyranosyluronic acid (or its 4-O-methyl derivative) residues at O-2 of β-D-Xylp, and/or with α-L-Araf residues at O-2 or O-3 of β-D-Xylp, see Figure 2 (Whistler et al., 1954; Hoffmann et al., 1992). Oligosaccharide side chains have also been reported in the glucuronarabinohexosyls of cereals. For example, L-Galp(1→4)-D-Xylp(1→2)-L-Araf was found attached at O-2 of the backbone β-D-Xylp residues of glucuronorabinoxylans from maize hulls (Whistler & Corbett, 1955). The sugar L-Galp rarely occurs in cell wall polysaccharides, but has also been found in the side chains of rhamnogalacturonan II (O’Neill et al., 2004).

Glucuronarabinohexosyls occur in the primary cell walls of a group of plants known as commelinid monocotyledons and have ester-linked ferulic acid attached, see Figure 2. Kato et al. (2001) reported that fucogalactoxyloglucans, the most commonly occurring type, induced cytoxicity in the model colon cancer cell line COLO 205; no activities was shown in xyloglucans without α-L-Fucp or β-D-Galp residues. This provided the first evidence that these monosaccharides in the side chains of xyloglucans play an important role in the cytotoxicity (Kato et al., 2001).

Heteromannans

Glucomannans are composed of both β-D-Glcp and β-D-Manp residues joined by (1→4) linkages in a linear chain (Figure 2). They are often present in large proportions in the viscous hydrogel of several medicinal orchids. Acemannan (acetylated glucomannan) extracted from the succulent leaves of Aloe spp. has shown significant clinical activity in wound healing (Mandal & Das, 1980; Paulsen, 2001). In vitro experiments have indicated that acemannan stimulated the production of mouse macrophage cytokine IL-6 and TNF-α (Zhang & Tizard, 1996). Heteromannans have also been shown to be effective adjuvants in avian vaccination against avian viral and tumoural diseases in vivo (Djeraba & Quere, 2000).

The detailed structures of the glucomannans extracted from the stems of the medicinal orchid Dendrobium huoshanense Z.Z.Tang & S.J.Cheng have been studied. The ratio of β-D-Manp to β-D-Glcp was found to be 5 : 1 and acetyl groups were found attached at O-2 of the β-D-Manp residues (Hsieh et al., 2008). The effects of D. huoshanense acetyl glucomannan on immune cytokines were studied and compared with the glucomannans from konjac (Amorphophallus konjac K.Koch) and a pure mannann, the (1→4)-β-D-mannan from ivory nut (Phytelephas macrocarpa Ruiz. & Pav.). Cytokine profiling indicated a significant increase in the expression of IFN-γ, IL-10, IL-6, and IL-1α. Significant amounts of hematopoietic growth factors GM-CSG and G-CSF were also induced in a dose-dependent manner, whereas konjac glucomannan and mannann from ivory nut failed to induce cytokine expression.

Conclusions

For decades, polysaccharides have been studied mostly for their structural and energy-storage roles. More recently, some polysaccharides have been shown to modulate immuno-activities. However, there is much still to be learnt. In particular, we need to understand the relationship between polysaccharide structure and biological recognition and activities. Certain fragments isolated from cell wall polysaccharides are valuable as they can lead to specific biological events, for example the anti-complement activity induced by Type II arabinogalactans of pectins and the expression of several cytokines induced by 2-O-acetyl glucomannans. The use of cell wall polysaccharides in carbohydrate-based drug discovery is promising.

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