International Journal of Biological Macromolecules 64 (2014) 257–266

Contents lists available at ScienceDirect

International Journal of Biological Macromolecules

journal homepage: www.elsevier.com/locate/ijbiomac

Review

Structural features and biological activities of the polysaccharides from *Astragalus membranaceus*

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ARTICLE INFO

Article history:
Received 11 September 2013
Received in revised form 6 November 2013
Accepted 2 December 2013
Available online 8 December 2013

Keywords:
Polysaccharide
Astragalus membranaceus
Bioactivities

ABSTRACT

Recently, a great deal of interest has been developed to isolate and investigate novel bioactive components with health benefit effects from natural resources. The dried root of *Astragalus membranaceus*, one of the most popular health-promoting herbal medicines, has been used historically as an immunomodulating agent for the treatment of common cold, diarrhea, fatigue and anorexia for more than 2000 years. Modern phytochemistry and pharmacological experiments have proved that polysaccharide is one of the major active ingredients in the root of *A. membranaceus* with various important bioactivities, such as immunomodulation, antioxidant, antitumor, anti-diabetes, antiviral, hepatoprotection, anti-inflammation, anti-atherosclerosis, hematopoiesis and neuroprotection. The aim of the present review is to summarize previous and current references and give a comprehensive summary regarding the structural features and biological activities of *A. membranaceus* polysaccharides in order to provide new insight for further development of these macromolecules.

Contents

1. Introduction

Astragalus membranaceus, also known as Huangqi in Chinese and *Radix Astragali* in Latin, is a perennial herbaceous plant of the Leguminosae family that is widely distributed throughout the temperate regions of the world [1,2]. The dried root of *A. membranaceus*, first documented in Shennong Bencao Jing (Shennong's Classic of

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0141-8130/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ijbiomac.2013.12.002

Materia Medica, 200–300 AD), is one of the most popular health-promoting herbal medicines commonly used in China for more than 2000 years [3]. It has been used historically as an immunomodulating agent for the treatment of common cold, diarrhea, fatigue and anorexia in traditional Chinese medicinal prescriptions, and it has also been prescribed to patients with cardiovascular diseases [4].

The bioactive constituents in the dried root of *A. membranaceus* are complicated. It contains more than 100 chemical compounds including polysaccharides, flavonoids, astragalosides, amino acids and trace elements [5]. Scientific investigations in the last two decades have revealed much insight into the pharmacological functions of these components, especially its polysaccharide fractions [3]. The polysaccharides have been identified as one of the major active ingredients responsible for the above bioactivities [6]. It has been proved that *A. membranaceus* polysaccharides (APS) had various biological activities, such as immunomodulation [3,7–9], antioxidant [10–13], antitumor [14–17], anti-diabetes [18–21], antiviral [22–25], hepatoprotection [1,26–28], anti-inflammation [29–32], anti-atherosclerosis [33,34], hematopoiesis [35] and neuroprotection [36]. Therefore, APS have great potential for further development as products in pharmaceutical and nutraceutical areas. The aim of the present review is to summarize previous and current references and give a comprehensive summary regarding the structural features and biological activities of APS in order to provide new insight for further development of these macromolecules.

2. Structural features

The structural features of a polysaccharide are defined by molecular weight, composition and sequence of monosaccharide, configuration and position of glycosidic linkages, type and polymerization degree of branch, spatial configuration, *etc*. [37]. Since the previous research on APS reported by Wang et al. [38], there were total 24 polysaccharides isolated and identified from the root of *A. membranaceus* up to date. Their structures have been investigated using a combination of techniques, such as partial acid hydrolysis, periodate oxidation, Smith degradation, gel-permeation chromatography, high performance liquid chromatography, gas chromatography, Fourier transform infrared spectra, gas chromatography–mass spectrometry, and nuclear magnetic resonance spectra. Their structural features such as molecular weight, monosaccharide composition and primary structure are shown in Table 1. Besides, their pharmacological properties and corresponding references are also included.

Most of the *A. membranaceus* polysaccharides reported are heteropolysaccharides. Due to different raw material or purification process, different results about structural features were given in various reports. These heteropolysaccharides had the molecular weight range of 8.7–4800 kDa with different ratio of 9 monosaccharides, namely glucose (Glc), galactose (Gal), arabinose (Ara), rhamnose (Rha), mannose (Man), xylose (Xyl), fucose (Fuc), fructose (Fru) and ribose (Rib). Meanwhile, they might also contain glucuronic acid (GlcA) and galacturonic acid (GalA). Furthermore, some structural and conformational information about these heteropolysaccharides was reported. Wang et al. [42] found that the minimal repeat unit of a water-soluble heteropolysaccharide (APSID3) isolated from *A. membranaceus* was composed of one terminal Ara, one 1,5-linked Ara, one 1,3-linked Rha, one 1,3,4-linked Rha, six 1,4-linked GlcA and five 1,4-linked GalA residues. The main chain was composed of 1,4-linked GalA, 1,4-linked GlcA and a small amount of 1,3-linked Rha, with the side chain composed of 1,5-linked Ara located at C-4 of 1,3-linked Rha. The structural analysis of two polysaccharides isolated from *A. membranaceus* using fractional precipitation, DEAE-Sephadex A-25 and Sephadex G-100 column chromatography indicated that their main chains were mainly composed of major α-(1 → 3) Glc and a few 1 → 4, 1 → 6 Glc with the side chain composed of Ara and Xyl [14]. Recently, Fu et al. [46] reported APS had a linear backbone mainly composed of 1,3-linked β-D-Gal residues with insertion of β-Glc, 1,6-linked α-Gal, 1,5-linked β-Xyl, 1,4-linked β-Gal, β-D-Gal, 1,2-linked α-Rha, 1,2,4-linked α-Rha residues, with C-2 and C-6 linked with H.

In addition, some glucans have also been isolated and purified from *A. membranaceus* except for heteropolysaccharides mentioned above. These glucans were mainly determined as α-(1 → 4)-D-glucans with a molecular weight range of 12–36 kDa. The primary structure of a water-soluble APS was investigated by Li and Zhang [30], and it was found that APS was an α-(1 → 4)-D-glucan, with a single α-D-Glc at the C-6 position every nine residue, on average, along the main chain. Li et al. [15] reported that the polysaccharide with antitumor properties from *A. membranaceus* was an α-(1 → 4)-D-glucan with α-(1 → 6) linked branches attached to the O-6 of branch points. It has also been reported that the chemical structure of APS was determined as a (1 → 4)-linked dextran backbone with a (1 → 6)-linked branch every 10 residues [12].

3. Biological activities

3.1. Immunomodulatory activity

Many experimental studies have demonstrated that APS possess strong immunomodulatory effects both *in vitro* and *in vivo*.

Lymphocytes play a crucial role in the activation cascade of both cellular and humoral immune responses [47]. APS could increase the number of lymphocytes and the proportion of $CD4^+$ lymphocyte subset in blood samples of weaned pigs, and improve the lymphocyte proliferation response to Concanavalin A (ConA) [7]. APS could also increase the percentage and proliferation of acid α-naphthyl acetate esterase-positive T-lymphocytes in peripheral blood of chicks [8] and dexamethasone-induced immunosuppressive dogs [9], and promote T-lymphocyte proliferation in cyclophosphamide (Cy)-induced immunosuppressive chickens [48].

Cytokines participate in many physiological processes including the initiation and regulation of both innate and adaptive immune response [49]. It has been found that APS could improve the gene expressions of interleukin (IL)-1β and tumor necrosis factor α (TNF-α) in the head kidney, gill and spleen of common carp [50]. APS could also enhance the levels of serum IL-2 or interferon-γ (IFN-γ) in weaned pigs [7], adriamycin-induced immunosuppressive mice [51], dexamethasone-induced immunosuppressive dogs [9] and Cy-induced immunosuppressive chickens [48].

Macrophages provide the defense line against tumor cells and somatic cells infected with parasite or fungus in host defense system. Shao et al. [41] demonstrated that APS activated mouse macrophages and B cells, rather than T cells, in terms of proliferation and cytokine production *via* the activation of Toll-like receptor 4 (TLR4). Wang et al. [38] previously found that APS could increase the number of peritoneal macrophages and the deposition of the third component of complement (C3) on peritoneal macrophages in mice. Xu et al. [52] reported that APS had strong promoting effects on the phagocytosis of *Mycobacterium tuberculosis* by macrophages and the secretion of IL-1β, IL-6 and TNF-α by activated macrophages. The effect of APS on isolated mouse peritoneal macrophages and RAW264.7 macrophages demonstrated APS could increase the levels of cytokines including TNF-α, granulocyte-macrophage colony-stimulating factor (GM-CSF), the production of nitric oxide (NO) and the transcription of inducible NO synthase (iNOS), which may through the activation of nuclear factor-κB/Rel (NF-κB/Rel) [45,53,54]. It suggested that