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Review article

Animal lectins: potential receptors for ginseng polysaccharides

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ABSTRACT

Panax ginseng Meyer, belonging to the genus *Panax* of the family Araliaceae, is known for its human immune system-related effects, such as immune-boosting effects. Ginseng polysaccharides (GPs) are the responsible ingredient of ginseng in immunomodulation, and are classified as acidic and neutral GPs. Although GPs participate in various immune reactions including the stimulation of immune cells and production of cytokines, the precise function of GPs together with its potential receptor(s) and their signal transduction pathways have remained largely unknown. Animal lectins are carbohydrate-binding proteins that are highly specific for sugar moieties. Among many different biological functions *in vivo*, animal lectins especially play important roles in the immune system by recognizing carbohydrates that are found exclusively on pathogens or that are inaccessible on host cells. This review summarizes the immunological activities of GPs and the diverse roles of animal lectins in the immune system, suggesting the possibility of animal lectins as the potential receptor candidates of GPs and giving insights into the development of GPs as therapeutic biomaterials for many immunological diseases.

1. Introduction

1.1. Ginseng polysaccharides

1.1.1. Ginseng

Panax ginseng Meyer is a well-known medicinal plant in the world. The ginseng is a deciduous perennial belonging to the family Araliaceae and genus *Panax*. The genus name of ginseng, *Panax*, is derived from the Greek *pan* (all) *akos* (cure), meaning "cure-all" or "all healing," which describes the traditional belief that ginseng has properties to heal all aspects of the body. The name ginseng comes from the Chinese words "Jen Sheng," meaning "man-herb," because of the humanoid shape of the root or rhizome of the plant, which is the part of the plant most commonly used for extraction [1,2]. There are about 13 different species of ginseng which have being identified all over the world. Among them, the most commonly used species of ginseng are Asian ginseng (*P. ginseng* Meyer, *Renshen*) and American ginseng (*Panax quinquefolius* L., *Xiyangshen*) which all belong to the *Panax* genus of the Araliaceae family [3]. Asian ginseng has been used for thousands of years as a tonic to improve overall health, restore the body to balance, help the body to heal itself, and reduce stress [4], and American ginseng has been used by Native Americans for at least hundreds of years [2,5]. Ginseng is prepared and used in several ways as fresh ginseng (sliced and eaten, or brewed in a tea), white ginseng (peeled and dried), red ginseng (peeled, steamed, and dried), extract (tincture or boiled extract), powder, tea, tablet, or capsule [1,2]. It has been reported that ginseng exhibits a wide range of beneficial pharmacological effects including immunomodulation, antitumor, antioxidation, antidepression, hypoglycemic, inhibition of gastric lesions, attenuation of leptin-induced cardiac hypertrophy, heart protection against ischemia and reperfusion injury, prevention of glucose-induced oxidative stress, prevention of diabetic nephropathy, retinopathy, and cardiomyopathy [6–10]. This broad spectrum of biological activity of ginseng has originated from its multiple bioactive components,

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namely ginsenosides, polysaccharides (PSs), peptides, polyacetylenic alcohols, and gintonin [11–13].

1.1.2. The composition of ginseng polysaccharides

Ginsenosides were considered to be responsible for most of ginseng's pharmacological effects. However, recent studies indicate that ginseng polysaccharides (GPs), one of the active components of ginseng [14], also possess a wide range of biological and pharmaceutical activities, including immune-modulation, antitumor, antiadhesive, antioxidant and hypoglycemic activities [8,15]. Especially, GPs are known for their immunostimulatory effects [10,16,17] and a major contributor to the bioactivity of herbal medicines, providing great potential applications in food, pharmaceuticals, and other industries. Therefore, GPs were extensively studied for their constituents and chemical structures. GPs are biopolymers formed from a complex chain of monosaccharides rich in L-arabinose, D-galactose, L-rhamnose, D-galacturonic acid, D-glucuronic acid, and D-galactosyl residue linked together through glycosidic bonds, resulting in complex macromolecular architectures [7,18,19]. Their molecular weights range from 3500 Da to 2,000,000 Da [19], which contributes to their diverse physicochemical properties and biological activities [8,15,19,20].

GPs include acidic and neutral PSs. The pharmacological effects of GPs, including immunomodulation, can be attributed to these acidic and neutral PS components [15]. While the acidic GPs contain different amounts of uronic acids and neutral sugars [15,21], the neutral PSs mainly contain different ratios of neutral sugar residues [3]. So far, the studies about American GPs have mainly been centered on acidic PSs, resulting in relatively limited research that explores neutral PSs. However, researchers also have interest in neutral PSs of American GPs, because neutral PSs are also one of the important active components in the American ginseng roots. The PSs from ginseng roots have many bioactivities, such as immunomodulation, antitumor, and hypoglycemic activities [11,22], and contain 60% neutral starch-like PSs, 15% arabinogalactans, and 25% pectins [20]. Similarly, the PSs from ginseng leaves are also bioactive, and contain about 70% arabinogalactans and 20% pectins.

1.1.3. The immune functions of GPs

GPs enable enhancement of the production of cytokines and reactive oxygen species by stimulating macrophages [23,24]. In a recent study, GP was shown to stimulate dendritic cells (DCs) resulting in enhanced production of interferon-γ (IFN-γ) [25]. It was reported that acidic GPs promoted the production of cytotoxic cells against tumors and stimulated macrophages to produce helper types 1 and 2 (Th1 and Th2) cytokines [26,27]. An acidic GP from *P. ginseng* has been shown to display immunomodulatory effects either in an immunostimulatory or in an immunosuppressive manner, depending on timing of treatments and disease environments [28]. This acidic GP was also shown to modulate the antioxidant defense systems such as superoxide dismutase and glutathione peroxidase enzymes, probably via inducing regulatory cytokines [15,29]. Therefore, acidic GPs have been considered as the major bioactive species for immune modulations. Tomoda et al [30] reported that two acidic PSs of *P. ginseng* enhance the phagocytic activity of macrophages, and Sonoda et al [31] found that an acidic GP of *P. ginseng* was a potent inducer of interleukin-8 (IL-8) production by human monocytes and THP-1 cells. Shin et al [32] reported that an acidic PS of *P. ginseng* shows immune modulatory activities via macrophage NO production. Recently, Lemmon et al [29] reported that the immunostimulatory effects of acidic GPs of *P. quinquefolius* are mediated by PS with a molecular weight higher than 100 kDa. It was reported that acidic GPs promoted the production of cytotoxic cells against tumors and stimulated macrophages to produce helper types 1 and 2 (Th1 and Th2) cytokines [26,27]. Intravenous pretreatment of GP attenuated the production of serum proinflammatory and antiinflammatory cytokines after septic bacterial infection [33].

In addition, Ginsan, an acidic GP from of *P. ginseng*, is a well-known medicinal herb and has been shown to have critical effects on immune cells, which shows an immunomodulatory acidic GP from *P. ginseng* [27]. Kim et al [26] showed that Ginsan induces Th1 cell and macrophage cytokines. Ginsan enhances the production of cytokines and reactive oxygen species by macrophages [24] and stimulates the phagocytic activity of macrophages [23]. Also, Ginsan induces the maturation of DCs [25], profoundly enhancing the production of IL-12, IL-10, and tumor necrosis factor alpha (TNF-α) by DCs and showed that Ginsan may modulate DC function by altering cytokine levels [25]. For neutral GPs, it was reported that neutral GPs of *P. ginseng* stimulate the proliferation of lymphocytes, increase the cytotoxicity of natural killer cell, enhance the phagocytosis and NO production by macrophages, and increase the level of TNF-α in serum [21,34]. Due to these results, many scientists have considered both acidic and neutral GPs as stimulators in the immune system. X. Zhang et al and Kim et al reported that both acidic and neutral GPs of *P. ginseng* (Asian ginseng) may stimulate B cells, T cells and macrophages [20,35]. In addition, they considered the relation of acidic and neutral GPs as the supporter, in which neutral GPs help the enhancement of immunostimulatory effects of acidic GPs. In fact, W. Ni et al reported that neutral GPs of *P. ginseng* enhance macrophage production of NO [21].

On the contrary to immunostimulatory effects of GPs, recent studies showed that GPs also suppress the proinflammatory responses. Recently, it was reported that a novel neutral PS (PPQN, 3.1 kDa) was isolated from American ginseng roots and could suppress inflammation by inhibiting the secretion of inflammatory-related mediator nitric oxide (NO) and cytokines (TNF-α, IL-6, and IL-1β) compared to Lipopolysaccharide (LPS) treatment, implicating the therapeutic implications of PPQN in inflammatory-related diseases like tumors, atherosclerosis, and so on [3]. As an example, one study reported that GPs inhibit immunological responses associated with collagen-induced arthritis [36]. Other studies also suggest that CVT-E002, a poly-furanosyl-pyranosyl polysaccharide-rich herbal and unique extract product of the root of American ginseng (*P. quinquefolium*), suppresses the inflammatory immune responses, reducing the activation of neutrophils [37], inducing the production of IL-2, IFN-γ, TNF-α, and IL-6 in spleen [7,19,38], and increasing the proliferation of splenic B lymphocytes, bone marrow, and natural killer cells.

1.1.4. The working mechanisms of GPs in pathogen protection

Intravenous pretreatment of GP attenuated the production of serum proinflammatory and antiinflammatory cytokines after septic bacterial infection [33]. Also, this intravenous pretreatment of GPs in mice enhances macrophage-mediated bactericidal activity by reducing the number of *Staphylococcus aureus* which is present in the spleen, kidney, and blood and exerts a protective effect against infected septic mice by suppressing early acute inflammation [33,39]. In addition, recent studies reported that pretreatment with GP suppressed acute inflammatory responses at an early phase resulting in the enhancement of antimicrobial activities and protection of mice from *Staphylococcus aureus*-induced sepsis as an antiinflammatory function [33,39]. As an example, CVT-E002 has been shown to be effective for preventing acute respiratory illness caused by influenza and respiratory syncytial virus [7,40]. Another study revealed that intranasal administration of GPs showed a protective effect on influenza viral infection by lowering the levels of inflammatory cytokines (IL-6) and lung viral titers [28]. Because GPs were reported to significantly increase the viability of peritoneal macrophage cells [8] and ginseng was shown to inhibit

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