Pharmacology of Polysaccharides from Ginseng Species

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In traditional Chinese medicine, Panax ginseng C.A. Meyer (PG) invigorates “qi” of kidney, spleen and lung, promotes body fluids production, calms the mind to promote intelligence, while P. quinquefolium L. (PQ) supplies “qi”, nourishes “Yin”, clears fire and promotes body fluid production, both are classified as “restoratives”. P. notoginseng (Burk) F.H. Chen (PN) removes blood stasis, stops bleeding, promotes blood circulation with analgesic effect, and is classified as “hemostatics”. The major bioactive principles of Panax species, ginseng saponins, are classified into dammarane, oleanane, and ocotillol types. PQ contains all three types of ginseng saponins. PG contains dammarane and oleanane types. PN contains only dammarane type, and a peptide like substance dencichine is the major active component to stop bleeding. PN contains the highest level of ginseng saponins (6.24-10.32%), followed by PQ (4.50-6.45%) and PG (3.50-4.84%). Besides ginseng saponin in which the chemistry and biological effects have been studied in detail, the polysaccharides, polyptides and fatty acids are also investigated by many scholars. In this paper, the separation and identification of ginseng saccharides, immuno-modifier, anti-inflammatory, anticancer, anti-ulcer or antiadihesive, anti-diabetic and anti-hyperlipidemic effects of such saccharides are reviewed, while the causes of succession cropping obstacle and future ways for the development of Panax species are discussed and suggested.

Keywords: ginseng polysaccharides, ginseng saponins, ginseng species, succession cropping obstacle

INTRODUCTION

The traditional Chinese medicine (TCM) believes that internal organs perform the vital function by generating and storing essential air of life, “Qi”. These organs are classified into heart (心, Xin), the utter superiority of the organ to all other organs; the emotions, intellect, thinking, memory, conscience all belong to the realm of the heart), liver (肝, Gan, a principal reservoir of blood, for issuance and distributing of blood and nutrients, promotion of high spirit in one’s outlook on life and the brightening of the vision), spleen (脾, Pi, as a messenger; the basic functions are transforming, transporting, and distribution of digested matter as well as a transitional storage, initiation of body movements, and clearing up internal pollution), lungs (肺, Fei, all bloodvessels converge towards the lungs and lungs promote the wholesomeness of the skin and hairs; there is reciprocal correlation between the lungs and the kidneys), and kidneys (肾, Shen, organs that responsible for the process of reproduction and food essence, the growth and development of the brain, marrow and bone) (Liu and Liu 1980).

Among the Araliaceae family, Panax ginseng, C.A. Meyer (PG), P. quinquefolium L. (PQ), and P. notoginseng (Burk) F.H. Chen (PN) are the most commonly used herbal drugs. PG was recognized by TCM to invigorate “Qi” of kidney, spleen and lung, promote body fluids production, calm the mind to promote intelligence, which could be administered even in substantial amounts or for sustained usage without causing damage to the body, thus it was considered as “top class” in the oldest Chinese Materia Medica “Shen-Nong-Ben-Cao-Jing” (Shen-Nong-Herbal Classic) edited around 200 A.D. PQ was first introduced by Wang Ang in “Essential of Materia Medica” in 1694, which supplies “Qi”, nourishes “Yin”, clears fire and promotes body fluid production. PG and PQ are classified as “restoratives”. PN was first mentioned in “Ben Cao Gong Mu” by Li Shi-Zhen (1518-1593) as to remove blood stasis, stop bleeding, promote blood circulation with analgesic effect, and is classified as “hemostatics”.

Saponins are major bioactive components or ingredients of Panax species. Until recently, more than 100 kinds of saponins are purified and identified from Araliaceae family (Jia and Zhao 2009; Jia et al. 2009). Such saponins are classified into dammarane, oleanane and ootillol types. PQ
contains all three types of ginseng saponins. PG contains dammarane and oleanane types. PN contains only dammarane type. Root of PN contains the highest level of ginseng saponins (6.24-10.32%), followed by PQ (4.50-6.45%) and PG (3.50-4.84%). However, an acre land can produce 600-700 kg of PG, 300 kg of PQ or 180 kg of PN root.

Besides ginseng saponins in which the chemistry and bioactive activities were studied in detail, the polysaccharides and glycosides are also investigated by other scholars. The pharmacological effects and chemical components, majorly ginseng saponins, of PG, PQ and PN have been reviewed (Vogler et al. 1999; Ellis and Reddy 2002; Cheng et al. 2005; Ng 2006; Zhang et al. 2006; Chen et al. 2008; Choi 2008; Jia and Zhao 2009; Jia et al. 2009). The results of such efforts in the study of ginseng demonstrated that ginseng meets the so-called adaptogen (Brekman and Oshima 1990) again prepared two acidic heteroglycans (IA and IIA) consisting of rhamnogalacturonan core with neutral oligosaccharides and polypeptides are also investigated by many researchers. Polymeric carbohydrates and pectic polysaccharide: Sun et al. (1996) isolated 5 hypoglycaemic panaxans A, B, C, D, E from PG roots. Tomoda et al. (1984) reported the partial structure of panaxan A. Then, 5 panaxans Q, R, S, T, and U in a water extract of PG roots from Nagano and Japan as well as 4 panaxans I, J, K, and L in a water extract of PG roots from Korea were isolated. All these panaxans remarkably reduce blood sugar levels in normal and alloxan-induced hyperglycemic mice (Konno et al. 1985; Oshima et al. 1985). Smolina et al. (1998) purified panaxan-I from PG root and panaxan-2 from PG cell culture and demonstrated their induction of interferon and tumor necrosis factor in human leukocytes. Oshima et al. (1987) isolated hypoglycemic quinquefolans A, B and C from PG roots.

Heteroglycans: Gao et al. (1989) prepared water-soluble and alkaline-soluble polysaccharide fractions from PG roots and leaves, and further fractionated into strongly acidic, weakly acidic, and neutral polysaccharide fractions by cetyltrimethylammonium bromide, respectively. Gao et al. (1990) again prepared two acidic heteroglycans (IA and IIA) from PG leaves, which are obtained by base-catalysed methylation analysis, nuclear magnetic resonance and paper electrophoresis. They contain a beta-eliminative degradation. IA and IIA contain Rha·Rha-ol-1,2-D, HexA·Rha-ol-1,2-D, and HexA·Rha·Rha-ol-1,2-D. IA and IIA consist mainly of 2-linked Rha, 4-linked GalA, and terminal and 6-linked Gal. IIA contains more 2-linked Rha than IA. Gao et al. (1991) purified two potent anti-complementary heteroglycans, neutral GL-Nla and acidic GL-Ala. GL-Ala is a capping linkage of analysis demodermated that GL-Nla mainly consisted of arabino-galactan moieties. Beta-elimination indicated that GL-Ala was pectic polysaccharides consisting of rhamnogalacturonate core with neutral side chains. Gao et al. (1996) prepared four immunostimulating heteroglycans (PF 3111, 3112 and PBGA 11, 12) from PN with MWs ranging from 37 kDa to 730 kDa, composed of glucose, galactose, arabinose, mannose, and xylose in different molar ratios.

Pectic polysaccharide: Sun et al. (1992a, 1992b) purified an anti-uler pectic polysaccharide, GL-4Hb1III, from the weakly acidic polysaccharide fraction GL-4 obtained from water-soluble crude polysaccharide (GL-2) of PG leaves. GL-4Hb1III (average relative molecular mass, 16,000) is composed mainly of galactose and galacturonic acid with small proportion of rhamnose, arabinose, mannose, glucose, and glucuronic acid. Same group of investigators (Kiyohara et al. 1994) purified another anti-uler GL-4Pb1 from the same source. Methylation analysis indicated that GL-BII consists mainly of terminal Arap, 4- or 5-substituted Ara, 2,4-disubstituted Rha, 4- and 6-substituted Gal, and 3,6-disubstituted Gal. Single radial gel diffusion using beta-glucose-Yavir antigen indicated that GL-BII contains a small proportion of [beta-(1→3,6)-galactan moiety. GL-BII also contains terminal, 4-substituted, and 3,4-disubstituted GalA, and terminal and 4-substituted Glc. Base-catalysed [beta]-elimination suggested that some 2- or 3-substituted Rha in GL-BII is attached to position 4 of a 4-substituted uronic acid. GL-BII contains a GalA-(1→4) Rha unit in addition to longer acidic units consisting of 2-substituted Rha and 4-substituted GalA. Lithium-mediated degradation of GL-BII followed by borohydride reduction gave small amounts of fractions containing long and intermediate neutral oligosaccharide-alditols and a large amount of fraction containing a fucose-alditol. The long neutral oligosaccharide-alditol fraction mainly comprises 4- or 5-substituted Ara, terminal Galf, 6-substituted Glc and 2-substituted Man, the intermediate oligosaccharide-alditol fraction consists mainly of terminal and 6-substituted Galp, 6-substituted Glc and 2-substituted Man, and the short oligosaccharide-alditol fraction contains at least 14 kinds of di- to tetra-saccharide-alditols. Shin et al. (1997) isolated a complex pectic polysaccharide (GL-4Hb2) from PG leaves, which consists of 15 different monosaccharides with the characteristic of rhamnogalacturanllon II (RG-II), and its molecular mass (11,000) are large than sycamore RG-II (5,000). It contains alpha-Rhap-(1→5)-Kdo and Arf-(1→5) Dha structural elements, an AceA-containing oligosaccharide, and uronic acid-rich oligosaccharide chain in addition to an alpha-(1→4)-galacturono-oligosaccharide chain. Zhu et al. (2005) characterized cell wall polysaccharides of PN roots, which include pectic polysaccharides (neutral Type I 4-galactan (21%), arabinan (5%), acidic rhamnogalacturan 1 (1.2%) and homogalacturan 24%, non-cellulosic polysaccharides (heteroxylan, 3%), xylloglucan (3%), heteromannan (1%) and cellulose (24%).

Acidic polysaccharides: Tomoda et al. (1993a) isolated two acidic polysaccharides, ginsenan PA and PB, from PG roots. Their structural features include mainly both alpha-arabinofuranosyl- and galactopyranosyl units as an anti-ulcer activity. They contain mainly alpha-arabinose: D-galactose: D-glucose: D-galacturonic acid in the molar ratio of 8:8:1 and 3:7:2:8:1, respectively. Tomoda et al. (1993b) also isolated two other acidic polysaccharides, ginsenan S-IA and S-IIA from PG roots. Ginsenan S-IA is composed of glucuronic acid and mannose, while ginsenan S-IIA is composed of glucose, galactose, arabinose, and xylose in different molar ratios. Furthermore, ginsenan S-I and S-IIA from PG roots. Ginsenan S-IA is composed of glucuronic acid and mannose, while ginsenan S-IIA is composed of glucose, galactose, arabinose, and xylose in different molar ratios. Additionally, ginsenan S-I is composed of glucose, galactose, and arabinose in different molar ratios. Ginsenan S-IIA is composed of glucose, galactose, and arabinose in different molar ratios. Moreover, ginsenan S-IA and S-IIA from PG roots. Ginsenan S-IA is composed of glucuronic acid and mannose, while ginsenan S-IIA is composed of glucose, galactose, arabinose, and xylose in different molar ratios. Furthermore, ginsenan S-I and S-IIA from PG roots. Ginsenan S-IA is composed of glucuronic acid and mannose, while ginsenan S-IIA is composed of glucose, galactose, arabinose, and xylose in different molar ratios. Additionally, ginsenan S-I is composed of glucose, galactose, and arabinose in different molar ratios. Ginsenan S-IIA is composed of glucose, galactose, arabinose, and xylose in different molar ratios. Moreover, ginsenan S-I is composed of glucose, galactose, and arabinose in different molar ratios.
chromatography followed by gel-permeation chromatography and strongly bound to the DEAE anion-exchange column with a MW of 1140 kDa. It is composed of acidic polysaccharides (glucuronoarabinoxylan, homogalacturonan, rhamnogalacturonan I), neutral polysaccharides (4-galactan and arabinan), and some protein. Lee et al. (2006) prepared P-G2, an acidic polysaccharide from PG, and showed its selective anti-adhesive activity against pathogens. P-G2 is a pectin-type polysaccharide with a mean MW of 2.0 x 10^5 Da. It consists primarily of galacturonic and galactonic acids along with rhamnose, arabinose, and galactose as minor components.

Wu and Wang (2008) purified an antiradical arabinogalactogalactan from PN roots through successive phosphate buffer (pH 7.0) extraction after cold-water pretreatment and purification by ion-exchange and gel-filtration chromatography. This arabinogalactogalactan possesses a backbone of (1→3)-linked β-d-galactofuranosyl residues, with branches of α-L-Ara (1→4)-β-D-Glc P (1→ residues at O-6).

Xu et al. (2008) reported the optimal extraction process of polysaccharide constituents from Panax japonicus. The conditions of the ideal extraction process using compound enzyme method are that of the pH value is at 5.0, the temperature of material, cellulose quality score is 1–2%, pectinex pound enzyme method are that of 4 h, the ideal pH used for precipitation is 4.8, with cold-water extraction and centrifugation. This arabinogalactogalactan possesses a backbone of (1→3)-linked β-d-galactofuranosyl residues, with branches of α-L-Ara (1→4)-β-D-Glc P (1→ residues at O-6).

Recently, Guan and Li (2010) determined the enzymatic hydrolysis properties of the polysaccharides from 9 traditional Chinese medicines including PG, P, PN and their saccharide mapping by using endo-carbohydrases and enzymatic digestion following by high performance size exclusion chromatography as well as derivatization with 1-phenyl-3-methyl-5-pyrazolone and HPLC analysis.

**IMMUNO-MODIFIER AND ANTI-INFLAMMATORY EFFECTS OF GINSENG POLYSACCHARIDES**

The anti-complement effects of water-soluble and alkaline-soluble polysaccharide fractions obtained from PG leaves are more potent than that obtained from PG roots, and neutral polysaccharide GL-N1a and acidic polysaccharide GL-A1a exhibit potent effect at low concentrations (Gao et al. 1989, 1991). Polymorphonuclear (PMN) leukocytes and macrophages stimulating effects of the polysaccharides from ginseng tissue culture were also reported (Solori et al. 1989). Then, anti-complementary or immunostimulatory polysaccharides such as GL-P1, GL-P1a, GL-P1v, PF3111, PF3112, PBGA11, and PBGA12 are identified (Gao et al. 1990, 1996; Park et al. 2001; Lim et al. 2004). Other acidic polysaccharides, named ginsenan PA and PB, were reported to dose-dependently potentiate reticuloendothelial system activity (Tomoda et al. 1993a). Tomoda et al. (1993b) again identified ginsenan S-IA and S-IIA, both showing promoting phagocytosis and anti-complement activities.

Ma et al. (1995) found that PG polysaccharides dose-dependently promote interleukin (IL)-2 production by peripheral blood mononuclear cell (PBMC) in healthy and kidney diseases patients. In addition to anticomplementary activity, the PN water-soluble polysaccharides, PF3111, PF3112, and PGBA12 have interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) inductive activities in vitro (Gao et al. 1996). Lee et al. (2007) demonstrated that PG acidic polysaccharide ginsan induces the expression of TNF-α, IFN-γ, IFN-β and inducible nitric oxide synthase mRNAs in spleen cells and peritoneal macrophages from C57Bl/6J mice. Ginsan also enhances the viability and proliferation of mouse spleen cells (Ko and Joo 2010). In addition, ginsan can stimulate dendritic cells by inducing maturation (Kim et al. 2009a) and enhances antibody response to orally delivered Salmonella antigen in mice, mediated by chemokine (C-C motif) ligand 3 (CCL3) via cyclooxygenase (Na et al. 2010).

Smolina et al. (2001) reported that panaxan-1 (from ginseng root) and panaxan-2 (from ginseng cell culture) can induce production of TNF and IFN-γ in human leukocytes. GL-41b2, a complex pectic polysaccharide from PG leaves has been shown to be a macrophage Fc receptor expression-enhancing polysaccharide (Shin et al. 1997). A part of polysaccharides from the stem and leaves of PG, named PGP-SL, exhibits anti-inflammatory effects on murine spleen lymphocytes by the Ca2+-calcineurin-nuclear factor of activated T-cells (NFAT) -IL-2 signaling pathway (Zhang et al. 2010). CVT-E002, an aqueous extract containing mainly oligosaccharides and polysaccharides from PQ stimulated the proliferation of normal mouse B lymphocytes, enhanced IL-1, IL-6, TNF-α and nitric oxide production of activated macrophages (Wang et al. 2001) and enhanced Con-A induced IL-2 and IFN-γ productions in murine spleen cells (Wang et al. 2004). CVT-E002 also modifies system immune responses and appears to affect gut-associated immunity (Biondo et al. 2008). Three days’ CVT-E002 (5 g/kg/day) treatment in C57BL/6J mice did not affect the tested activities of various drug-metabolizing enzymes. Thus, CVT-E002 has low potential of incidence of metabolite-based drug interaction (Ueng and Chen 2002).

Choi et al. (2008) showed the synergistic effect of red ginseng acidic polysaccharide in combination with IFN-γ in enhancing macrophase function through nuclear factor-kappa B (NF-κB) pathway activation in murine melanoma B16 cells. The synergistic immunostimulatory effect of ginsan is demonstrated to be attributed to enhanced bacterial clearance, and reduced proinflammatory cytokines via the Toll-like receptor (TLR) signaling pathway (Ahn et al. 2006b). Ginsan also has antiallergic effect on ovalbumin-induced asthma in mice partially by up-regulating cyclooxygenase expression and prostaglandin E2 production (Lim et al. 2009). Ginsan is also demonstrated to effectively prevent carbon tetrachloride-induced liver injury in mice, mainly through down-regulation of oxidative stress and inflammatory response (Shim et al. 2010). Furthermore, ginsan can act as an effective anti-fibrotic agent against transforming growth factor-beta (TGF-β) induced fibrosis by blocking multiple TGF-β signaling pathways in murine or human normal lung fibroblasts (Ahn et al. 2011).

The anti-inflammatory and immunosuppressive effects of whole extract of PN are stronger than ginsenosides Rb1 and Rg1 in LPS activated RAW264.7 macrophage (Rhule et al. 2006). PN flower extract also attenuates LPS-induced inflammatory response via blocking of NF-κB signaling pathway in RAW264.7 macrophage (Jung et al. 2009). Furthermore, PN flower extract inhibits the production of specific inflammatory molecules and innate immune responsiveness by cultured dendritic cells (DC2.4) following TLR activation (Rhule et al. 2008). In addition, arabinogalactan from PN root exhibits high scavenging activity against 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radicals (Wu and Wang 2008).

Among the PN high-molecular-weight fractions, the strong alkalii (1 M KOH) extract fraction and its sub-fraction 1MD3-G2 show the highest complement-fixing activity.

and priming of reactive oxygen species (ROS) production by human polymorphonuclear neutrophils, and mitogenic and IFN-γ productive effects on peripheral blood mononuclear cells (Zha et al. 2005, 2006).

**ANTICANCER EFFECTS**

Ginsan exhibits significant in vivo antitumor activity against B16 melanoma cells and in the benz(a)pyrene-induced autochthonous lung tumor model (Lee et al. 1997), partially by generating LAK cells from both NK and T cells through endogenously produced multiple cytokines (Kim et al. 1998). Ginsan also has radioprotective effect on bone marrow cells (Kim et al. 2007), partially through reduction of radiation-induced genotoxicity (Ivanova et al. 2006). Ginsan also can act a defense against small intestinal damage by whole-body gamma irradiation of mice, indicating ginsan might be a useful adjunct to therapeutic irradiation as a protective agent for the gastrointestinal tract of cancer patients (Park et al. 2011). Post-treatment of ginsan reduces the adverse effects of cyclophosphamide on tumor bearing mice (Shim et al. 2007).

Ginseng polysaccharides can improve immune function in nasopharyngeal carcinoma patients during radiotherapy (Xie et al. 2001). Red ginseng acidic polysaccharide enhances the antitumor effects of paclitaxel in mice transplanted with sarcoma 180 (S180) and B16 melanoma (Shin et al. 2004). In S180 tumor-bearing mice, intragastric administration with a neutral polysaccharide fraction (WGPN) from PG alone inhibits S180 tumor growth in a bell-shaped dose-response curve, and the combination with 5-fluorouracil (5-FU) shows a synergistic effect. In combination with 5-FU, WGPN mitigates 5-FU-induced damage to the immune system in S180-bearing mice (Ni et al. 2010).

Different ginseng polysaccharide fractions and their temperature-modified products have been compared for their antiproliferative effects on HT-29 human colon cancer cells, showing that the HG-rich pectin exerts its antiproliferative effect via cell cycle arrest and the temperature modification markedly increased the antiproliferative effect (Cheng et al. 2011). In contrast, ginseng polysaccharide was showed no direct effect on killing of tumor cells (K562, HL-60, and KGlalpha cells), but it can stimulate mouse peritoneal macrophage-mediated cytotoxic activity against these tumor cells (Wang et al. 2010c).

**ANTI-ULCER OR ANTI-ADHESIVE EFFECT**

The anti-ulcer effect of polysaccharides was reported by Cheng et al. (1985). The anti-ulcer and cytoprotective effects of pectic polysaccharide from PG root or leaves were reported by Yamada’s group (Sun et al. 1991, 1992a, 1992b; Kiyohara et al. 1994). Belogortseva et al. (2000) demonstrated the inhibiting effects of PG acidic polysaccharides on Helicobacter pylori-induced hemagglutination. Lee et al. (2004a, 2004b) showed that acidic polysaccharides (0.2-2.8 mg/ml) from PG inhibited Helicobacter pylori adhesion to human gastric epithelial cells and the ability of Porphyromonas gingivalis to agglutinate erythrocytes. Lee et al. (2006, 2009) again demonstrated that this pectin type acidic polysaccharides also inhibited the adhesion of Actinobacillus actinomycetemcomitans, Propionibacterium acnes and Staphylococcus aureus to host cells but had no effect against Lactobacillus acidophilus, Escherichia coli, or Staphylococcus epidermidis. However, complete hydrolysis of these acidic polysaccharides via chemical or carboxydiolase enzyme treatment caused complete loss of its anti-adhesive activity.

Two pectic polysaccharides, named as GP50-dHR (56.0 kDa) and GP50-eHR (77.0 kDa), from hot water extract of ginseng rescues cell viability from rovatirus infection (the leading cause of severe diarrhea) via inhibiting rovatirus attachment to cells (Baek et al. 2010).

**ANTI-DIABETIC AND ANTI-HYPERLIPIDEMIC EFFECTS**

Kimura et al. (1981) demonstrated in alloxan diabetic mice that hypoglycemic components must be existed in ginseng radix which is different from saponin. Then, Hikino and his colleagues (Konno et al. 1984; Tomoda et al. 1984; Konno et al. 1985; Osakima et al. 1985; Hikino et al. 1986; Oshima et al. 1987) isolated panaxans A, B, C, D, E, I, K, L, Q, R, S, T, and U from PG roots, eleutherans A, B, C, D, E, F, and G and from Eleutherococcus senticosus (Siberian ginseng) roots, and quinquelolans A, B, and C from PQ and demonstrated their hypoglycemic effect in alloxan-induced hyperglycemic mice. In diabetic ob/ob mice, the anti-hyperglycemic effect of intraperitoneal administration of polysaccharides from PQ berry has been reported by Xie et al. (2004). The hypoglycemic effects of ginseng polypeptide and glypeptide have been reported by Wang et al. (1990a, 1990b, 2003a, 2003b). However, Yang and Wang (1991) reported that ginseng polysaccharide GH1 can reduce liver glycogen and increase adenosine-3',5'-cyclic monophosphate (cAMP) level and adeny cyclase activity in mice.

In addition to the immunostimulatory and anti-tumor activities, red ginseng acidic polysaccharide also exhibits anti-hyperlipidemic effects in hyperlipidemic rats acutely induced by Triton WR1339 (an inducer of endogenous model hyperlipidemia) or corn oil (an inducer of exogenous model hyperlipidemia) intravenously injected (Kwak et al. 2010).

**OTHER PHARMACOLOGICAL EFFECTS**

The learning and memory enhancing effects, and anti-amnestic effects of Panax species and ginseng saponins have been reported and reviewed (Ellis and Reddy 2002; Cheng et al. 2005; Chen et al. 2008; Choi 2008; Jia and Zhao 2009; Jia et al. 2009). However, only Lyubimov et al. (1997) demonstrated that a polysaccharide fraction of PG enhances the learning and memory in rats by using an active escape response. Oral administration of the acidic polysaccharide portion of PG root (WGPA, 100 mg/kg once daily for 1 week) to mice had no effects on spontaneous activity or anxiety-like behavior in the elevated plus-maze test, but WGPA treatment exhibited antidepressant-like effects by showing reduced immobility time in the forced swim test (FST), increase in social interactions and decrease in aggressive behaviors (Wang et al. 2010a). Oral administration to mice once daily for 15 days of ginseng polysaccharides (WGPA), the neutral portion (WPON) or the acidic portion (WGPA) was found to have anti-fatigue activity in the FST and to inhibit the physiological markers for fatigue. The acidic polysaccharide is more potent than the neutral polysaccharide (Wang et al. 2010b). Using chronic hypoxia model, PG polysaccharide was demonstrated to have the pharmacological activities of antihypoxia, antioxidation and improving energy status (Li et al. 2009).

Treatment with ginsan (100 mg/kg, i.p.) in mice did not seem to cause hepatic injury, because serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) activities and levels of total bilirubin and albumin were not changed (Song et al. 2004).

**THE CULTIVATION OF GINSENG SPECIES**

The root of PG, PQ, and PN are the most commonly used herbal supplement medicine. The duration of the cultivation of ginseng species roots for the harvest are long, where sunproof sheds are necessary to block direct sunlight and there are so-called succession cropping obstacles (SCO). All increase the capital expenditure and worsen the quantity and quality of ginseng products. The soil environmental factors (air, moisture, nutrient and microorganisms), active substances (phytoxins, residue decomposition substances, microbial toxin), and pathogenic microbes on root exudates under continuous cropping of crops, vegetables, fruit trees
and nursery seedlings have been introduced (Gao and Zhang 1998; Wu and Zhao 2003; Zheng et al. 2005). Guan et al. (2006) stated the relationship between root rot in PG and soil microbes. Chun et al. (2009) isolated nine phenolic and five aliphatic autotoxic compounds from aqueous extracts of fibrous roots of PQ, and these compounds were also verified in the plow layer soil of commercially cultivated PQ fields. Therefore, SCO are caused by over cropping and agricultural chemical treatment, or the increase of harmful microorganisms, salt accumulation, soil acidification, and plant autotoxicity after long duration of cultivation (Liu et al. 2009). Jian et al. (2008) summarized the research progress of SCO on Panax species, and included the way to control SCO by soil sterilizing, decomposing allelopathy using available fungus, supply with fertilizer and rotating or intercropping. For the rotating or intercropping of ginseng species, it is necessary to find the new fields which further worsen the ecological environment.


For the more fundamental approach, the pathway for the biosynthesis of squalene was reported by Kuzuyama (2002). Jung et al. (2003) sequenced 11,636 expressed sequence tag (EST) of ginseng to find the genes for ginsenoside biosynthesis. The squalene synthase was cloned from PG (PgsS1) and the effect of methyl jasmonate (MeJA) treatment on PgsS1 was studied by Lee et al. (2004). Choi et al. (2005) identified 3,134 ESTs in MeJA-treated ginseng hairy roots. Han et al. (2006) characterized the gene encoding dammarenediol synthase in PG, while Tansakul identified 3,134 ESTs in MeJA-treated ginseng hairy roots. Asaka et al. (1993) characterized the dammarenediol synthase in PG, while Tansakul identified 3,134 ESTs in MeJA-treated ginseng hairy roots. Choi et al. (2009b) reported that upregulation of ginsenoside and gene expression in ginseng hairy root cultures is elicited by MeJA. Such genomic and proteomic approaches are valuable for the more successful bioengineering production of ginsenosides.

CONCLUSION AND SUGGESTION

Human complement system, PMN and PBMC are used by Zhu et al. (2006) to determine the complement-fixing activity, priming of ROS production, and mitogenic effect of phenol-acetic acid-water, hot water, weak and strong alkali soluble fractions of ginseng polysaccharides. They found that starch of PN did not show any significant biological activity, the weak alkali fraction was the most potent, but the other fractions of polysaccharides all showed immunomodulatory effects. The report of Zhu et al. (2006) let us consider whether it is necessary to purify the so-called bioactive component. The human GI tract, with pH values ranged from 2 in stomach to 8.6 in small intestine, are the good place to dissolve polysaccharides, of course the digestive enzymes and bacterial flora will enhance this digestive process. Thus, polysaccharides can be digested in human and their bioactivities should occur in body.

Thus, it is suggested that the future ways for the development of Panax species are:

1. Study the similarity and difference of bioactive components;
2. Learn how to well utilize the different parts of plants;
3. Improve the technique for the large quantity isolation of bioactive components;
4. Study the stability of active components (polysaccharides, peptides, glycoproteins);
5. Study the pharmacokinetics of active components;
6. Identify and characterize the genes and enzymes involved in the biosynthesis of active components; and
7. Develop cell, tissue cultures or bioengineering techniques instead of field cultivation.

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REFERENCES

Ahn JY, Song JY, Yun YS, Jeong G, Choi IS (2006b) Protection of Staphylococcus aureus-infected septic mice by suppression of early acute inflammation and enhanced antimicrobial activity by ginsan. FEMS Immunology and Medical Microbiology 46 (2), 187-197
Baek SH, Lee JG, Park SY, Bae ON, Kim DH, Park JH (2010) Pectic polysaccharides from Panax ginseng as the antirotavirus principals in ginseng. Biomacromolecules 11 (8), 2044-2052
Chun NH, Wei WG, Tia XY, Wu B, Xue SZ, Yang TS (2009) Identification of autotoxic compounds from fibrous roots of Panax quinquefolium L. Plant and Soil 318 (1-2), 63-72
Du XF, Jiang CZ, Wu CF, Won EK, Cheong SY (2008) Synergistic immunomodulatory effect of pidotimod and red ginseng acidic polysaccharide on humoral immunity of immunosuppressed mice. Die Pharmaz 63 (12), 904-908


Han SK, Song JY, Yun YS, Yi SY (2005) Ginsan improved Th1 immune response inhibited by gamma radiation. Archives of Pharmaceutical Research 28 (3), 343-348


Ivanova T, Han Y, Son HJ, Yun YS, Song JY (2006) Antimutagenic effect of polysaccharide ginsan from Panax ginseng. Food and Chemical Toxicology 44 (4), 517-521


Lee JH, Lee JS, Chung MS, Kim KH (2004a) In vitro anti-adhesive activity of acidic polysaccharide from Panax ginseng on Porphyromonas gingivalis binding to erythrocytes. Planta Medica 70 (6), 566-568

Lee JH, Park EK, Umh CS, Chung MS, Kim KH (2004b) Inhibition of Helicobacter pylori adhesion to human gastric adenocarcinoma epithelial cells by acidic polysaccharides from Artemisia capillaris and Panax ginseng. Planta Medica 70 (7), 615-619

Lee JH, Shim JS, Chung MS, Lim ST, Kim KH (2009) Inhibition of pathogen adhesion to host cells by polysaccharides from Panax ginseng. Biosci, Biotechnology, and Biochemistry 73 (1), 209-212


Lee YS, Chung IS, Lee IR, Kim KH, Hong WS, Yun YS (1997) Activation of multiple effector pathways of immune system by the antiinflammatory stimulatory acidic polysaccharide ginsan isolated from Panax ginseng. Anti-cancer Research 17 (1A), 323-331


Lim YJ, Na HS, Yun YS, Choi IS, Oh JS, Rhee JH, Cho BH, Lee HC (2009) Suppressive effects of ginseng on the development of allergic reaction in murine asthma model. International Archives of Allergy and Immunology 150 (1), 32-42


Oshima Y, Konno C, Hikino H (1985) Isolation and hypoglycemic activity of
Park E, Hwang I, Song JY, Jee Y (2011) Acidic polysaccharide of Panax ginseng as a defense against small intestinal damage by whole-body gamma irradiation of mice. Acta Histochemica 113 (1), 19-23
Smolina TP, Soloveva TF, Besednova NN (2001) Immunotropic activity of panaxan - bioglycans isolated from ginseng. Antibiotiki i Khimioterapiia 46 (7), 19-23
Song JY, Han SK, Bae KG, Lim DS, Son SJ, Jung IS, Yi SY, Yun YS (2003) Radioprotective effects of ginsan, an immunomodulator. Radiation Research 160 (3), 294-301
Song JY, Han SK, Son EH, Pyo SN, Yun YS, Yi SY (2002) Induction of secretory and tumorolytic activities in peritoneal macrophages by ginseng polysaccharide. International Immunopharmacology 3 (1), 485-532
Zheng SD, Yin XY, Wei Qi (2010) Immunopotentiator on murine spleen lymphocytes induced by polysaccharide fraction of Panax ginseng via upregulating calcineurin activity. AMPS 118 (4), 288-296
Pharmacology of ginseng polysaccharides. Liao Ya ku - gaku Zasshi 83, 298-300
Takahara N, Nagakawa I (1963b) Studies on oligosaccharides. VI. Ginseng trisaccharides. (2). Yakugaku Zasshi 83, 305-308
Takahara N, Nagakawa I (1963c) Studies on oligosaccharides. V. Ginseng trisaccharides. (1). Yakugaku Zasshi 83, 298-300