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Pharmacology of Polysaccharides from Ginseng Species

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ABSTRACT

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, polypeptides 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 antiadhesive, 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

CONTENTS

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 blood-vessels 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 (腎 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 ocotillol types. PQ

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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 polypeptides are also investigated by many 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 Dardymov 1969) and the effects of ginseng mentioned in the classic Chinese medicine. In this paper, the isolation, identification, and the pharmacology of polysaccharides will be reviewed, and the causes of succession cropping obstacle (SCO) and the future ways for ginseng research will also be discussed and suggested.

SEPARATION AND IDENTIFICATION OF GINSENG SACCHARIDES

The diversity of the molecular mass, acidic to alkali properties, composition of various sugars, the way of sugars linkage or chain formation, and biological activities remain saccharides as a mysterious area to be investigated.

Separation and identification of saccharides from *Panax* species and the study of their bioactivities have been reported. They include disaccharides, trisaccharides, oligosaccharides and polysaccharides (Takiura and Nakagawa 1963a, 1963b, 1963c). Li (1987) determined the content of polysaccharides in PG (Jilin red ginseng and Korean ginseng). Konno *et al.* (1984) 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-1 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 PQ 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 cetyltrimethyammonium bromide, respectively. Gao *et al.* (1990) again prepared two acidic heteroglycans (IA and IIA) from PG leaves, which are obtained by base-catalysed beta-elimination in the presence of sodium borodeuteride or enzymic digestion with endo-α-D-(1→4)-polygalacturonase, and beta-eliminative degradation. IA and IIA contain Rha··· Rha-ol-L-D, HexA···Rha-ol-L-D, and HexA···Rha···Rha-ol-L-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. Glycosyl linkage analysis demonstrated that GL-Nla mainly consisted of arabinogalactan moieties. Beta-elimination indicated that GL-Ala was pectic polysaccharides consisting of rhamnogalacturonan 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-ulcer pectic polysaccharide, GL-4IIIb1III, from the weakly acidic polysaccharide fraction GL-4 obtained from water-soluble crude polysaccharide (GL-2) of PG leaves. GL-4IIIb1III (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-ulcer polysaccharide (GL-BIII) from PG leaves. Methylation analysis indicated that GL-BIII 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 β-glucose-Yavir antigen indicated that GL-BIII contains a small proportion of β-(1→3,6)-galactan moiety. GL-BIII also contains terminal, 4-substituted, and 3,4-disubstituted Ga1A, and terminal and 4-substituted GlcA. Base-catalysed β-elimination suggested that some 2-substituted Rha in GL-BIII is attached to position 4 of a 4-substituted uronic acid. GL-BIII contains a GalA-(1→4) Rha unit in addition to longer acidic units consisting of 2-substituted Rha and 4-subsitituted GalA. Lithium-mediated degradation of GL-BIII followed by borohydride reduction gave small amounts of fractions containing long and intermediate neutral oligosaccharide-alditols and a large amount of a fraction containing short oligosaccharide-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-4IIb2) from PG leaves, which consists of 15 different monosaccharides with the characteristic of rhamnogalacturonan II (RG-II), and its molecular mass (11,000) are large than sycamore RG-II (5,000). It contains α-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 α-(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 rhamnoglacturonan 1 (1.2%) and homogalacturonan (24%), non-cellulosic polysaccharides (heteroxylan, 3%), xyloglucan (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-arabino-β-3,6-galactan type and rhamnogalacturonan type structural unit as analysis by reduction of carboxyl groups, methylation analysis, nuclear magnetic resonance and periodate oxidation. The molecular masses of PA and PB are 1.6×10^5 and 5.5×10^4 and composed of L-arabinose: D-galactose: L-rhamnose: D-galacturonic acid: D-glucuronic acid as 11: 22: 1: 6: 1 and 3: 7: 2: 8: 1, respectively. Tomada *et al.* (1993b) also isolated two other acidic polysaccharides, ginsenan S-IA and SIIA, from PG roots. Ginsenan S-IA (molecular mass 5.6×10^4) is composed of L-arabinose: D-galactose: D-galacturonic acid in the molar ratio of 8:8:1 and ginsenan S-IIA (molecular mass 1.0×10^5) is composed of L-arabinose: D-galactose: D-glucose: D-galacturonic acid as 15: 10: 2: 5. About a half (ginsenan S-IA) and about a quarter (ginsenan S-IIA) of the hexuronic acid residues exist as methyl esters. Their structural features include mainly α-1,5-linked L-arabino-β-3,6-branched D-galactan type structural units. Lee *et al.* (1997) purified an acidic polysaccharide, ginsan from an ethanol-insoluble fraction of PG with a molecular weight of 150,000 and devoid of lectin properties, which is demonstrated as an anti-neoplastic immunostimulator. Ginsan contains glucopyranoside and fructofuranoside. Zhu *et al.* (2006) prepared immunoactive polysaccharide-rich fraction 1MD3-G2, the fraction obtained from the strong alkali (1 M KOH) extract fraction of PQ high-molecular-weight polymers by anion-exchange

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 PG-F2, an acidic polysaccharide from PG, and showed its selective antiadhesive activity against pathogenic bacteria. PG-F2 is a pectin-type polysaccharide with mean MW1.2×10^4 Da and consists primarily of galacturonic and glucuronic acids along with rhamnose, arabinose, and galactose as minor components.

Wu and Wang (2008) purified an antiradical arabinoglucogalactan 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 arabinoglucogalactan possesses a backbone of (1→3)-linked β-d-galactofuranosyl residues, with branches of α-1-Ara f-(1→4)-β-d-Glc P-(-1→ residues at O-6).

Xu *et al.* (2008) reported the optimum 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 extraction temperature is at 50°C, solvent volume is 50 times of material, cellulose quality score is 1–2%, pectinex quality score is 1.0%, and the extraction time is 2 h. Under these conditions, the yield of polysaccharide extract from *P. japonicus* was up to 14.3%.

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

IMMUNO-MODIFIER AND ANTI-INFLAMMATORY EFFECTS OF GINSENG POLYSACCHARIDES

The anti-complementary 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 (Solo'vera *et al.* 1989). Then, anti-complementary or immunostimulating polysaccharides such as GL-PI, GL-PII, GL-PIV, 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 PBGA 12 have interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) inductive activities *in vitro* (Gao *et al*. 1996).

Lee *et al.* (1997) 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 C3H/HeN 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* cyclooxgenase (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-4IIb2, 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, termed PGP-SL, exhibits immunopotentiation effects on murine spleen lymphocytes by the Ca^{2+}-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 exudate 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 metabolism-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 macrophage function through nuclear factor-*kappa* B (NF-κB) pathway activation in murine melanoma B16 cells. The synergistic immunostimulatory effect of pidotimod, a biological immuno-regulatory modifier, and red ginseng acidic polysaccharide against cyclophosphamide-induced immunosuppression was also reported by Du *et al.* (2008).

Lim *et al.* (2002) reported that a PG polysaccharide possesses a potent anti-septicemic activity by stimulating macrophage and a potentiality as an immunomodulator against sepsis occurred by *Staphylococcus aureus*. And Song *et al.* (2002) reported that ginsan activated the peritoneal macrophage secretory and tumoricidal activities. Similarly, Ahn *et al*. (2006a) showed that ginsan protects mice from *S. aureus*-induced sepsis through the suppression of acute inflammatory responses at an early phase and the enhancement of antimicrobial activities at subsequent phases of infection. Furthermore, the antiseptic activity 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 mediated through enhancing the cycloxygenase expression and prostaglandin E_2 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 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, arabinoglucogalactan 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 alkali (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 (Zhu *et al.* 2005, 2006).

ANTICANCER EFFECTS

Ginsan exhibits significant *in vivo* antitumor activity against B16 melanoma cells and in the benzo(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 KG1alpha 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 adenocarcinoma 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 carbohydrolase 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 rotavirus infection (the leading cause of severe diarrhea) *via* inhibiting rotavirus 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; Oshima *et al.* 1985; Hikino *et al.* 1986; Oshima *et al.* 1987) isolated panaxans A, B, C, D, E, I, J, K, L, Q, R, S, T, and U from PG roots, eleutherans A, B, C, D, E, F, and G from *Eleutherococcus senticosus* (Siberian ginseng) roots, and quinquefolans 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 adenyl 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-ammestic 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 (WGP), the neutral portion (WGPN) 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 (SCOs). 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 (phytotoxin, 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 agrochemical 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.

Biotechnological approaches for the replace of field cultivation have been performed. Chang and Hsing (1980) cultured mature PG root callus in chemically defined medium, and these embryoids produce flowers and fertile pollen without establishing normal seeding. Yoshikawa and Furuya (1987) cultured hairy-root of PG. Yu *et al.* (2002) cultured adventitious root of PG and used jasmonic acid to improve gensenoside accumulation. Asaka *et al.* (1993) cultured embryogenic tissues of PG in bioreactors. Furuya and Ushiyama (1994) as well as Wu and Zhong (1999) cell cultured PG. Wang and Zhong (2002) cell cultured PN by addition of jasmonates. Choi *et al.* (2000) used bioreactor to culture adventitious root and Kim *et al.* (2004) studied the effect of methyl jasmonate on adventitious root growth and ginsenoside accumulation in PG cultures.

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 *et al.* (2006) characterized the dammarenediol-II synthase in PG. Kim *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 G-I 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 folia 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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