Review

DOI: 10.5582/ddt.2015.01004

Chemical constituents and bioactivities of *Panax ginseng* (C. A. Mey.)

Wenwen Ru[1,2], Dongliang Wang[1,2,*], Yunpeng Xu[1,2], Xianxian He[1,2], Yang-En Sun[1,2], Liyan Qian[1,2], Xiangshan Zhou[1,2], Yufeng Qin[2]

[1] *National Engineering Technology Research Center of Glue of Traditional Medicine, Dong'e, Shandong, China;*
[2] *Shandong Dong-E-E-Jiao Co., Ltd., Dong'e, Shandong, China.*

Summary **Ginseng, *Panax ginseng* (C. A. Mey.), is a well-known Chinese traditional medicine in the Far East and has gained popularity in the West during the last decade. There is extensive literature on the chemical constituents and bioactivities of ginseng. In this paper we compiled the chemical constituents isolated and detected from ginseng including polysaccharides, ginsenosides, peptides, polyacetylenic alcohols, fatty acids, *etc*. Meanwhile we summarized the biological activities of ginseng, which have been reported over the past few decades, including: anti-aging activity, anti-diabetic activity, immunoregulatory activity, anti-cancer activity, neuroregulation activity, wound and ulcer healing activity, *etc*. Nevertheless, further studies to exploit other kinds of constituents and new biological activities of ginseng are still necessary to facilitate research and development in the future.**

Keywords: *Panax ginseng* (C. A. Mey.), chemical constituents, biological activities

1. Introduction

Ginseng, the roots and rhizomes of *Panax ginseng* C. A. Mey. (Araliaceae), is widely distributed in northeast China, the Korean peninsula, and Russia. According to different processing technology, it is divided into three categories, including fresh ginseng, white ginseng, and red ginseng. Ginseng has always been a valuable and important folk medicine for more than 2000 years in the East Asian countries, such as China, Korea, and Japan. Recently, along with the popularization of traditional Chinese herbs as dietary supplement in Western countries, *Panax ginseng* has been used more and more in North America and Europe as well as other parts of the world. Until now, a large amount of literature has been reported on the chemical constituents and bioactivities of ginseng. As listed in the literature, active constituents found in ginseng mainly include polysaccharides, ginsenosides, peptides, polyacetylenic alcohols, fatty acids and so on. In addition, pharmacological effects of ginseng have been demonstrated in cancer, diabetes mellitus, cardiovascular system, immune system, central nervous system, and so on (*1-3*).

In this review, we compile the major active components isolated from the three main kinds of ginseng over the past few decades. The biological activities of the crude extract and its constituents are also discussed.

2. Chemical constituents

Several classes of compounds have been isolated from Ginseng, including polysaccharides, ginsenoside, peptides, and ligans, *etc*. Some of their names, **1-85**, are collected in Table 1, and some of their structures, **1-85**, are shown in Figure 1. As can be seen, ginsenosides are the predominant active constituents of ginseng.

2.1. *Polysaccharides*

Polysaccharides are the most abundant components of ginseng. It has been reported that the polysaccharide content in ginseng is nearly 40% (by weight). This class of compounds was first isolated and documented in 1966 (*4*). The more biologically active carbohydrates in ginseng are acidic polysaccharides, known as ginsan,

**Address correspondence to:*
Dr. Dongliang Wang, National Engineering Technology Research Center of Glue of Traditional Medicine, Shandong Dong-E-E-Jiao Co. Ltd, Dong'e 252201, Shandong, China.
E-mail: wangdljp@126.com

which have the typical structure of pectin (*5,6*). In 2012, several water-soluble ginseng oligosaccharides with a degree of polymerization ranging from 2 to 10 were obtained from a warm-water extract of ginseng roots, among them, α-Glcp-(1-6)-α-Glcp, α-Glcp-(1-6)-α-Glcp-(1-4)-α-Glcp, α-Glcp-(1-6)-α-Glcp-(1-6)-α-Glcp-(1-4)-α-Glcp, and another six malto-oligosaccharides (*i.e.*, maltopentaose, maltohexaose, maltoheptaose, maltooctaose, maltononaose, maltodecaose) were detected (*7*).

2.2. *Ginsenosides*

Ginsenosides, known as saponins, are considered to be the major bioactive constituents of ginseng. The first saponin isolated from ginseng could be traced back to

Table 1. Chemical constituents of *Panax ginseng* C. A. Mey.

No.	Name	R_1	R_2	Reference
Protopanaxadiol ginsenosides				
1	20*S*-ginsengoside Ra_1	-glc(2-1)glc	-glc(6-1) ara(p) (4-1) xyl	*11,12*
2	20*S*-ginsengoside Ra_2	-glc(2-1)glc	-glc(6-1) ara(f) (2-1) xyl	*11,12*
3	20*S*-ginsengoside Ra_3	-glc(2-1)glc	-glc(6-1) glc(3-1) xyl	*13*
4	20*S*-ginsengoside Ra_4	-glc(2-1)glc(6) Bu	-glc(6-1) ara(p) (4-1) xyl	*14*
5	20*S*-ginsengoside Ra_5	-glc(2-1)glc(6) Ac	-glc(6-1) ara(p) (4-1) xyl	*14*
6	20*S*-ginsengoside Ra_6	-glc(2-1)glc(6) Bu	-glc(6-1) glc	*14*
7	20*S*-ginsengoside Ra_7	-glc(2-1)glc(6) Bu	-glc(6-1) ara(p)	*14*
8	20*S*-ginsengoside Ra_8	-glc(2-1)glc(4) Bu	-glc(6-1) ara(f)	*14*
9	20*S*-ginsengoside Ra_9	-glc(2-1)glc(6)Bu	-glc(6-1) ara(f)	*14*
10	20*S*-ginsengoside Rb_1	-glc(2-1)glc	-glc(6-1) glc	*12,15,16*
11	20*S*-ginsengoside Rb_2	-glc(2-1)glc	-glc(6-1) ara(p)	*12,15,16*
12	20*S*-ginsengoside Rb_3	-glc(2-1)glc	-glc(6-1) xyl	*12,17*
13	20*S*-ginsengoside Rc	-glc(2-1)glc	-glc(6-1) ara(f)	*12,15,16*
14	20*S*-ginsengoside Rd	-glc(2-1)glc	-glc	*12,15,16*
15	20*S*-ginsengoside Rg_3	-glc(2-1)glc	-H	*12,16,18*
16	20*R*-ginsengoside Rg_3	-glc(2-1)glc	-H	*16*
17	20*R*-ginsengoside Rh_2	-glc	-H	*19*
18	20*S*-ginsengoside Rh_2	-glc	-H	*16*
19	20*S*-ginsengoside Rs_1	-glc(2-1)glc(6) Ac	-glc(6-1) ara(p)	*12,14*
20	20*S*-ginsengoside Rs_2	-glc(2-1)glc(6) Ac	-glc(6-1) ara(f)	*12,14*
21	20*S*-ginsengoside Rs_3	-glc(2-1)glc(6) Ac	-glc(6-1) ara(f)	*20*
22	malonyl-20*S*-ginsengosideRa_3	-glc(2-1)glc(6) mal	-glc(6-1) ara(3-1)xyl	*21*
23	malonyl-20*S*-ginsengosideRb_1	-glc(2-1)glc(6) mal	-glc(6-1) glc	*14,22*
24	malonyl-20*S*-ginsengosideRb_2	-glc(2-1)glc(6) mal	-glc(6-1) ara(p)	*22*
25	malonyl-20*S*-ginsengosideRc	-glc(2-1)glc(6) mal	-glc(6-1) ara(f)	*22*
26	malonyl-20*S*-ginsengosideRd	-glc(2-1)glc(6) mal	-glc	*22*
27	malonyl-20*S*-notoginsengosideR_4	-glc(2-1)glc(6) mal	-glc(6-1) glc(6-1) xyl	*23*
28	20*S*-gypenosideXVII	-glc	-glc(6-1) glc	*14*
29	20*S*-notoginsenoside-Fe	-glc	-glc(6-1) ara(f)	*24*
30	20*S*-notoginsenoside R_4	-glc(2-1)glc	-glc(6-1) glc(6-1) xyl	*13,25*
31	20*S*-pseudo-ginsenoside R_{C1}	-glc(2-1)glc(6) Ac	-glc	*14*
32	20*S*-quinquenoside R_1	-glc(2-1)glc(6) Ac	-glc(6-1) glc	*12,14*
33	20*S*-vinaginsenoside R_{16}	-glc(2-1)xyl	-glc	*14*
Protopanaxatriol ginsenosides				
34	20*S*-ginsenoside Re	-glc(2-1) rha	-glc	*12,16,26*
35	20*S*-ginsenoside Re_1	-glc	-glc(3-1) glc	*27*
36	20*S*-ginsenoside Re_2	-glc(3-1) glc	-glc	*27*
37	20*S*-ginsenoside Re_3	-glc	-glc(4-1) glc	*27*
38	20*S*-ginsenoside Re_4	-glc	-glc(6-1) ara(f)	*27*
39	20*S*-ginsenoside Re_6	-glc	-glc(6) Bu	*27*
40	20*S*-ginsenoside Rf	-glc(2-1) glc	-H	*12,16,26*
41	20*S*-ginsenoside Rg_1	-glc	-glc	*12,16,18,28*
42	20*S*-ginsenoside Rg_2	-glc(2-1) rha	-H	*12,16,26*
43	20*R*-ginsenoside Rg_2	-glc(2-1) rha	-H	*12,16,25*
44	20-gluco-20*S*-ginsenoside Rf	-glc(2-1) glc	-glc	*12,17*
45	20*S*-ginsenoside Rh_1	-glc	-H	*16,18*
46	20*R*-ginsenoside Rh_1	-glc	-H	*16*
47	20*S*-koryoginsenoside R_1	-glc(6-1) Bu	-glc	*18,24,27*
48	20*S*-notoginsenoside N	-glc(4-1) glc	-glc	*27*
49	20*S*-notoginsenoside R_1	-glc(2-1) xyl	-glc	*12,18,27*
50	20*S*-notoginsenoside R_2	-glc(2-1) xyl	-H	*25,27*
51	20*S*-yesanchinoside D	-glc(6)Ac	-glc	*27*

(to continue)

Table 1 (continued). Chemical constituents of *Panax ginseng* C. A. Mey.

No.	Name		R_1	R_2	Reference
Protopanaxadiol and Protopanaxatriol ginsenosides with modified side chain					
52	Ginsenjilinol	I-2-1	-glc(2-1) glc	-H	*24*
53	ginsenoside F_4	I-2-2	-glc(2-1) rha	-	*29,30*
54	ginsenoside Re_5	I-2-3	-glc(2-1) glc	-H	*27*
55	ginsenoside Rf_2	I-2-4	-glc(2-1) rha	-	*31*
56	ginsenoside Rg_5	I-1-1	-glc(2-1) glc	-	*30,32,33*
57	ginsenoside Rg_6	I-2-5	-glc(2-1) rha	-	*30,34*
58	ginsenoside Rh_4	I-2-6	-glc	-	*30,35,36*
59	ginsenoside Rk_1	I-1-2	-glc(2-1) glc	-H	*30,36*
60	ginsenoside Rk_2	I-1-3	-glc	-H	*36*
61	ginsenoside Rk_3	I-2-7	-H	-Oglc	*30,36*
62	ginsenoside Rs_4	I-1-4	-glc(2-1) glc(6)Ac	-	*30,37*
63	ginsenoside Rs_5	I-1-5	-glc(2-1) glc(6)Ac	-H	*30,37*
64	ginsenoside Rs_6	I-2-8	-glc(6)Ac	-	*37*
65	ginsenoside Rs_7	I-2-9	-H	-glc(6)Ac	*38*
66	koryoginsenosideR_2	I-1-6	-glc(2-1) glc	-glc(6-1)glc	*18*
Oleanane ginsenosides					
67	ginsenoside Ro	II-1	-glcUA(2-1)glc	-glc	*12,15*
68	ginsenoside Ri	II-1	-H	-ara(f)	*38*
69	ginsenoside Romethyl ester	II-1	-(6'-Me)glcUA(2-1)glc	-glc	*39*
70	polyacetyleneginsenoside-Ro	II-1	-(6'-PAE)glcUA(2-1)glc	-glc	*39*
Alkaloids					
71	N_9-formylharman				*40,41*
72	ethyl β-carboline				*40,41*
73	perlolyrine				*40, 41*
74	1-carbobutoxy-β-carboline				*42, 43*
75	1-carbomethoxy-β-carboline				*42, 43*
Glucosides					
76	isomaltol-α-D-glucopyranoside				*44, 45*
77	ketopropyl-α-D-glucopyranoside				*44, 45*
78	adenosine				*44, 45*
Phenolic acids					
79	maltol (3-hydroxy-2-methyl-4-pyrone)				*46*
80	salicylic acid				*47*
81	vanillic acid				*47*
82	*p*-hydroxycinnamic acid				*47*
Others					
83	thiazole				*43*
84	gomisin N				*48*
85	gomisin A				*48*

1854 (*3*). Later, the chemical structures of several ginseng saponins were characterized in the 1960s (*8*). Saponin components are a type of triterpenoidal dammarane glycosides, named ginsengosides Rx according to their mobility on TLC plates, with polarity decreasing from "a" to "h" (*9*). According to the positioning of sugar moieties at carbon -3 and -6, ginsenosides can be divided into protopanaxadiol type (protopanaxadiol type, I-1 type) and protopanaxatriol type (protopanaxatriol type, I-2 type); since the I-1 and I-2-type chiral carbon C-20 position substituted poor isobutyl, and is further divided into 20 (S) and 20 (R). To date, more than 70 ginsenosides, **1-70**, have been isolated from the three main kinds of ginseng, among them, ginsenosides Rb_1, Rb_2, Rc, Rd, Rgl, Rg_2, and Re are major constituents of white and red ginsengs, while ginsenosides Rg_3, Rg_5, and Rg_6 are known to be unique constituents of red ginseng (*10*). Names of the compounds and their corresponding reference are compiled in Table 1, and structures of **1-70** are shown in Figure 1.

2.3. *Alkaloids*

In 1986, three β-carboline alkaloids were isolated from the root of ginseng by Han *et al*. for the first time (*40,41*). In the following year, two other β-carboline alkaloids were reported by Jong *et al*. (*42,43*). Their structures, **71-75**, are shown in Figure 1.

2.4. *Glucosides*

Based on spectral and chemical evidence, three

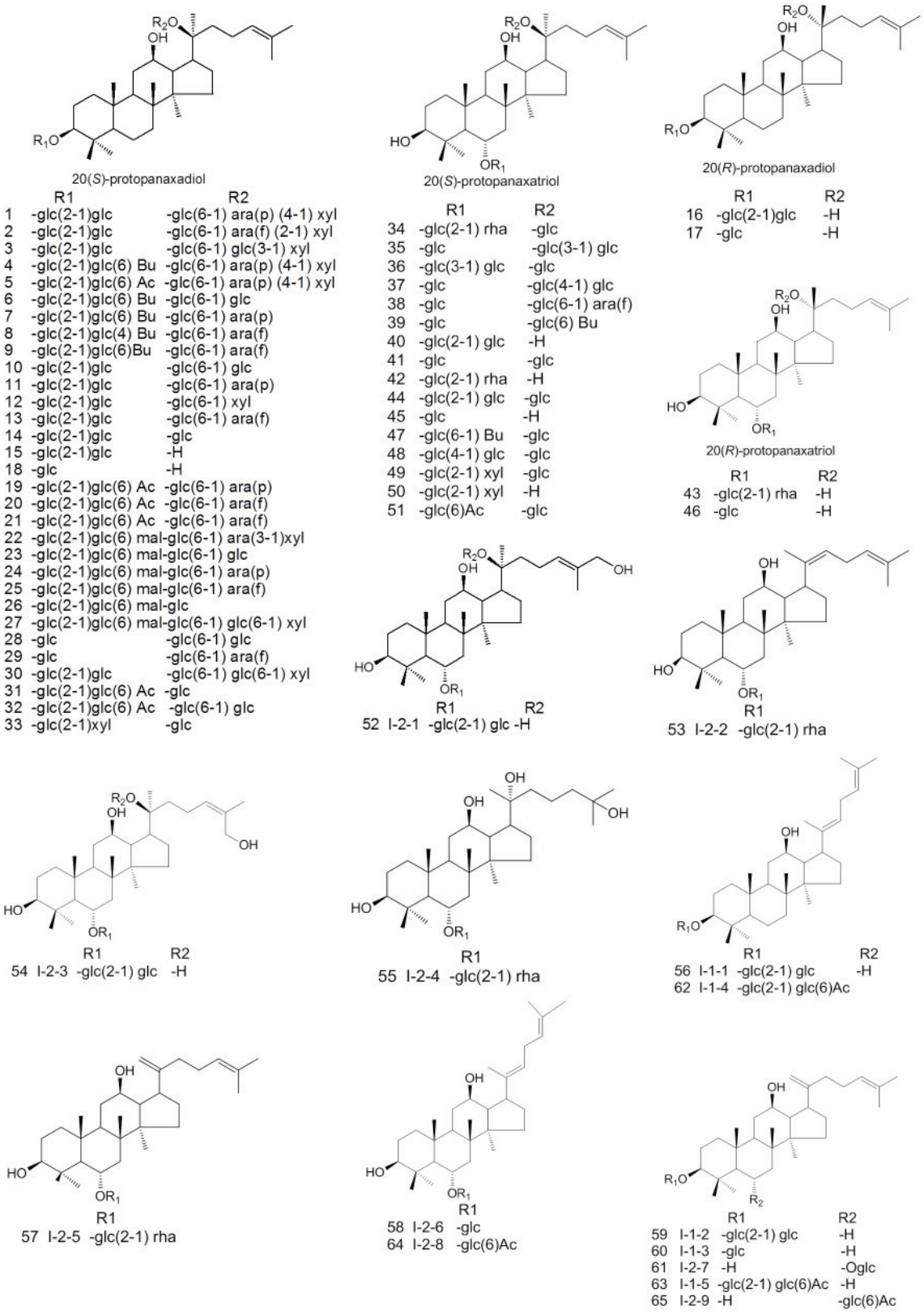

Figure 1. The structure of chemical constituents of Panax ginseng C. A. Mey. (to continue)

glycosides isolated from red ginseng were characterized as isomaltol-α-D-glucopyranoside (**76**), ketopropyl-α-D -glucopyranoside (**77**) and adenosine (**78**). However, these compounds are not found in white ginseng (*44,45*).

2.5. *Phenolic acid*

In 1979, maltol (3-hydroxy-2-methyl-4-pyrone) (**79**) was isolated from ginseng (*46*). In 1981, another three

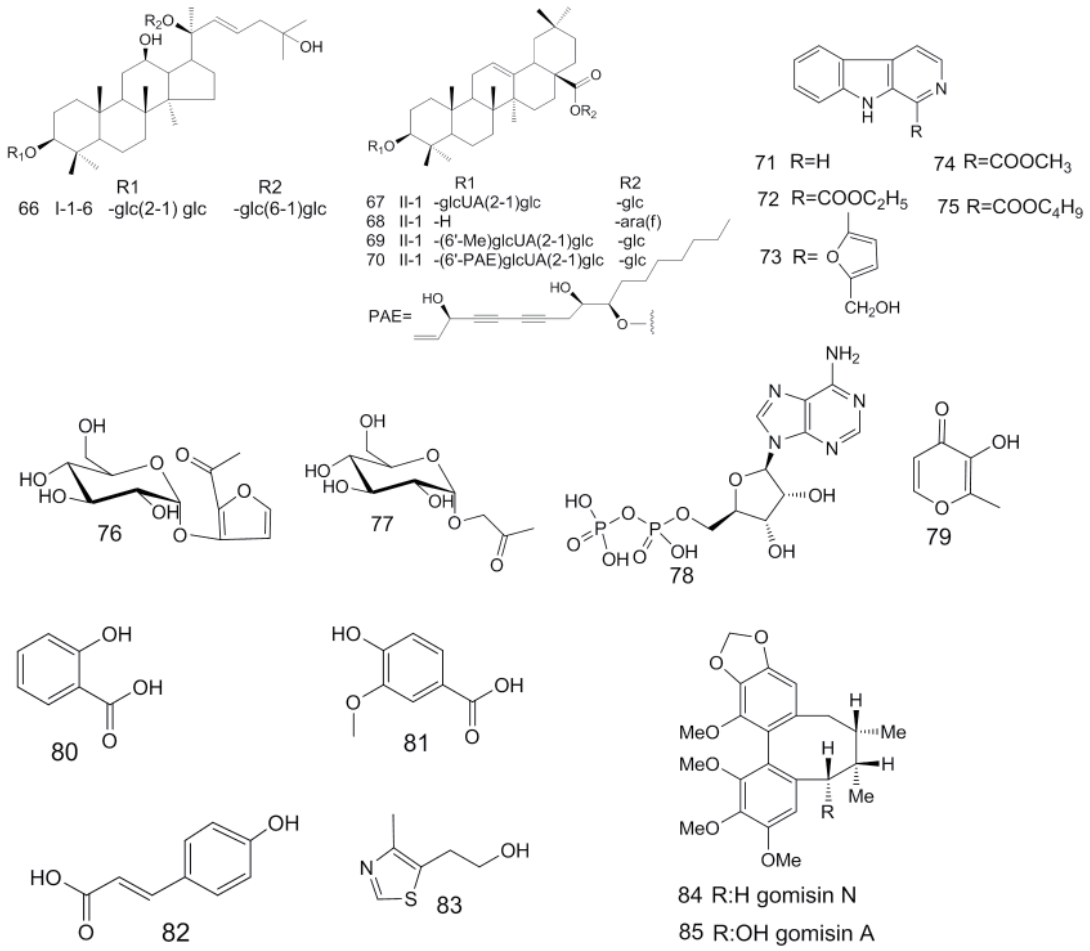

Figure 1 (continued). The structure of chemical constituents of Panax ginseng C. A. Mey.

phenolic acids were obtained from the ether-soluble acidic fraction of fresh ginseng, and they were identified by chemical and spectrometric methods to be salicylic acid (**80**), vanillic acid (**81**), and p-hydroxycinnamic acid (**82**) (*47*).

2.6. *Others*

Besides all the constituents listed above, in 1988, a thiazole (**83**) was isolated by Jong *et al*. (*43*). In 1990, two lingans were isolated from Korean red ginseng and their chemical structures were elucidated as gomisin N (**84**) and gomisin A (**85**) by spectrometric analysis (*48*).

3. Biological activities

3.1. *Anti-aging activity*

Ginseng, as a well-known traditional medicine and tonic, has been used for a panacea or promoting longevity. Abundant evidence suggested that oxidative stress plays a central role in the process of biological aging (*49*). Excessive oxidative stress leads to cell death and mitochondrial dysfunction (*50*). Some research indicated that ginseng extracts had been shown to improve learning and memory in normal, aged or brain-damaged animals (*51,52*). In 1981, Han *et al*. identified that salicylic acid (**80**) and vanillic acid (**81**) had potent antioxidant activity in the liver of ethanol-intoxicated mice, whereas p-hydroxycinnamic acid (**82**) did not have the effect (*47*). In 1991, Bernhard *et al*. reported that ginseng extract could enhance the age-dependency of learning ability in the passive avoidance test in female rats (*53*). In 1996, it was found that maltol (**79**) was an antioxidant with little prooxidant activity by comparing it with some antioxidant phenolic compounds (*54*). It has been reported that several ginsenosides have the function of ameliorating impaired memory function. For example, ginsenosides Rb_1 (**10**) and Rg_1 (**41**) have been shown to accelerate memory acquisition of rats on a Y-maze task and they also enhanced the cognitive function of mice in a Morris water maze (*55*). Yamaguchi *et al*. have also reported that Rg_1 (**41**) improved the scopolamine-induced impaired performance of rats in a radial-arm maze. Rb_1 (**10**) and its metabolite M_1 were reported to improve

memory disorders, axonal atrophy, and synaptic loss in a mouse model of Alzheimers disease (AD) that was induced by an *i.c.v*, injection of $A_{\beta(25-35)}$ (*56*). In 2005, Bao *et al*. indicated that ginsenosides Rg_3(S) (**15**) Rg_5 (**56**) and Rk_1 (**59**) significantly reversed the memory dysfunction induced by ethanol or scopolamine, and their neuroprotective actions against excitotoxicity may be attributed to their memory enhancing effects (*57*).

3.2. *Anti-diabetic activity*

In 1990, ginseng had been reported to improve glucose homeostasis and insulin sensitivity (*58*). In 2001, Chung *et al*. reported that oral administration of ginseng root to diabetic KKAy mice for 4 weeks reduced blood glucose levels similar to that of an insulin sensitizer (*59*). Rb_2 (**11**) was found to be the most effective component of ginsenosides for streptozatocin-diabetic rats (*60*). In 2004, it was reported that wild ginseng ethanol extract could prevent type 2 diabetes mellitus and possibly obesity in IRC mice through improving the insulin resistance index and decreasing white and brown adipocytes diameters (*61*). In 2011, Lee *et al*. reported that Rb_2 might inhibit palmitate-induced gluconeogenesis *via* AMP-activated protein kinase (AMPK)-induced small heterodimer partner (SHP) by relieving estrogen receptor (ER) stress (*62,63*).

3.3. *Immunoregulatory activity*

Ginseng has been used for more than 2000 years in oriental countries to enhance stamina and immune function. In 1994, the antigenicity of the aqueous extract of red ginseng (ARG) was evaluated in guinea pigs, the results suggested that ARG has no antigenicity but it was confirmed not to suppress immune reactions (*64*). Ginsan, a polysaccharide isolated from ginseng, had been shown to be a potent immunomodulator, producing several cytokines (tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-12 (IL-12), interferon-γ (IFN-γ), granulocyte-macrophage colony-stimulating factor (GM-CSF)) and stimulating lymphoid cells to proliferate (*65*). In 2004, the mechanism of the immunomodulator activity of ginsan was investigated, and the results showed that ginsan at a dose of 100 mg/kg could cause marked elevation (1.7-2 fold) of heme oxygenase (HO) activity, decrease total hepatic cytochrome P-450 (CYP450) levels (by 20-34%), and prolong zoxazolamine-induced paralysis time (by 65-70%), and did not seem to cause hepatic injury, since serum aspartate aminotransferase (AST), alanineaminotransferase (ALT), and alkaline phosphatase (ALP) activities and levels of total bilirubin and albumin were not changed (*66*). In 2005, ginsan was found to improve γ radiation-induced immunosuppression through inducing mRNA expression of Th1 and Th2 type cytokines, and restoring mRNA expression of INF-γ and Th1 cytokines (*67*). In 2008, it was reported that red ginseng acidic polysaccharide and pidotimod had synergistic immunostimulating activity against cyclophosphamide-induced immunosuppression through stimulating splenic T cell and B cell proliferation and increasing the nitric oxide from peritoneal macrophages and natural killer cell (NK cell) activity (*68*). In 2013, Wang *et al*. demonstrated that ginseng acidic polysaccharide had potential therapeutic effects for chronic fatigue syndrome by enhancing malondialdehyde and lactate dehydrogenase levels in serum and lowering superoxide dismutase and glutathione peroxidase in mice *in vivo* (*69*).

3.4. *Anti-cancer activity*

Ginseng has been shown to have powerful anticancer properties. Saponin and non-saponin compounds from ginseng roots were reported to show cytotoxic activities against various kinds of cancer cell lines in culture, such as L1210, L5187Y, Hela cells, Sarcoma 180 cells, A549, SK-OV-3, SK-Mel-2, P388, and K562 *et al*. (*70*). In 1991, Kikuchi *et al*. reported that ginsenoside Rh_2 (**17/18**) inhibited human ovarian cancer growth in a nude mice model (*71*). In 2002, Lee *et al*. reported that ginsenoside Rb_1 (**10**), Rc (**13**) and Re (**34**) could act as a weak phytoestrogen in MCF-7 human breast cancer cells by binding and activating the estrogen receptors at both the mRNA and protein levels (*72,73*). In 2004, it was found that ginsenoside Rg_3 (**15/16**) and Rh_2 (**17/18**)-induced cell detachment and inhibition of the proliferation of prostate cancer cells and might be associated with modulation of three modules of MAP kinases (extracellular signal-regulated kinase, *p38* mitogen-activated protein kinase, and c-Jun N-terminal kinase). Furthermore, the increase of LogP and decrease of C-6 steric hindrance, which were caused by deglycosylation by intestinal bacteria could increase anti-androgen-independent prostate cancer activity (*74,75*). In 2005, compound K, ginsenoside metabolite, was found to inhibit the growth of human monocytic leukemia cells U937 through up-regulating of *p21* and activating Jun N-terminal kinase in the G1 phase (*76*). Rg_3 (**15/16**) was discovered to inhibit tumor cell proliferation and induce cell apoptosis in mice with induced liver cancer (*77*). In 2009, Fishbein *et al*. suggested a potential for red ginseng as an adjuvant therapy in the treatment of colorectal cancer, *via* a synergistic action (*78*). In 2011, Rk_1 (**59**) was found to induce apoptosis in SK-MEL-2 human melanoma *in vitro* through up-regulation of Fas, FasL, and Bax protein expression and down-regulation of procaspase-8, procaspase-3, mutant *p53* and *bcl-2* protein expression (*79*).

3.5. *Neuroregulation activity*

In 1985, Kim *et al*. elucidated that supplement of the

saponin fraction of ginseng could increase the amount of norepinephrine and dopamine (DA) in mouse brain. In 1997, it was reported that ginseng total saponin (GTS) could modulate the methamphetamine-induced striatal dopaminergic neuronal systems by inhibiting methamphetamine-induced DA increase (*80*). In 1998, Kim *et al*. reported GTS can modulate dopaminergic activity at both presynaptic and postsynaptic dopamine receptors (*81*). Furthermore, it was found that GTS might be useful in the prevention and therapy of the behavioral side effects induced by psychotropic agents by attenuating the morphine-induced cAMP signaling pathway (*82*). In 2004, ginsenoside Rh_2 (**17**/**18**) and compound K were found to improve ischemic brain injury (*83*). In 2008, ginsenosides Rb_1 (**10**), Rb_2 (**11**), Rc (**13**), Rd (**14**), Re (**34**), Rf (**40**) and Rg_1 (**41**) were found to regulate nociceptive processing induced by pro-inflammatory cytokines (TNF-α, IL-1β, and IFN-γ) (*84*). In 2009, it was reported that red ginseng extract could modulate nerve growth factors (NGF) expression in the steroid-induced polycystic ovary (POC) rat model by decreasing ovarian concentrations of NGF protein and NGF mRNA (*85*).

3.6. *Lipid-regulating and antithrombotic activities*

It was found that ginseng saponin, one of major component of *Panax ginseng* had influence on lipid metabolism. Saponin stimulated the absorption, metabolism and transport of lipids (*86*). It had been also reported that ginseng saponin decreased plasma cholesterol and triglyceride levels and inhibited aortic atheroma formation in animals with hypercholesterolemia caused by long administration of high cholesterol or feeding on a diet containing high cholesterol (*86*). In 1984, it was reported that red ginseng saponin showed no significant change of high-density lipoproteincholesterol-cholesterol (HDL-cholesterol) level but it lowered plasma levels of total cholesterol and highly elevated those of triglyceride in Wistar male rats fed on a diet high in cholesterol and triglyceride (*86*). In 2006, it was identified that Rg_3 (**15**/**16**) might be effective in metabolic syndrome (MetSyn) by comparing the anti-MetSyn effect of vinegar-processed ginseng radix and non-processed ginseng radix in a high fat diet induced MetSyn ICR mouse model (*87*). In the same year, it was reported that red ginseng had a potent antithrombotic effect *in vivo*, which may be due to antiplatelet rather than anticoagulation activity, and its intake may be beneficial to individuals with high risk of thrombotic and cardiovascular diseases (*88*).

3.7. *Wound and ulcer healing activity*

In 2002, it was reported that ginsenoside Rb_2 (**11**) could enhance epidermal cell proliferation by upregulating the expression of proliferation- related factors (*89*). In 2006, Shin *et al*. reported that ginsenoside Rh_3 metabolized from ginsenoside R_5 (**56**) could improve chronic dermatitis or psoriasis by the regulation of IL-1β, TNF-α and IFN-γ produced by macrophage cells and Th cells (*90*). In 2003, Rb_1 (**10**) was found to exhibit an anti-ulcer effect through increasing mucus secretion (*91,92*).

3.8. *Other activities*

In 1986, Lee *et al*. reported that ginseng saponin could interact directly with Na^+-K^+-ATPase before disruption of membrane barriers of sarcolemmal vesicles, however, it decreased the number of phosphorylation sites (*93*). In 1996, it was reported that GTS could modulate various cellular activities by inhibiting gap junction channel reconstitution (*94*). In 2001, Ginseng saponin had been reported to induce IP_3-mediated Ca^{2+} release from ERs for the activation of Ca^{2+}-activated Cl- channel in *Xenopus* oocytes (*95,96*). Furthermore, it was found that CaM could modulate ginseng saponin-mediated Ca^{2+}-activated Cl^- channel activation (*97*). In 2003, Rc (**13**) was found to enhance I_{GABA} in oocytes expressing human $GABA_A$ receptor in *Xenopus* oocytes (*98*). In 2006, it was reported that tissue culture root of wild *Panax ginseng* had feasibility as a therapeutic agent for spermatogenic disorders (*99*).

4. Conclusions

Panax ginseng (C. A. Mey.) has been used as traditional Chinese medicine for more than two thousand years. More than a hundred compounds were isolated from the root of ginseng, and a majority of them were ginsenosides, which showed a broad range of biological activities. Nevertheless, further studies to exploit other kinds of constituents and new biological activities of ginseng are still necessary to facilitate research and development in the future.

Acknowledgements

The authors are grateful for financial support from National Engineering Technology Research Center of Glue of Traditional Medicine, Shandong Dong-E-E-Jiao Co. Ltd. and National "Major Drug Discovery" Science and Technology Major Project (Project No. 2011ZX09201-201-10).

References

1. Hu SY. The genus *Panax ginseng* in Chinese medicine. Economic Botany. 1976; 30:11-28.
2. Cao H, Bi PX, Hu XY. The ginseng plants: Commercial products and quality assessment. J Chin Integr Tradit Western Med. 1997; 4:25.
3. Park JD, Rhee DK, Lee YH. Biological activities and

chemistry of saponins from *Panax ginseng* CA Meyer. Phytochem Reviews. 2005; 4:159-175.
4. Ovodov YS, Solov'eva TF. Polysaccharides of *Panax ginseng*. Chem Natural Compounds. 1966; 2:243-245.
5. Tomoda M, Takeda K, Shimizu N, Gonda R, Ohara N, Takada K, Hirabayashi K. Characterization of two acidic polysaccharides having immunological activities from the root of *Panax ginseng*. Biol Pharm Bull. 1993; 16:22-25.
6. Baek SH, Lee JG, Park SY, Bae ON, Kim DH, Park JH. Pectic polysaccharides from *Panax ginseng* as the antirotavirus principals in ginseng. Biomacromolecules, 2010; 11:2044-2052.
7. Wan D, Jiao L, Yang H, Liu S. Structural characterization and immunological activities of the water-soluble oligosaccharides isolated from the *Panax ginseng* roots. Planta. 2012; 235:1289-1297.
8. Uvarova NI, Gorshkova RP, Strigina LI, Elyakov GB, Kochetkov NK. Glycosides from ginseng roots IV. Isolation of new glycosides from ginseng. Chem Natural Comp. 1965; 1:63-66.
9. Huang KC. The pharmacology of Chinese herbs. CRC press, 1998.
10. Ryu JH, Park JH, Eun JH, Jung JH, Sohn DH. A dammarane glycoside from Korean red ginseng. Phytochem. 1997; 44:931-933.
11. Besso H, Kasai R, Saruwatari Y, Ginsenoside-Ra1 and Ginsenoside-Ra2, new dammarane-saponins of ginseng roots. Chem Pharm Bull.1982; 30:2380-2385.
12. Kasai R, Besso H, Tanaka O, Fuwa T. Saponins of red ginseng. Chem Pharm Bull. 1983; 31:2120.
13. Matsuura H, Kasai R, Tanaka O, Saruwatari Y, Kunihiro K, Fuwa T. Further studies on dammarane-saponins of ginseng roots. Chem Pharm Bull. 1984; 32:1188-1192.
14. Zhu GY, Li YW, Hau DKP, Jiang ZH, Yu ZL, Fong WF. Protopanaxatriol-type ginsenosides from the root of *Panax ginseng*. J Agric Food Chem. 2010; 59:200-205.
15. Sanada S, Kondo N, Shoji J, Tanaka O, Shibata S. Studies on saponins of ginseng, strctures of ginsenoside-Re, ginsenoside-Rf and ginsenoside-Rg2. Chem Pharm Bull. 1974; 22:2407-2412.
16. Isao KM, Yoshiawa MY. Chemical studies on crude drug precession 1. On the constituents of ginseng radix rubra (1). Yakugaku Zasshi. 1983; 103:611-613.
17. Sanada S, Shoji J, Shibata S. Quantitative analysis of ginseng saponins. Chem Pharm Bull. 1978; 26:1694-1697.
18. Kim DS, Chang YJ, Zedk U, Zhao P, Liu Y Q, Yang CR. Dammarane saponins from *Panax ginseng*. Phytochemistry. 1995; 40:1493-1497.
19. Zhong FL, Liu JP, Lu D, Li YP. Studies on chemical consitituents of *Panax ginseng*. Chin Trad Med. 2008; 30:241-243.
20. Baek NI, Kim JM, Park JH, Ryu JH, Kim DS, Lee YH, Kim SI. Ginsenoside Rs3, a genuine dammarane-glycoside from Korean red ginseng. Arch Pharm Res. 1997; 20:280-282.
21. Ruan CC, Liu Z, Li X, Liu X, Wang LJ, Pan HY, Zhang LX. Isolation and characterization of a new ginsenoside from the fresh root of *Panax ginseng*. Molecules. 2010; 15:2319-2325.
22. Kitagawa I, Taniyama T, Hayashi T, Yoshikawa M. Malonyl-ginsenoside Rb1, Malonyl-ginsenoside Rb_2, Malonyl-ginsenoside Rc, and Malonyl-ginsenoside Rd 4 new malonylated dammarane-type triterpene oligoglycosides from ginseng radix. Chem Pharm Bull. 1983; 31:3353-3356.
23. Sun GZ, Li XG, Liu Z, Wang JY, Zheng YN, Yang XW. Isolation and structure characterization of malonyl-notoginsenoside-R4 from the root of *Panax ginseng*. Chem J Chin Univ. 2007; 28:1316.
24. Wang HP, Yang XB, Yang XW, Liu JX, Wang YP, Zhang LX. Chemical constituents from roots and rhizomes of *panax ginseng* cultivated in Jilin province. Chin J Chin Mater Med. 2013; 38:2807.
25. Dou DQ, Ren J, Chen Y, Pei YP, Chen YJ. Study on the chemical constituents of the roots of commercial ginseng. Chin J Chin Mater Med. 2003; 28:522-524.
26. Sanada S, Kondo N, Shoji J, Tanaka O, Shibata S. Studies on saponins of ginseng structures of ginsenoside-Re, ginsenoside-Rf and ginsenoside-Rg2. Chem Pharm Bull. 1974; 22:2407-2412.
27. Yu JL, Dou DQ, Chen XH, Yang HZ, Guo N, Cheng GF. Protopanaxatriol-type ginsenosides differentially modulate type 1 and type 2 cytokines production from murine splenocytes. Planta Medica, 2005; 71:202-207.
28. Nagai Y, Tanaka O, Shibata S. Chemical studies on the oriental plant drugs XXIV: Structure of ginsenoside-Rg_1, a neutral saponin of ginseng root. Tetrahedron. 1971; 27:881-892.
29. Ryu JH, Park JH, Kim TH, Sohn DH, Kim JM, Park JH. A genuine dammarane glycoside, (20E)-ginsenosideRf 4 from Korean red ginseng. Arch Pharm Res. 1996; 19:335-336.
30. Zhang YC, Pi ZF, Liu CM, Song FR, Liu ZQ, Liu SY. Analysis of low-polar ginsenosides in steamed *Panax ginseng* at high-temperature by HPLC-ESI-MS/MS. Chem Res Chin Univ. 2012; 8:31-36.
31. Park JD, Lee YH, Kim SI. Ginsenoside Rf2, a new dammarane glycoside from Korean red ginseng (*Panax ginseng*). Arch Pharm Res. 1998; 21:615-617.
32. Baek NI, Kim SI, Park JH. Ginsenoside Rg5, a genuine dammarane glycoside from Korean red ginseng. The Ginseng Review. 1996; 22:88-92.
33. Kim SI, Park JH, Ryu JH, Park JD, Lee YH, Park JH, Baek NI. Ginsenoside Rg5, a genuine dammarane glycoside from Korean red ginseng. Arch Pharm Res. 1996; 19:551-553.
34. Baek NI, Kim DS, Lee YH, Park JD, Lee CB, Kim SI. Ginsenoside Rh4, a genuine dammarane glycoside from Korean Red Ginseng. Planta medica. 1996; 62:86-87.
35. Baek NI, Kim DS, Lee YH, Park JD. Isolation of a novel dammarane-glycoside, ginsenoside Rh4, from Korean red ginseng. The Ginseng Review. 1995; 20:84-86.
36. Park IH, Kim NY, Han SB, Kim JM, Kwon SW, Kim HJ, Park JH. Three new dammarane glycosides from heat processed ginseng. Arch Pharm Res. 2002; 25:428-432.
37. Park IH, Han SB, Kim JM, Piao L, Kwon SW, Kim NY, Park JH. Four new acetylated ginsenosides from processed ginseng (sun ginseng). Arch Pharm Res. 2002; 25:837-841.
38. Fu L, Li XG, Yang SR. Isolated and identified of new gisenoside of oleanolic acid type from fresh *Panax ginseng* roots. J Jilin Agr Univ. 1998; 20:30-34.
39. Zhang H, Lu Z, Tan GT, Qiu S, Farnsworth NR, Pezzuto JM, Fong HH Polyacetyleneginsenoside-Ro, a novel triterpene saponin from *Panax ginseng*. Tetrahedron lett. 2002; 43:973-977.
40. Han BH, Park MH, Han YN, Woo LK. Alkaloidal components of *Panax ginseng*. Arch Pharm Res. 1986;

9:21-23.
41. Han YN, Ryu SY, Han BH, Woo LK. Spinacine from *Panax ginseng*. Arch Pharm Res. 1987; 10:258-259.
42. Park JD, Kim MW, Yoo SJ, Wee JJ. Chemical studies on the ether-soluble alkaloidal fraction of *Panax ginseng*. Isolation of 1-carbobutoxy-β-carboline and 1-carbomethoxy-β-carboline. Arch Pharm Res. 1987; 10:197-199.
43. Park JD, Kim MW, Yoo SJ, Wee JJ. A thiazole and two β-carboline constitutents from *Panax ginseng*. Arch Pharm Res. 1988; 11:52-55.
44. Matsuura H, Hirao Y, Yoshida S, Kunihiro K, Fuwa T, Kasai R, Tanaka O. Study of red ginseng: New glucosides and a note on the occurence of rnaltol. Chem Pharm Bull. 1984; 32:4674.
45. Han BH, Park MH, Han YN. Isolation of isomaltol-α-D-glucopyranoside and ketopropyl-α-D-glucopyranoside from Korean red ginseng. Arch Pharm Res. 1985; 8:257-260.
46. Han BH, Park MH, Woo LK, Woo WS, Han YN. Antioxidant components of Korean ginseng. Korean Biochem J. 1979; 12:33.
47. Han BH, Park MH, Han YN. Studies on the antioxidant components of Korean ginseng (III). Arch Pharm Res. 1981; 4:53-58.
48. Huh BH, Lee IR, Han BH. Lingans from Korean red ginseng. Arch Pharm Res. 1990; 13:278-281.
49. Muller FL, Lustgarten MS, Jang Y, Richardson A, Van Remmen H. Trends in oxidative aging theories. Free Radical Bio Med. 2007; 43:477-503.
50. Bolli R. Preconditioning: A paradigm shift in the biology of myocardial ischemia. Am J Physiol Heart Circ Physiol. 2007; 292:19-27.
51. Zhong YM, Nishijo H, Uwano T, Tamura R, Kawanishi K, Ono T. Red ginseng ameliorated place navigation deficits in young rats with hippocampal lesions and aged rats. Physiol Behav. 2000; 69:511-525.
52. Kennedy DO, Scholey AB. Ginseng: Potential for the enhancement of cognitive performance and mood. Pharmacol Biochem Behav. 2003; 75:687-700.
53. Jaenicke B, Kim EJ, Ahn JW, Lee HS. Effect of *Panax ginseng* extract on passive avoidance retention in old rats. Arch Pharm Res. 1991; 14:25-29.
54. Suh DY, Han YN, Han BH. Maltol, an antioxidant component of Korean red ginseng, shows little prooxidant activity. Arch Pharm Res. 1996; 19:112-115.
55. Mook JI, Hong HS, Boo JH, Lee KH, Yun SH, Cheong MY, Joo I, Huh K, Jung MW. Ginsenoside Rb1 and Rg_1 improve spatial learning and increase hippocampal synaptophysin level in mice. J Neurosci Res. 2001; 63:509-515.
56. Tohda C, Matsumoto N, Zou K, Meselhy MR, Komatsu K. β(25-35)-induced memory impairment, axonal atrophy, and synaptic loss are ameliorated by M1, A metabolite of protopanaxadiol-type saponins. Neuropsychopharmacology. 2004; 29:860-868.
57. Bao HY, Zhang J, Yeo SJ, Myung CS, Kim HM, Kim JM, Kang JS. Memory enhancing and neuroprotective effects of selected ginsenosides. Arch Pharm Res. 2005; 28:335-342.
58. Sonnenborn U, Proppert Y. Ginseng (*Panax ginseng* CA Meyer). Brit J Phytother. 1991; 2:3-14.
59. Chung SH, Choi CG, Park SH. Comparisons between white ginseng radix and rootlet for antidiabetic activity and mechanism in KKAy mice. Arch Pharm Res. 2001; 24:214-218.
60. Yokozawa T, Kobayashi T, Oura H, Kawashima Y. Hyperlipemia-improving effects of ginsenoside-Rb_2 in strepzotocin-diabetic rats. Chem Pharm Bull. 1985; 33:3893-3898.
61. Yun SN, Moon SJ, Ko SK, Im BO, Chung SH. Wild ginseng prevents the onset of high-fat diet induced hyperglycemia and obesity in ICR mice. Arch Pharm Res. 2004; 27:790-796.
62. Lee KT, Jung TW, Lee HJ, Kim SG, Shin YS, Whang WK. The antidiabetic effect of ginsenoside Rb_2 *via* activation of AMPK. Arch Pharm Res. 2011; 34:1201-1208.
63. Jung MS, Chung SH. AMP-activated protein kinase: A potential target for ginsenosides. Arch Pharm Res. 2011; 34:1037-1040.
64. Lee JW, Rhee MH, Park KH. Antigenicity studies of the aqueous extract of red ginseng in guinea pigs. Arch Pharm Res. 1994; 17:154-160.
65. Song JY, Han SK, Bae KG, Lim DS, Son SJ, Jung IS, Yi SY, Yun YS. Radioprotective effects of ginsan, an immunomodulator. Radiat Res. 2003; 159:768-774.
66. Song JY, Akhalaia M, Platonov A, Kim HD, Jung IS, Han YS, Yun YS. Effects of polysaccharide ginsan from *Panax ginseng* on liver function. Arch Pharm Res. 2004; 27:531-538.
67. Han SK, Song JY, Yun YS, Yi SY. Ginsan improved Th1 immune response inhibited by gamma radiation. Arch Pharm Res. 2005; 28:343-350.
68. Du XF, Jiang CZ, Wu CF, Won EK, Choung SY. Synergistic immunostimulating activity of pidotimod and red ginseng acidic polysaccharide against cyclophosphamide-induced immunosuppression. Arch Pharm Res. 2008; 31:1153-1159.
69. Wang J, Sun C, Zheng Y, Pan H, Zhou Y, Fan Y. The effective mechanism of the polysaccharides from *Panax ginseng* on chronic fatigue syndrome. Arch Pharm Res. 2014; 37:530-538.
70. Baek NI, Kim DS, Lee YH, Park JD, Lee CB, Kim SI. Cytotoxicities of ginseng saponins and their degradation products against some cancer cell lines. Arch Pharm Res. 1995; 18:164-168.
71. Kikuchi Y, Sasa H, Kita T, Hirata J, Tode T, Nagata I. Inhibition of human ovarian cancer cell proliferation *in vitro* by ginsenoside Rh_2 and adjuvant effects to cisplatin *in vivo*. Anti-cancer Drugs. 1991; 2:63-68.
72. Lee YJ, Jin YR, Lim WC, Park WK, Cho JY, Jang S, Lee SK. Ginsenoside-Rb1 acts as a weak phytoestrogen in MCF-7 human breast cancer cells. Arch Pharm Res.2003; 26:58-63.
73. Lee YJ, Jin YR, Lim WC, Ji SM, Cho JY, Ban JJ, Lee SK. Ginsenoside Rc and Re stimulate c-fos expression in MCF-7 human breast carcinoma cells. Arch Pharm Res. 2003; 26:53-57.
74. Kim HS, Lee EH, Ko SR, Choi KJ, Park JH, Im DS. Effects of ginsenosides Rg_3 and Rh_2 on the proliferation of prostate cancer cells. Arch Pharm Res. 2004; 27:429-435.
75. Li W, Liu Y, Zhang JW, Ai CZ, Xiang N, Liu HX, Yang L. Anti-androgen-independent prostate cancer effects of ginsenoside metabolites *in vitro*: Mechanism and possible structure-activity relationship investigation. Arch Pharm Res. 2009; 32:49-57.
76. Kang KA, Kim YW, Kim SU, Chae S, Koh YS, Kim HS, Hyun JW. G1 phase arrest of the cell cycle by a ginseng

metabolite, compound K, in U937 human monocytic leukemia cells. Arch Pharm Res. 2005; 28:685-690.
77. Li X, Guan YS, Zhou XP, Sun L, Liu Y, He Q, Mao YQ. Anticarcinogenic effect of 20 (R)-ginsenoside Rg3 on induced hepatocellular carcinoma in rats. J Sichuan Univ (Med Sci Edi). 2005; 36:217-220.
78. Fishbein AB, Wang CZ, Li XL, Mehendale SR, Sun S, Aung HH, Yuan CS. Asian ginseng enhances the anti-proliferative effect of 5-fluorouracil on human colorectal cancer: Comparison between white and red ginseng. Arch Pharm Res. 2009; 32:505-513.
79. Kim JS, Joo EJ, Chun J, Ha YW, Lee JH, Han Y, Kim YS. Induction of apoptosis by ginsenoside Rk1 in SK-MEL-2-human melanoma. Arch Pharm Res. 2012; 35:717-722.
80. Oh KW, Kim HS, Wagner GC. Inhibitory effects of ginseng total saponin on methamphetamine-induced striatal dopamine increase in mice. Arch Pharm Res. 1997; 20:516-518.
81. Kim HS, Zhang YH, Fang LH, Lee MK. Effect of ginseng total saponin on bovine adrenal tyrosine hydroxylase. Arch Pharm Res. 1998; 21:782-784.
82. Kim HC, Shin EJ, Jang CG, Lee MK, Eun JS, Hong JT, Oh KW. Pharmacological action of *Panax Ginseng* on the behavioral toxicities induced by psychotropic agents. Arch Pharm Res. 2005; 28:995-1001.
83. Bae EA, Hyun YJ, Choo MK, Oh JK, Ryu JH, Kim DH. Protective effect of fermented red ginseng on transient focal ischemic rats. Arch Pharm Res. 2004; 27:1136-1140.
84. Seo YJ, Kwon MS, Choi HW, Jang JE, Lee JK, Sun Y, Suh HW. Intracerebroventricular gisenosides are antinociceptive in proinflammatory cytokine-induced pain behaviors of mice. Arch Pharm Res. 2008; 31:364-369.
85. Pak SC, Kim SE, Oh DM, Shim KM, Jeong MJ, Lim SC, Bae CS. Effect of Korean red ginseng extract in a steroid-induced polycystic ovary murine model. Arch Pharm Res. 2009; 32:347-352.
86. Moon CK, Kang NY, Yun YP, Lee SH, Lee HA, Kang TL. Effects of red ginseng-crude saponin on plasma lipid levels in rats fed on a diet high in cholesterol and triglyceride. Arch Pharm Res. 1984; 7:41-45.
87. Yun SN, Ko SK, Lee KH, Chung SH. Vinegar-processed ginseng radix improves metabolic syndrome induced by a high fat diet in ICR mice. Arch Pharm Res. 2007; 30:587-595.
88. Yu JY, Jin YR, Lee JJ, Chung JH, Noh JY, You SH, Yun YP. Antiplatelet and antithrombotic activities of Korean Red Ginseng. Arch. Pharm. Res. 2006; 29:898-903.
89. Choi S. Epidermis proliferative effect of the *Panax ginseng* Ginsenoside Rb_2. Arch Pharm Res. 2002; 25:71-76.
90. Shin YW, Bae EA, Kim DH. Inhibitory effect of ginsenoside Rg5 and its metabolite ginsenoside Rh3 in an oxazolone-induced mouse chronic dermatitis model. Arch Pharm Res. 2006; 29:685-690.
91. Jeong CS. Effect of butanol fraction of *Panax ginseng* head on gastric lesion and ulcer. Arch Pharm Res. 2002; 25:61-66.
92. Jeong CS, Hyun JE, Kim YS, Lee ES. Ginsenoside Rb1 the anti-ulcer constituent from the head of *Panax ginseng*. Arch Pharm Res. 2003; 26:906-911.
93. Lee SW, Lee JS, Kim YH, Jin KD. Effect of ginseng saponin on the Na^+, K^+-ATPase of dog cardiac sarcolemma. Arch Pharm Res. 1986; 9:29-38.
94. Hong EJ, Huh K, Rhee SK. Effect of ginseng saponin on gap junction channel reconstituted with connexin 32. Arch Pharm Res. 1996; 19:264-268.
95. Choi S, Rho SH, Jung SY, Kim SC, Park CS, Nah SY. A novel activation of Ca^{2+}-activated Cl^- channel in Xenopus oocytes by ginseng saponins: Evidence for the involvement of phospholipase C and intracellular Ca^{2+} mobilization. Br J Pharmacol. 2001; 132:641-648.
96. Choi S, Kim HJ, Ko YS, Jeong SW, Kim YI, Simonds WF, Nah SY. Gαq/11 coupled to mammalian phospholipase C β3-like enzyme mediates the ginsenoside effect on Ca^{2+}-activated Cl^- current in the Xenopus oocyte. J Biol Chem. 2001; 276:48797-48802.
97. Lee JH, Jeong SM, Lee BH, Kim JH, Ko SR, Kim SH, Nah SY. Effect of calmodulin on ginseng saponin-induced Ca^{2+}-Activated CI-channel activation in Xenopus laevis oocytes. Arch Pharm Res. 2005; 28:413-420.
98. Choi SE, Choi S, Lee JH, Whiting PJ, Lee SM, Nah SY. Effects of ginsenosides on GABAA receptor channels expressed in Xenopus oocytes. Arch Pharm Res. 2003; 26:28-33.
99. Park JS, Hwang SY, Lee WS, Yu KW, Paek KY, Hwang BY, Han K. The therapeutic effect of tissue cultured root of wild *Panax ginseng* CA Mayer on spermatogenetic disorder. Arch Pharm Res. 2006; 29:800-807.

(Received January 23, 2015; Revised February 3, 2015; Accepted February 10, 2015)