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인삼과 진세노사이드의 항비만 효과에 대한 문헌 고찰

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Anti-Obese Effects of Ginseng/Ginsenosides : A Literature Review from 1983 to 2012

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Abstracts

Compared to the large numbers of studies on the diabetes, hyperlipidemia and cancer therpeutic effects of ginseng, the anti-obese effect and mechanisms of ginsengs have not been studied as much. To determine the effects of ginseng on obesity, 14 keywords (ginseng, ginsenoside, obesity, weight, fat, diet, overeat, appetite, lipid, 3T3-L1, adipocyte, food intake, adipogenesis and lipolysis) were combined in searching a database. Fifty-six articles published from 1983 to 2012 as well as 656 patents registered until Aug 17th, 2012, were screened for anti-obese effects of ginseng. In the classification of experimental methods, 16 papers on 3T3-L1 cells, 38 papers on animals and three papers on human were reviewed. In terms of obese mechanisms of action, the most commonly used biomarkers were in order of lipid profiles > weight change > blood glucose > adipocytokine. Most ginseng studies on obesity focused on AMPK, PPARγ, GLUT-4, PI3K and SREBP-1. Korean white ginseng extracts and Re repressed the lipogenesis genes such as PPARc2, SREBP-1c, LPL, FAS and DGAT1. However, ginseng or ginsenosides, PD (Rb1) and PT (Re), showed different or contradictory results. Water and ethanol extraction of ginseng showed contradictory effects on the secretion of inflammatory cytokines, wheras IL-6 was repressed by ethanol extracts and TNF-α repressed by Re *in vitro*. Based on the literature, further studies on anti-obese mechanisms of ginseng, such as the inflammation-related obesity or cross signals between the adipocytes and the environments, are needed, instead of more studies on its hypolipidemic and hypoglycemic effects.

Key words : Ginseng, ginsenosides, obesity, lipolysis, inflammation

INTRODUCTION

According to the 2010 National Health and Nutrition Examination Survey on the Korean adults, the ratios of adults with BMI greater than 25 were 31.7% in 2007, 30.7% in 2008 and increased to 31.3% in 2009. (KNHANES IV 2010) Obesity is often generated by excessive fat accumulation, glucose tolerance impairment, and high blood triglyceride levels. Obesity predisposes one to development of type 2 diabetes mellitus and cardiovascular disease, and has also been considered a low-grade inflammatory disease (Laclaustra *et al* 2007, Mehta & Farmer 2007). Importantly, it has been well established that a reduction in body weight in the range of 5% to 10% can significantly slow the progression of these conditions (Pi-Sunyer FX 1996). Therefore, strategies to decrease weight by pharmacologic or nutritional supplementation represent a very attractive approach. Obesity is caused by increased adipose tissue mass, which results from the multiplication of fat cells through adipogenesis and/or from increased deposition of cytoplasmic.

Recent ginseng studies have primarily focused on the inhibition of diabetic- and metabolic disorder effects (Xie *et al* 2005a). Active substances present in ginseng have been verified through several studies, which are ginseng saponin (ginsenoside), polysaccharide, peptides, fatty acids and polyacetylenic alcohols (Attle *et al* 1999, Leung & Wong 2010). The most physiologically active ginseng saponin is known to be beneficial in anti-inflammatory, anti-oxidant and anti-cancer effects (Cho *et al* 2006, Lee *et al* 2005, Park *et al* 2009). However, it was difficult to figure out the anti-obese effect of ginseng because

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the inhibition and increase of adipogenesis vary depending on the types and doses of drugs used in treatment (Huang *et al* 2010, Park *et al* 2008b, Shang *et al* 2007). Moreover, studies on the increase of lipid synthesis have focused that obesity effect is enhanced by increasing insulin sensitivity. On 2013, the Korea Food and Drug Administration (KFDA) approved only 13 natural materials which help to reduce the body fat mass (Rao & Sakariah 1988, Rahman *et al* 2001, Maki *et al* 2002, Kim *et al* 2003, Sanders *et al* 2004, Henderson *et al* 2005, Nagao *et al* 2005, Lee *et al* 2008, De Morais *et al* 2009, Kim & Kim 2009, Maki *et al* 2009, Gwak JH 2010, Galloway *et al* 2011). Verified active materials of anti- obesity products such as Garcinia cambogia, Hibiscus, Green Mate and others are mostly imported abroad and the majority of raw materials including green tea extracts have been analyzed internationally. It is time to develop new biocompounds with domestic technology using good sources like ginseng, which is the Korean agricultural product that needs to be further investigated as anti-obesity material. This review aims to identify study subjects and evaluation criteria of studies per- formed to reduce or prevent recently surging obese population mainly based on published research papers in the international journals. The results on anti-obesity effects of ginseng were classified by treated subjects such as cells, animals and clinical trials and by their mechanisms according to different types of ginseng or ginsenosides.

SUBJECTS OF RESEARCH PAPERS AND PATENTS

1. Subjects of Research Papers

This study searched articles related with the anti-obesity effects of ginseng and published from Jan 1983 to Jun 2012 using search engines, PubMED and Web of Science. We searched papers by combining 14 keywords related with ginseng (ginseng and ginsenoside) and obesity (obesity, weight, fat, diet, overeat, appetite, lipid, 3T3-L1, adipocyte, food intake, adipose and lipolysis). Excluding papers unrelated with the anti-obese mechanisms of ginseng, closed contents and presented results in academic conferences, 56 papers were reviewed.We rearranged papers according to the types of ginseng and presented as percentage of all papers with frequency analysis.

An increasing number of ginseng studies have mainly been reported in recent three yr since the 2000's when the prevalence of obesity has increased. As the seriousness of obesity has drawn attention, studies on food preventing and treating obesity have surged, including studies on the target materials of ginseng in spite of few. Without black ginseng study, there are 21 studies on white ginseng, 8 studies on red ginseng, and 30 studies on the anti-obesity of ginsenoside. Among papers on ginseng, there were studies performed using fruits or leaves, fermented vinegar of ginseng, and pectinase treated ginseng. Specific ginsenoside of Rg_3 contained in red ginseng is known to be present five times higher in black ginseng (Kim & Kang 2009) and its function including anti-cancer, anti-diabetes, anti-oxidant activities has been acknowledged (Shinkai *et al* 1996, Hwang *et al* 2009, Kang *et al* 2007). However, no studies have investigated the anti-obesity of black ginseng. Ginsenosides are classified into protopanaxadiol type (PD; Rb_1, Rb_2, Rc, Rd, Rg_3 and Rh2), protopanaxatriol type (PT; Re, Rg_1, Rg_2 and Rh_1) and oleanane. Among 30 studies on the anti-obesity effects of ginsenosides, 15 papers used PD type in particular to Rb1, 9 papers used PT type with four Re, 4 studies used compound K, and the others were about saponin. Table 1 shows the biomarkers or mechanisms manifesting the anti-obesity effects of ginseng reported in the searched papers. The most used biomarker in obese researches is lipid profile, followed by weight change, blood glucose, and adipocytokine in cell and animal experiments. The most frequently used mechanism is peroxisome proliferator activated receptor (PPAR γ), followed by glucose transporter type 4 (GLUT-4) and AMP-activated protein kinase (AMPK).

2. Subjects of Patents

We reviewed 656 patents registered until Aug 17th, 2012 in patent search engine (Kipris) and released by the Patent Korea Institute of Patent Information. 448 patents (68.3%) were related with 3T3-L1, accounting for the largest portion of all patents, and 49 patents (7.5%) were related with weight (Table 2). When we searched for patents by combining two keywords such as obesity and ginseng, only 12 patents were found inclu- ding three patents of red ginseng. Six patents were about ginseng extracts and two patents were about the extracts of leaves and fruits. A patent was related with ginsenoside Rg and compound K and the other patent was about mixed composition of different substances. A patent was about fermented red ginseng inhibiting fat cell differentiation and plasma phospholipid level, and the other two patents were about mixed composition.

Table 1. Targeting biomarkers & mechanisms approached by ginseng on anti-obesity effects

	Result	Gingseng case (n=21)	Red gingseng case (n=8)	Ginsenoside case (n=30)	Total Case (n=59)(%)	
Targeting	Lipid profile	11	8	16	35	23.3
	Body weight change	13	7	12	32	21.3
	Blood glucose	12	6	7	25	16.7
	Adipocytokine	6	3	4	13	8.7
	Adipose tissue H&E or Oil Red O	6	1	5	12	8.0
	Adipose tissue weight	2	4	5	11	7.3
	Lipolysis or LPL	2	3	6	11	7.3
	Glucose uptake	-	-	6	6	4.0
	Pro-inflammatory cytokine	1	-	1	2	1.3
	Anti-oxidant enzyme	2	-	-	2	1.3
	FA oxidation	-	1	-	1	0.7
	Sum	55	33	62	150	100
Mechanism approach	PPARγ	4	1	8	13	17.8
	GLUT-4	5	-	7	12	16.4
	AMPK	5	-	6	11	15.1
	FAS	2	1	4	7	9.6
	SREBP1	3	1	1	5	6.9
	PPARα	2	2	-	4	5.5
	HOMA-IR	3	-	1	4	5.5
	PI3K	-	-	4	4	5.5
	cell cycle	4	-	-	4	5.5
	C/EBPα	1	-	3	4	5.5
	AP2	-	-	3	3	4.1
	HMG-coA	1	-	1	2	2.7
	Sum	30	5	38	73	100

IN VITRO STUDIES OF GINSENG ON ANTIOBESITY

Collected research papers have been classified according to experimental subjects, and 38 papers (66.7%) were animal experiment, 16 papers (28.1%) were cell experiment, and 3 papers (5.3%) were clinical trials. All 16 papers on cell experiments were performed using 3T3-L1 cells (Table 3). When the papers were reviewed by treated substances, 12 studies verified the effect of ginsenoside, accounting for the largest portion, and the rest were conducted by treating ginseng extracts. Studies on ginsenoside treatment more investigated PD compare to PT ginsenosides. According to the classification by mechanism, studies on PPARγ have been most commonly performed, followed by studies on GLUT-4, phosphatidylinositol 3-kinase (PI3K) and AMPK.

1. Peroxisome Proliferator Activated Receptor (PPARγ)

PPARγ is required for adipocyte differentiation, an adipogenesis marker, but is also expressed in other cell types, notably macrophages, where it influences atherosclerosis, insulin resistance and inflammation. Thus, the cell-specificity of PPARγ function is regulated by cell-specific transcription factors and PPARγ regulation is also depending on the treated substances. Both the mRNA and protein levels of PPARγ repressed when 250, 500 and 1,000 μg/ml of segment lyophilized *Panax ginseng* were treated 3T3-L1 adipocyte (Mollah *et al* 2011). The treatment of 20 μM Rb_1 reduced PPARγ mRNA along with CCAAT-enhancer-binding protein α (C/EBPα) and adipocyte protein (aP2). When 20 and 40 μM of Rh_2 were treated,

Table 2. Patents registered by patent Korea Institute for anti-obesity effect of ginseng

Result	Ginseng	Ginsenoside	Total	(%)
Obesity*	12	5	17	2.6
Weight	33	16	49	7.5
Fat	23	7	30	4.6
Diet	30	9	39	5.9
Overeat	0	0	0	0
Appetit	0	0	0	0
Lipid	33	11	44	6.7
3T3-L1	321	127	448	68.3
Adipocyte	8	9	17	2.6
Food intake	3	0	3	0.5
Adipose	4	3	7	1.1
Lipolysis	1	1	2	0.3
Total	468	188	656	100

* Compositions for preventing or treating obesity; 10-2008-0099362.
1. Polysaccharides of plants belonging to Panax having effect on treatment and prevention of obesity; 10-2005-0041802.
2. Extract of antiobestic ginseng with anti-obesity effect comprising high concentration of less polar ginsenoside and method of preparing the same; 10-091934.
3. Novel polyacetylene group compound from ginseng, process for extraction there of and anti-obesity agent including thereof; 10-2003-0011474.
4. Composition for inhibiting obesity comprising ginseng extract by supercritical carbon dioxide extraction;10-2011-0108820.
5. Preventing and treating composition for obesity comprising the extracts of fermented red ginseng; 10-2012-0076331.
6. Ginseng leaf extract for inhibiting obesity and improving hyperlipidemia; 10-2011-0051105.
7. Food composition containing ginseng fruit extract for preventing and improving obesity; 10-2008-0105470.
8. Compositions for preventing or treating obesity; 10-2007-0042755.
9. Composition for prevention or treatment of diabete or obesity comprising punicagranatum extract and red ginseng extract; 10-1144059.
10. Compositions for preventing or treating obesity; 10-2009-0108230.
11. Red ginseng mixture composition having anti-obesity activity; 10-0815200.

mRNA and transcriptional activity of PPARγ were verified to decrease and 5 μM compound K reduced PPARγ mRNA by 41% (Park & Yoon 2012, Hwang *et al* 2007). Unlike the research papers on the PPARγ repression, the treatment of 10 μM Rb1 increased the level of PPARγ2 mRNA by 4.5 times, as well as the level of protein (Shang *et al* 2007, Han *et al* 2006). According to Han's study, the treatment of 10 μM PT ginsenoside increased transcriptional activity and target genes of PPARγ, by 7.7 times in aP2, 8.9 times in LPL, and 3.9 times in phosphoenol pyruvate carboxykinase (PEPCK). In addition, the investigation identified an increase of GLUT-4 expression that reportedly decreases insulin resistance as PT works as PPARγ agonist (Han *et al* 2006).

2. Glucose Transporter Type 4 (GLUT-4)

GLUTs are integral membrane proteins that facilitate glucose transport in various tissues such as adipocyte and muscle cells as GLUT-4 responds to insulin. Since the regulation of thirteen identified GLUT isoforms strongly depends on tissue types and cell-specific environments, an increase of GLUT-4 expression was observed regardless of treated substances (Shang *et al* 2007, Shang *et al* 2008, Zhang *et al* 2008, Huang *et al* 2010, Lee *et al* 2011). Three papers examined GLUT-4 along with GLUT-1 and showed different results by the types and concentrations of ginsenoside. In a study of Shang *et al* (2008), the treatment of 10 μM Rb_1 elevated the levels of GLUT-4 mRNA and protein, but GLUT-1 was not expressed (Shang *et al* 2007). When 0.001 to 0.1 μM of Rg_1 and compound K were treated, GLUT-4 at both the mRNA and protein levels was expressed but GLUT-1 was not (Huang *et al* 2010). In contrast, the treatment of 1 μM Rb_1 led to the translocation of both GLUT-1 and GLUT-4 (Shang *et al* 2008). The kinds of ginsenosides such as 10 μM Re, 10 μM Rg_3, 20 μM Rb_1, 20 μM Rg_1, 1 μM Rb_1, 0.001~0.1 μM Compund K and 0.001 ~0.1 μM Rg_1 elevated both of GLUTs and PI3K at protein level (Han *et al* 2006, Hwang *et al* 2007, Park *et al* 2008a, Zhang *et al* 2008, Huang *et al* 2010). However, glucose uptake was slightly decreased by adding of PI3K inhibitor in treatment of 20 μM Rb1 and Rg_1 or 0.001 to 0.1 μM of compound K and Rg_1 (Park *et al* 2008b, Huang *et al* 2010). Despite of incosistant results on glucose uptakes accorsing to types of ginsenosides, Rb_1, Rg_1, CK, Re and Rg_3 may affect improvement of glucose tolerance.

3. AMP-Activated Protein Kinase (AMPK)

A study on the mechanism of AMPK, the metabolic master protein, reported that an increase of AMPK aids the reduction of adipocyte differentiation and it also inhibits adipogenesis. Rg_3 (40 μM) time-dependently increased the level of AMPK

Table 3. Anti-obesity studies of ginseng on 3T3-L1 *in vitro*

Types	Dose	Model	Targeting	Mechanism approach
White ginseng				
Methanol extract (*Panax. quinquefolius*) (Yeo *et al* 2011a)	20.2, 40.3 μg/mL PT>PD	3T3-L1	Lipid	Lipid acquisition ↓, 20.2 μg/mL:13% ↓, 40.3 μg/mL:22% ↓, Oil red O ↓
			Adipocytokine	acrp30(protein) ↑
			Cell cycle	cells in S phase ↓
Methanol extract (*Panax ginseng*) (Yeo *et al* 2011b)	0.1, 1, 10 μg/mL PD>PT		Lipid	Media TG ↓
			Adipocytokine	acrp30 (protein) ↑
			Cell cycle	G0/G1& S ↑, G2 ↓
Powder (*Panax ginseng*) (Mollah *et al* 2011)	250, 500, 1,000 μg/mL		Differentiation	Differentiation (PPARγ/ CEBPα) ↓ adiponectin (protein level) ↓
			Cell cycle	Block at Sub-G1↓
Water, ethanol extract (North American ginseng) (Wilson *et al* 2012)	25,50 μg/mL		Inflammatiomatory cytokines	Dose dependent
	Water extract (AQ)			IL-6/Ccl5 (gene/protein) ↑ NF-Kb/TNF-α (gene) ↑
	Polysaccharide enriched from water extract (50 μg/mL)			IL-6/Ccl-5/TNF-α (gene) ↑
	Ginsenoside enriched from water extract (50 μg/mL)			IL-6 (gene) ↑
	EtOH extract			No changes (IL-6, Ccl-5, TNF-α, NF-Kb) (gene) IL-6 (protein)↓
				Number of down regulated genes / Number of upregulated genes
	50 μg/mL: AQ			490 / 133
	25 μg/mL: AQ			400 / 89
	50 μg/mL: EtOH			10 / 10
	25 μg/mL: EtOH			9 / 13
Ginsenosides				
Rb_1, Rg_1 (Park *et al* 2008b)	20 μM		Lipid	TG↓ / PKA, cAMP↑
			Glucose uptake	↑(8 h)
			Adipogenesis	Glucose uptake↓ PPARγ/C/EBPα/Ap2 (m RNA)↓
			Min 6 cell	IRS(m RNA) ↑
			Insulin signal	Rb2/Rc/Rd/Re :no change
			cell viability	viability↑
			insulin secretion	insulin secretion ↑
Rg_3 (Hwang *et al* 2009)	40 μM		Differentiation	differentiation↓, AMPK(protein)↑, time-dependent
			HEK293 cell differentiation	PPARγ (mRNA, activity)↓

Table 3. Continued

Types	Dose	Model	Targeting	Mechanism approach
Rh_2 (Hwang *et al* 2007)	20, 40 μM	3T3-L1	Differentiation	differentiation ↓, Oil red O ↓, PPARγ (mRNA, transcriptional activity) ↓
			Lypolysis	AMPK inhibitor → CPT-1, UCP-2 ↓ ROS inhibitor → AMPK (protein) ↓
			Cell viability	cell viability ↓ (over 80 μM)
C-K (Park & Yoon, 2012)	5 μM		Differentiation	Lipid accumulation↓
			Adipocyte factor	PPARγ/leptin/ap2/C/EBPα(mRNA)↓
			Angiogenesis	Angiogenic factor, VEGF-A/ FGF-2 (m RNA)↓
			MMPs	MMP-2/MMP-9 (m RNA) ↓ TIMP-1/TIMP-2(mRNA)↑ proMMP-2/proMMP-9 ↓
Total ginsenoside (not all) (Masuno *et al* 1996)	25～200 μM		LPL activity	Each ginsenoside shows different effect
PT (Han *et al* 2006)	10 μM		Differentiation	Differentiation ↑
			Adipogenesis	Oil red O ↑, PPARγ, Ap2, LPL, PEPCK (mRNA) ↑
			Insulin signal	GLUT-4(protein) ↑
Re (Zhang *et al* 2008)	10 μM		Insulin signal	IRS-1 ↑, PI3K activity ↑, GLUT-4 tanslocation ↑
			Inflammation	JNK(protein) ↓, NF-kB ↓
Re (Lee *et al* 2011)	10 μM		Glucose uptake	(12%) ↑
			Insulin signal	GLUT-4(mRNA)↑, PI3K(protein) ↑, IRS-1(mRNA) ↑
Rb_1 (Shang *et al* 2007)	10 μM		Lipogenesis	Adipogenesis ↑, TG ↑
			Differentiation	PPARγ2(mRNA)↑, C/EBPα(mRNA) ↑ PPARγ2, C/EBPα (protein) ↑, Ap2(mRNA) ↑
			Insulin signal	GLUT-4, not GLUT-1 (m RNA, protein) ↑
Rb_1 (Shang *et al* 2008)	1 μM	3T3-L1, C2C12 (insulin sensitive cell)	Glucose uptake	↑(3 h),
			Insulin signal	IRS-1,Akt ↑, PI3K ↑, GLUT-1, GLUT-4↑
Rg_1 (Huang *et al* 2010)	0.001~0.1 μM	3T3-L1	Glucose uptake	glucose uptake ↑ (149～255%, dose-dependent)
			Insulin signal	GLUT-4, notGLUT-1 (mRNA, protein) ↑
			Lipid	TG↑
Rb_2 (Kim *et al* 2009b)	10 μg/mL		Lipid	High cholesterol condition (10 μg/mL): TG/TC ↓
			Lipid metabolism	SREBP (m RNA) ↑, FAS activity ↑, FBS presence condition, FAS ↑
			Lipid	High fatty acid condition: TG ↓
			Lipid metabolism	SREBP/Leptin (mRNA) ↑, Although FAS, GPDH ↑, TG, TC ↓

Table 3. Continued

Types	Dose	Model	Targeting	Mechanism approach
Rg_3 (Lee *et al* 2012)	10 μM	3T3-L1	Glucose uptake Insulin signal	↑ (10%), GLUT-4(mRNA) ↑, PI3K(protein) ↑, IRS-1(mRNA) ↑
C-K (Huang *et al* 2010)	0.001~ 0.1 μM		Glucose uptake, insulin signal	Glucose uptake ↑, GLUT-4 (mRNA/protein) ↑
			Lipid	TG ↓

protein (Hwang *et al* 2009). The treatment of Rh_2 ginsenoside (20 and 40 μM) increased the number of lipolysis biomarkers such as carnitine palmitoyltransferase-1 (CPT-1) and uncoupling protein-2 (UCP-2). However, the addition of 20 μM AMPK inhibitor, compound C, for 30 min before Rh_2 treatment led to decreases in CPT-1 and UCP-2, verifying the involvement of AMPK in lipolysis (Hwang *et al* 2007). Huang *et al* .(2010) identified a decrease in glucose uptake when compound K and 0.1 μM Rg_1 were treated with 1 μM of PI3K inhibitor, LY-294002, and AMPK inhibitor. They proved the involvement of PI3K and AMPK on the elevation of glucose uptake when Rg_1 and compound K were treated together. Therefore, anti-obesity effect manifested by Rh_2 increased the expression of UCP-2 and CPT-1 through AMPK activity (Hwang *et al* 2007).

4. Cell Cycling

When studies on cell cycle were analyzed, the influence of PD ginsenoside on cell cycle was found to be contradicting. The treatment of PT ginsenoside, a 40.3 μg/mL of *Panax quinquefolius* methanol extract particularly abundant with Re (Re : 8.2 mg/g, Rb_1 : 1.5 mg/g, Rg_1 : 0.3 mg/g), resulted a decrease in the number of 3T3-L1 cells in S phase (Yeo *et al* 2011a). In contrast, the number of cells S phase elevated when 0.1, 1 and 10 μg/mL of *Panax ginseng* extracts (Rc : 78.8 mg/g, Rb_2 : 56.8 mg/g, Rb_1 : 21.7 mg/g, Re : 61.6 mg/g, Rg_1 : 47.4 mg/g) abundant with PD were treated (Yeo *et al* 2011b).

5. Anti-Inflammatory Effect

The modern rise in obesity and its strong association with metabolic inflammation, termed metaflammation, in various metabolic tissues have elicited interest in the underlying mechanisms of inflammatory obesity. Therefore, anti-inflammatory therapies for their potential in the treatment of obesity-related metabolic dysfunction such as insulin resistance are focusing on. The anti-inflammatory effect of ginsenoside Re reduces insulin resistance, and this is associated to anti-obesity effect (Zhang *et al* 2008). Ginsenoside Re, an anti-inflammatory factor, prohibits c-Jun N-terminal kinases (JNK) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-Kb) that increase insulin resistance, and decreases Ser 307 phosphorylation of IRS-1 elevated by tumor necrosis factor-α (TNF-α). Phospho-JNK particularly decreased when 10 μM Re was treated for 24 h and 1 nM TNF-α, an inflammation inducer, was treated for 30 min. When a 10 μM of ginsenoside Re was treated for 24 h, the inhibitor of NF-Kb (IkBα) degradation was prohibited. When water extract of the North American ginseng was treated, the greatest change was exhibited in inflammation regulating genes compared to the insignificance of ethanol extract of the North American ginseng (Wilson *et al* 2012). In the concentrations of 25 μg/mL and 50 μg/mL, up-regulated genes were 400 and 490 each, respectively, and down-regulated genes were 89 and 133 each, respectively. Although the treatment of water extract increased the expression of IL-6, Ccl-5, NF-Kb and TNF-α, no significant change was observed in ethanol extraction. The levels of IL-6 increased with the treatment of water extraction, and decreased with the treatment of ethanol extract. Since the expression of IL-6 mRNA was reduced by 43% as TLR-4 inhibitor in water extraction of the North American ginseng was added, IL-6 was the downstream signal of TLR-4 which mediates inflammatory response.

6. Anti-Lipogenic Effect

Compound K and Rg_1 at the concentrations between 0.001 and 0.1 μM showed increasing tendencies in glucose uptake, and the expression of GLUT-4, AMPK and PI3K, and others (Huang *et al* 2010). However, they exhibited contradicting outcome in triacylglycerides (TG) accumulation. When a 0.001 μM of Rg_1 was administered, TG increased to 214% of control. When a 0.1 μM of Rg_1 was administered, TG increased to 159% of control and discharged glycerol to a medium was reduced to 62% of control. A 0.1 μM of compound K resulted

the largest decrease compare with 0.001 and 0.01 μM, decreasing to about 69% of control. In a 0.1 μM, discharged glycerol level increased to 154% of control. Anti-lipogenesis effect could be explained by compound K that inhibits angiogenesis-related factors and matrix metalloproteinases (MMP) system (Park *et al* 2012). The administration of 5 μM compound K led to decreases in vascular endothelial growth factor A (VEGF-A), an angiogenic factor, and fibroblast growth factor-2 (FGF-2). MMP-2 and MMP-9 decreased by 30% and 9%, respectively.

Rb_1 and Rg_1 reduced TG accumulation through increases in protein kinase A (PKA) and cAMP (Park *et al* 2008b). Although Rb_1 and Rg_1 reduced PPARγ, C/EBPα and aP2 at mRNA level, this process did not appear when H89, a PKA inhibitor, was administered. Therefore, Rb_1 and Rg_1 were considered to decrease TG accumulation through PKA-dependent pathway, and increase glucose-uptake through PI3K. Kim *et al* (2009b) explained that Rb_2 lowers TG accumulation by increasing mRNA of sterol regulatory element-binding proteins (SREBP) and leptin in 3T3-L1 cultured in high energy-density condition. SREBP mRNA was reduced in high cholesterol and high fatty acid conditions, and elevated with 10 μg/mL Rb_2 administration.

In a study of the effect on the secretion of lipoprotein lipase (LPL), different outcomes were shown depending on the types and doses of ginsenoside. When 100 μg/mL of Re, Rg_1 and Rh1 ginsenoside were treated each, LPL activity increased by 107%, 56% and 32%, respectively. When 100 μg/mL of Rb2 and Rd were treated each, LPL activity decreased by 39% and 29%, respectively. Therefore, the results of PD and PT ginsenosides contradicted (Masuno *et al* 1996). Han *et al* (2006) reported an increase in LPL mRNA when a 10 μg/mL of PT ginsenoside was treated in 3T3L-1. In the comparison of those two studies, LPL activity elevated regardless of the concentration of PT types. On the other hand, PD types, Rb_2 and Rd, were identified to decrease LPL activity.

IN VIVO STUDIES OF GINSENG ON ANTICBESITY

A total of 38 studies were performed using animal models and only 3 studies have tested this in humans (Table 4 & 5). The most commonly used *in vivo* model was dietary-induced obese (DIO) animal model applied in 18 papers (50%). DIO animal model induces obesity in rats and mice with normal body weight by freely feeding food on a high-fat diet (45~60 %E) for 4~8 wk. The second most frequently used models were *db/db* and ob/ob mice in 6 papers each. Among the total 18 papers, there were 16 studies on white ginseng extract, 7 studies on Korean red ginseng extract, and 2 studies on compound K (an overlapping study on cell and red ginseng each). In terms of evaluation criteria, assessment on body weight changes has been most commonly studied in 29 papers (Xie *et al* 2002, Dey *et al* 2003, Xie *et al* 2005a, Han *et al* 2005, Kim *et al* 2005, Xie *et al* 2005b, Han *et al* 2007, Karu *et al* 2007, Xie *et al* 2007, Yun *et al* 2007, Chen *et al* 2008, Han *et al* 2008, Kang *et al* 2008, Liu *et al* 2008, Min *et al* 2008, Kim *et al* 2009c, Lee *et al* 2009, Lim *et al* 2009, Mollah *et al* 2009, Lee *et al* 2010, Liu *et al* 2010, Yuan *et al* 2010, Xiong *et al* 2010, Xia *et al* 2011, Kim *et al* 2012, Lee *et al* 2012, Li *et al* 2012, Yuan *et al* 2012, Song *et al* 2012), followed by 23 studies on eva- luating serum lipid profiles including total cholesterol (TC), TG, low-density lipoprotein cholesterol (LDLc) and high-density lipoprotein cholesterol (HDLc) (Park *et al* 2002, Cicero *et al* 2003, Han *et al* 2005, Park *et al* 2005, Ji & Gong 2007, Karu *et al* 2007, Yun *et al* 2007, Chen *et al* 2008, Han *et al* 2008, Liu *et al* 2008, Min *et al* 2008, Kim *et al* 2009b, Lee *et al* 2009, Wan *et al* 2009, Kwak *et al* 2010, Lee *et al* 2010, Liu *et al* 2010, Xiong *et al* 2010, Yuan *et al* 2010, Xia *et al* 2011, Li *et al* 2012, Quan *et al* 2012, Song *et al* 2012). The majority of studies have approached the mechanism of anti-obesity effect by analyzing protein and gene expression, in addition to final results of anti-obesity effect of different ginseng types. According to the classification by mechanism, studies on AMPK have been most commonly per- formed, followed by studies on GLUT-4, PPARγ and SREBP1.

1. AMP-Activated Protein Kinase (AMPK) Signaling

Even though the phosphorylation of AMPK in both the mRNA and protein level according to type of ginseng are different, it was cleared that AMPK activation affected the reduction of fat or body weights (Lim *et al* 2009, Yuan *et al* 2010). In particular, the fermented white ginseng attenuates hepatic lipid accumulation and hyperglycemia through AMPK activation in *db/db* mice (Kim *et al* 2009a). Quan *et al* (2012) also reported that Ginsenosides Re 20 mg/kg treatment groups fed a high-fat diet for 6 wk were markedly lowered blood

Table 4. anti-obesity effect of ginseng's on *in vivo* animal studies

Types	Dose (mg/kg body wt).	Model	Targeting	Mechanism approach
White Ginseng				
Ethanol extract (*Panax ginseng*) (Lee *et al* 2010)	0.8, 1.6% Diet	ICR, mice-HFD	Body weight↓ (only 1.6%), White adipose tissue weight↓ (only 1.6%), Serum TG↓, Plasma adiponectin-, Leptin↓ (only 1.6%), epididymal fat cell size↓	PPARγ2, SREBP-1c, FAS, LPL, mRNA in adipose tissue ↓
Methanol extract (*Panax notoginseng*) (Ji & Gong 2007)	30, 60, 100 mg/kg body wt	SD, rats-high-fat/high-cholesterol diet	Serum TG↓ (only 60, 100 mg), Serum TC↓, LDL-C↓	ABCA1, ABCG5, LDLR mRNA in liver↑, SREBP-1C mRNA in liver↓, FXR, LXR agonist
(*Panax notoginseng*) (Cicero *et al* 2003)	4.3, 8.6 mg/kg body wt	Wistar rats-HFD	Serum TG↓, Serum TC↓, LDL-C↓, Fibrinogenaemia↓	-
(*Panax ginseng*) (Mollah *et al* 2009)	100, 200 mg/kg body wt	*ob/ob* mice	Body weight↓, Blood glucose↓ (only 200 mg), epididymal fat cell size↓	PPARγ mRNA↑ (only 200 mg), GLUT-4, IR, LPL mRNA↑
Fermented ginseng (Kim *et al* 2009a)	100, 200 mg/kg body wt	*db/db* mice	Blood glucose↓, Serum insulin↑(only 200 mg), HbA1c↓, Leptin↑, Serum TG-, Plasma adiponectin-, NEFA-	AMPK, GLUT-4↑, SREBP-1a, SCD1, FAS↓, CD36, PPARα↑
Vinegar extract (*Panax ginseng*) (Lim *et al* 2009)	300, 500 mg/kg body wt	OLETF rats	Body weight↓, Blood glucose↓	PPARγ, pAMPK, GLUT-4, protein expression↑
Vinegar-processed Ginseng (*Panax ginseng*) (Han *et al* 2007)	300, 500 mg/kg body wt	*db/db* mice	Blood glucose↓, HOMA-IR↓, HDL-C↑ (only 500 mg), Serum TG↓, Serum TC↓, Hepatic TG↓, Hepatic TC↓, Body weight -	AMPK, GLUT- 4↑, PEPCK, G6Pase ↓ (500 mg)
Vinegar-processed ginseng (Rg_3↑) (*Panax ginseng*) (Yun *et al* 2007)	500 mg/kg body wt	ICR, mice-HFD	Body weight↓, Blood glucose↓, Serum insulin↓, HOMA IR↓, Serum TG↓, Serum TC↓, HDL-C↑, LDL-C↓, NEFA↓, epididymal fat mass↓	-
Pectinase-Processed (Yuan *et al* 2012)	75, 150 mg/kg body wt	ICR, mice-HFD	Blood glucose↓, Body weight↓, Serum insulin↑, HOMA-IR↑	pAMPK, GLUT-4 protein expression ↑
American ginseng berry extract (Xie *et al* 2002)	150 mg/kg body wt	*ob/ob* mice	Blood glucose↓, Body weight↓	-
American ginseng berry juice (Rb_3 ↑) (Xie *et al* 2007)	0.6 mL/kg body wt	*ob/ob* mice	Blood glucose↓, Body weight↓	-
Ginseng leaf extract (Yuan *et al* 2010)	250, 500 mg/kg body wt	ICR, mice-HFD	Body weight↓ (only 500 mg), Blood glucose↓, Food intake efficiency↓ (only 500 mg), Serum Insulin↓, Serum TG↓, Serum TC↓, NEFA↓	pAMPK mRNA↑ PPARα, CD36 mRNA↑, PEPCK, mRNA ↓
Ginseng root (Rg_1, Rb_1↑) (*Panax notoginseng*) (Chen *et al* 2008)	50, 200 mg/kg body wt	KK-Ay mice	Body weight↓(only 200 mg), Serum TG↓, Blood glucose↓(only 200 mg), Food intake efficiency↓(only 200 mg)	-
Ginseng root (Rb_1, Rg_1↑) or berry (Re↑) extract (*Panax ginseng*) (Dey *et al* 2003)	150 mg/kg body wt	*ob/ob* mice	Blood glucose↓, Body weight↓ (only berry)	-

Table 4. Continued

Types	Dose (mg/kg body wt).	Model	Targeting	Mechanism approach
Ginseng root (*Panax notoginseng*) (Xia *et al* 2011)	0.25, 0.5, 1% diet	Sprague–Dawley rats-HFD	Food intake↓, Body weight↓, Serum TG↓, Serum TC↓, LDL-C↓, HDL-C↑,	HMG-CoA reductase activity↓ (only 0.5, 1%)
Steam-dried ginseng berry (*Panax ginseng*) (Kim *et al* 2012)	100 mg/kg body wt	*db/db* mice	Body weight↓, Blood glucose↓, Serum *i*nsulin↑	-
Red Ginseng				
Ethanol extract (Song *et al* 2012)	5,000, 10,000, 30,000 mg/kg body wt	C57BL/6Jmice-HFD	Body weight↓, Liver tissue weight↓, perirenal fat mass↓, total fat mass↓, Serum TC↓, LDL-C↓, Serum TG-, leptin↓, Serum insulin↓, Plasma adiponectin↑	Lipa, Cyp7a1, Il1rn↓
Ethanol extract (Kwak *et al* 2010)	100, 300, 500, 1,000 mg/kg body wt	SD rats -Hyperlipidemic model	Serum TG↓, Serum TC-, NEFA↓, Serum LPL activity↑	
Water extract (Park *et al* 2005)	100 mg/kg body wt	*db/db* mice	Blood glucose↓, HbA1c↓, Plasma adiponectin↑, Plasma leptin↑, NEFA↓, TG↓, Body weight -	SREBP-1a, FAS mRNA↓, PPARα, CD36mRNA↑, AMPK↑
Water extract (Min *et al* 2008)	50,100 mg/kg body wt	ICR mice-hyperlipidemic model	Serum TG↓, Serum TC↓, Body weight-, Epididymal fat mass↓	HMG-CoA reductase, Lipase↓
Water extract (Lee *et al* 2009)	200 mg/kg body wt	OLETF rat	Blood glucose↓, HbA1C↓, Serum TG↓, Serum TC↓, AST- ALT-, Body weight↑, Epididymal fat mass↓	pAMPK, PGC1 protein expression ↑, NRF-1, cytochrome C, COX-4↑, GLUT-4↑
Water extract (Lee *et al* 2012)	200 mg/kg body wt	SD rats-HFD	Body weight↓, Food intake-, Epididymal fat mass↓, subcutaneus fat mass↓, Blood glucose↓, plasma adiponectin /fat mass↑, Leptin↓	IRS-1, Akt, GLUT-4↑
Water extract (Yuan *et al* 2010)	0.5% Diet	*db/db* mice	Body weight-, Blood glucose↓, Serum *i*nsulin↓, HbA1C↓, Serum TG↓	LPL, PPARγmRNA in the adipose tissue↑, PPARα↑
Ginsenosides				
Total saponins (Karu *et al* 2007)	3% Diet	Balb/c mice -HFD	Body weight↓, LPL activity↓, TG ↓	-
Total saponins (Wan *et al* 2009)	4, 12 mg/kg body wt	ApoE KO mice	Atherosclerotic lesions↓, Serum TG↓, Serum TC↓, LDL-C↓, HDL-C↓	-
Total saponins (Re, Rg_2, Rg_1 ↑) (Xie *et al* 2005c)	150, 300 mg/kg body wt	*ob/ob* mice	Blood glucose↓, Body weight↓ (only 300 mg)	-
Total saponins (Han *et al* 2005)	1, 3% Diet	ICR mice HFD	Body weight↓, TG in feces↑, Hepatic TG↓, Parametrial adipose tissue mass↓, pancreatic Lipase activity↓	-
Total saponins (Rc, Rb_1, Rb_2↑) (Liu *et al* 2008)	10, 30 mg/kg body wt	ICR mice-HFD	Body weight↓, Serum TG↓, parametrial fat mass↓	-
Crude saponin (Kim *et al* 2005)	200 mg/kg body wt	SD rats-HFD	Body weight↓, Food intake↓, epididymal fat mass -, Perirenal fat mass↓, Peritoneal fat mass↓, Leptin↓,	NPY↓

Table 4. Continued

Types	Dose (mg/kg body wt).	model	Targeting	Mechanism approach
PD, PT (Kim *et al* 2009c)	50 mg/kg body wt	SD rats-HFD	Body weight↓, Food intake↓, epididymal fat mass↓ (only PD), Perirenal fat mass↓, Serum TG↓, Serum TC↓, Leptin↓	NPY in LH, PVN↓, not ARC (only PD), CCK↑ in PVN(PD)
PD (Li *et al* 2012)	300 mg/kg body wt	ICR mice-HFD	Serum TG↓, Blood glucose↓, Body weight -	-
PD (Rb_1, Rc, Rb_2, Rb_3 and Rd) (Liu *et al* 2010)	0.02, 0.05% diet	Kunming mice -HFD	Body weight↓, Live tissue weight↓, fat mass↓, Serum TG↓, Serum TC↓ (only 0.05%), LDL-C↓, Lipase activity↓	-
Re (Xie *et al* 2005b)	7, 20, 60 mg/kg body wt	ob/ob mice	Blood glucose↓, Serum insulin↓, Body weight-	SCD, FAS, LDL gene↓
Re (Quan *et al* 2012)	5, 10, 20 mg/kg body wt	C57BL/6J mice -HFD	Blood glucose↓ (only 20 mg), Serum TG↓ (only 20 mg), Serum insulin↓(only 20 mg), NEFA↓	pAMPK protein expression↑, SREBP-1c, FAS, PEPCK, SCD-1 mRNA in liver↓
Re (Zhang *et al* 2008)	40 mg/kg body wt	Wistar rats-HFD	Visceral fat mass↓, sc fat mass↓	-
Rg_3 (Kwak *et al* 2010)	10, 25 mg/kg body wt	ICR mice -hyperlipidemic model	Serum TC↓, Body weight-, Epididymal fat mass↓	-
20(S)-Rg_3 (Kang *et al* 2008)	5, 10, 20 mg/kg body wt	Wistar rats	Body weight-, Renal dysfuction, Serum TBA-reactive substance↓	Urinary protein↓, urinary excretion↓, NMDA-NR1 protein ↓
20(S)-Rg_3 (Park *et al* 2008a)	12.5, 25 mg/kg body wt	ICR mice	Blood glucose↓	AMPK↑
Rb_1 (Xiong *et al* 2010)	10 mg/kg body wt	Long-Evans rats-HFD	food intake↓, Body weight↓, Fat mass ↓, Serum TG↓, Serum TC↓, Visceral, Inguinal FAT↓, Blood glucose↓	NPY mRNA↓, PI3K↑
Rb_1 (Park *et al* 2002)	10 mg/kg body wt	SD rats	Hepatic TG↓, Serum TC↑, HDL-C↑, FFA↓	Activity of NADH cytochrome P-450 reductase↓, cAMP↑
Compound K (Han *et al* 2008)	10, 20 mg/kg body wt	*db/db* mice	Blood glucose↓, Serum insulin↑, HOMA IR↓, HbA1c↓, Plasma adiponectin↑, NEFA↓, HDL-C↑, Body weight-	PPARγ, SCD-1, FAS, GLUT- 4 gene↑
Compound K (Li *et al* 2012)	30 mg/kg body wt	ICR mice-HFD	Serum TG↓, Blood glucose↓, Body weight -	PEPCK, G6Pase ↓

glucose and decrease lipogenesis by inhibiting SREBP-1c target genes through activation of AMPK. In contrast, water extract of red ginseng (200 mg/kg) decreased the body weight rather than that of the control until 32nd wk (Lee *et al* 2009). However, the body weight fed red ginseng was higher than that of the control group after 32nd wk during the total of 50 wk through an increase of AMPK.

2. Glucose Transporter Type 4 (GLUT-4)

GLUT4 protein expression was dose-dependently enhanced in pectinase-processed ginseng radix-treated groups in the skeletal muscle. Pectinase-processed ginseng radix decreased plasma glucose and insulin levels when compared to the HFD control group via activating AMPK-GLUT4 signaling pathway (Yuan *et al* 2012). Vinegar-processed Ginseng (*Panax ginseng*) reduced the blood glucose concentration and decreased an insulin resistance index. In addition, Vinegar-processed Ginseng increased the phosphorlation of AMPK and GLUT4 expressions in the liver and skeletal muscle (Han *et al* 2008). Korean red ginseng (*Panax ginseng*) water extract increased insulin sensitivity by increasing phosphorylation of IR, IRS-1, Akt and membranous GLUT4 in muscle in the Korean red ginseng

Table 5. Ginseng's anti-obesity effect on human clinical studies

	Types	Dose(g/d)	Subjects	Result
White ginseng (*Panax ginseng*)	PGE extract (Kim & Park 2003)	2 g	Male student	Serum TG↓, Serum TC↓, HDL-C↑, LDL-C↓, MDA↓, SOD↑, CAT↑
Red ginseng	Korean red ginseng extract (Reeds *et al* 2011)	8 g	Overweight, obese adults	Body weight-, Serum TG-, Serum TC-, HDL-C-, LDL-C-

treated high fat fed group (Lee *et al* 2012). Compound K (CK), a final metabolite of panaxadiol ginsenosides, showed the hypoglycemic activity and improved glucose tolerance (Han *et al* 2007), and Rg_3 ginsenoside 25 mg/kg reduces blood glucose (Park *et al* 2008a). CK increased glucose utilization by increasing glucokinase (GK) and glucose-6-phosphate dehydrogenase (G6PD) enzyme activity in the liver and increased expression of genes responsible for adipocytokine signaling (PPAR-γ, GLUT4) and fatty acid synthesis/metabolism pathways (FAS, SCD-1, ACOx2) in the adipose tissue of *db/db* mice (Han *et al* 2007).

3. Lipogenesis Related Genes

In studies for compound K, PPARγ was decreased when the ethanol extract of white ginseng was mixed in feeding food at 0.8% and 1.6% contents (Lim *et al* 2009). However, PPARγ was increased in adipose tissues without reduction of epididymal fat cell size as mice were fed a 0.5%-red ginseng water extract diet (Mollah *et al* 2009, Lee *et al* 2010). The administration of compound K increased SCD-1 and FAS gene along with PPARγ, and reduced blood glucose (Han *et al* 2007). All five studies to verify the mechanism of SREBP1 were efficacy in obesity by reducing SREBP1. Korean white ginseng extracts significantly repressed mRNA levels of lipogenesis-related genes, PPARc2, SREBP-1c, LPL, FAS and DGAT1, with plasma TG reduction in DIO mice (Lee *et al* 2010). Ginseng leaf extract significantly fewer lipid droplets in the livers and increased phosphorylation of AMPK and ACC, but no differences in the expression of lipogenic genes such as SREBP-1c, FAS and SCD-1 in high-fat diet-fed mice (Yuan *et al* 2010). Re ginsenoside significantly reduced gene expression of SCD, FAS and LDL mRNA in ob/ob mice without changing of body weight (Xie *et al* 2005b). In human studies, panax ginseng extract decreased serum TC, TG, LDL and plasma MDA levels in male subjects for 8 wk, but HDL was increased (Kim & Park 2003). However, there were no evidence that Korean red ginseng extracts or 200~250 mg/d ginsenoside Re treatment improves insulin sensitivity in overweight and obese subjects with impaired glucose tolerance or diabetes (Reeds *et al* 2011).

PERSPECTIVES

The prevalence of obesity-related diseases such as metabolic syndrome, coronary arteriosclerosis and others has recently surged in Korea. In particular, an increase in childhood obesity is often led to high early prevalence of adult chronic diseases. Since drug therapy is limitedly prescribed to severely overweight patients due to the adverse reactions including attack, apoplexy and others, large numbers of obesity-related studies are proactively performed to discover weight loss supplements from food. Thirteen non-prescriptional supplements for the weight reduction were certificated by KFDA, but studies for ginseng on special target of obesity are a few so far. The aim of this review is to facilitate investigational studies on anti-obesity by analyzing the current status of obesity-related studies in Korea as the country from which ginseng has originated through the review of papers published internationally. Unfortunately, most ginseng effects on obesity would be explained by the hypolipidemic and hypoglycemic effects rather than specific mechanisms such as AMPK-triggered lipolysis, inflammatory adipogenesis and so on. Meanwhile, only a single study has been reported by combining terms of ginseng, obesity and inflammation compared to 7,445 studies for obesity, 155 studies for ginseng and inflammation, or 61 studies for obesity and ginseng. Even though the ginseng products were consumed in the first place of the functional foods in Korea, we found only three human clinical studies. Therefore, through this literature of ginseng, further ginseng studies on obesity would be needed such as a) biochemical study to elucidate the anti-obese from various ginseng types, b) chemical study to develop extraction technology of active compounds in ginseng, and c) clinical study to prove the obese mechanisms like inflammatory obesity, interaction between adipocytes and environments along with

macrophages and endothelial cells.

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