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Efficacy and safety of ginsam, a vinegar extract from *Panax ginseng*, in type 2 diabetic patients: Results of a double-blind, placebo-controlled study

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ABSTRACT

Aims/Introduction: The efficacy, dose–response relationship and safety of ginsam, a vinegar extract from *Panax ginseng*, were evaluated in an 8-week, double-blind, randomized, placebo-controlled study in drug-naïve patients with type 2 diabetes.

Materials and Methods: A total of 72 diabetic patients were randomized to receive 1500, 2000 or 3000 mg of ginsam, or placebo daily for 8 weeks ($n = 18$ in each group). The primary end-point was the changes from the baseline HbA_{1c} level. The secondary end-points were the changes of fasting and postprandial 2-h glucose concentration, and the proportion of patients achieving a reduction in HbA_{1c} >0.5%.

Results: In the intention-to-treat analysis, ginsam treatment reduced HbA_{1c} level significantly: $-0.56 \pm 0.25\%$ in the 1500 mg group, $-0.31 \pm 0.12\%$ in the 2000 mg group, and $-0.29 \pm 0.11\%$ in the 3000 mg group (all $P < 0.05$), with a significant difference between the 1500 mg ginsam and the placebo group ($-0.02 \pm 0.12\%$, $P = 0.021$). The changes in fasting glucose concentration followed the same pattern: -21.40 , -14.27 and -6.76 mg/dL for 1500, 2000, and 3000 mg, respectively, vs -2.25 mg/dL for the placebo. The percentage of patients whose HbA_{1c} level decreased by >0.5% differed significantly between the placebo group (11.1%) and the 1500 mg (27.8%) and 2000 mg (27.8%) groups. No severe adverse events were observed in any group.

Conclusions: An 8-week treatment with ginsam, a vinegar extract from *P. ginseng*, moderately improved HbA_{1c} level and was well tolerated in type 2 diabetic patients with inadequate glycemic control. This trial was registered with ClinicalTrials.gov (no. NCT01008163). (*J Diabetes Invest*, doi: 10.1111/j.2040-1124.2011.00185.x, 2012)

KEY WORDS: Ginsam, Oral antidiabetic therapy, *Panax ginseng*

INTRODUCTION

Ginseng is one of the most popular oriental herbal medicines. Ginseng was originally referred to as the root of *Panax ginseng* CA Mey. In traditional oriental medicine, ginseng is considered an adaptogen, aphrodisiac and nourishing stimulant, and has been used historically in the treatment of various aging-associated diseases^{1,2}.

The various pharmacological properties of ginseng have been documented^{3–5}. Several studies showed that ginseng had anti-

diabetic effects^{6,7}. In addition, the berry and leaf of ginseng have been reported to lower blood glucose concentration and body-weight in models of diabetes and obesity^{8,9}. Most studies use simple extracts from the roots, leaves or berries of ginseng, which contain various concentrations of saponins and non-saponins. Ginsenosides, which belong to the saponin family, are the major active compounds of ginseng, and more than 30 ginsenosides have been isolated from ginseng¹⁰. Among these ginsenoside components, Rg3 is thought to be one of the most active components in terms of its pharmacological effects of ginseng on glucose and lipid levels, as well as obesity^{11–13}. A substantial effort has been focused on improving the pharmacological properties of ginseng by extracting the most biologically active components.

Ginsam is a vinegar extraction from *P. ginseng* that is enriched with ginsenoside Rg3¹⁴. A study comparing the effects of ginsam and unprocessed ginseng extracts in an animal model of metabolic syndrome found that ginsam decreased insulin

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resistance and inhibited weight gain more significantly than the unprocessed ginseng extracts¹⁴. In our previous study, ginsam had distinct beneficial effects on glucose metabolism and body-weight control in an obese animal model of insulin resistance by changing the expression of genes involved in glucose and fatty acid metabolism¹⁵. Our group has also reported that Rg3 improves insulin signaling and glucose uptake primarily by stimulating the expression of insulin receptor substrate-1 and GLUT4¹². However, no study has investigated the glucose-lowering effect of ginsam in humans. Identifying the proper dosage of extracts from ginseng associated with antihyperglycemic activity might help develop a new class of antidiabetic agent. We evaluated the efficacy, dose–response relationship and safety of ginsam, a vinegar extract from *P. ginseng*. We measured the concentrations of biomarkers, such as high-sensitivity C-reactive protein (hsCRP), tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), adiponectin and leptin, to identify any links between the glucose-lowering effect of ginsam and changes in these biomarkers.

MATERIALS AND METHODS

Patients

The inclusion criteria included patients older than 18 years and who had type 2 diabetes without any antidiabetic medication for more than 3 months, fasting plasma glucose (FPG) concentration in the range 7.0–15.0 mmol/L and HbA_{1c} level of 7.0–12.0% (53–108 mmol/mol). The exclusion criteria included subjects who had type 1 diabetes or secondary diabetes; had chronic hepatitis (except healthy hepatitis B virus carriers) or active liver diseases (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] greater than twice the upper normal value), serum creatinine concentration >1.5 mg/dL or a history of malignant neoplasm in the previous 5 years; or were taking medication that can affect glycemic control, such as systemic glucocorticoids; or women who were pregnant or lactating, and women of childbearing potential who intended to become pregnant or who did not agree to use adequate contraceptive methods during the study. Patients taking any other active ingredients, plant extracts or other complementary therapies contributing to blood glucose lowering potentials were excluded. A total of 96 patients were screened, and 24 patients were excluded. Of those excluded, 11 had HbA_{1c} levels >12% (108 mmol/mol), seven had active liver diseases and four took medications that could affect the study results. Another two patients withdrew their consent without giving a reason. Finally, 72 patients (44 men and 28 women) with inadequate glycemic control (7.0–9.0% [53–75 mmol/mol] of HbA_{1c}), despite medical nutritional therapy and exercise, were selected. A total of 11 patients (15.3%) dropped out during the study period: three in the control group, three in the 1500 mg ginsam group, four in the 2000 mg ginsam group and one in the 3000 mg ginsam group (Figure 1).

Each patient's medical history, including use of medication and lifestyle details, such as alcohol intake, smoking status and

exercise habits, were recorded by trained nurses. All assessments were carried out at Seoul National University Bundang Hospital in Seongnam, Korea, from January 2008 through to June 2009. The study was approved by the institutional review board of Seoul National University Bundang Hospital (IRB No. B-0708/048-002), and all patients gave written, informed consent. The present study was carried out after registration at ClinicalTrials.gov (NCT 01008163).

Study Design

This was a double-blind, placebo-controlled, randomized study. Patients were randomized into one of four groups: 1500 mg (500 mg t.i.d.), 2000 mg (1000 mg b.i.d. + placebo before lunch) or 3000 mg (1000 mg t.i.d.) of ginsam (YuYu Pharmaceutical, Seoul, Korea), or a matching placebo (t.i.d.). The dosage of ginsam in the present study was determined on the basis of previous clinical studies^{16,17}. Ginsam or placebo was taken three times daily before meals during the 8-week study. The taste and smell of the placebo was the same as the active agent. The study was double-blind, and a permuted block-randomization method was used. We provided pertinent diabetes education, including a therapeutic lifestyle change program, to standardize every patient's education level. The study participants were scheduled to visit the research laboratory at baseline and after 4 and 8 weeks of treatment, and were monitored, as a withdrawal criterion was a FPG concentration of \geq 15.0 mmol/L. Compliance with medication was assessed by pill count at every visit.

Study End-points

The primary end-points were to investigate the efficacy of ginsam treatment by comparing the changes from baseline in HbA_{1c} levels after 8-week treatment between the ginsam groups and placebo group. The secondary efficacy end-points were: (i) FPG concentration and 2-h postload glucose (2-h PG) concentration after a 75-g oral glucose tolerance test (OGTT) at 8 weeks; (ii) the proportion of patients achieving a glycemic response, which was defined as a reduction in HbA_{1c} level of >0.5%; (iii) changes from baseline in the homeostasis model assessment of insulin resistance (HOMA-IR) and β -cell function (HOMA-B), and quantitative insulin sensitivity check index (QUICKI); and (iv) changes from baseline in biomarker levels (hsCRP, TNF- α , IL-6, adiponectin and leptin).

The safety end-points included adverse events (AE), serious adverse events (SAE), hypoglycemia, and changes in blood pressure, liver and renal functions. The relationships between AE and treatment were classified as certain, probable, possible, unlikely, not related or not assessable. A SAE was defined as an AE that resulted in death, threat to life, admission to hospital or the prolongation of in-patient treatment, de novo cancer, or any other important medical events in the opinion of the investigators. Patients were educated to measure their blood glucose concentration whenever they experienced a hypoglycemic symptom and to record the blood glucose value in a diary. This entry was transcribed in the AE form by study nurses.

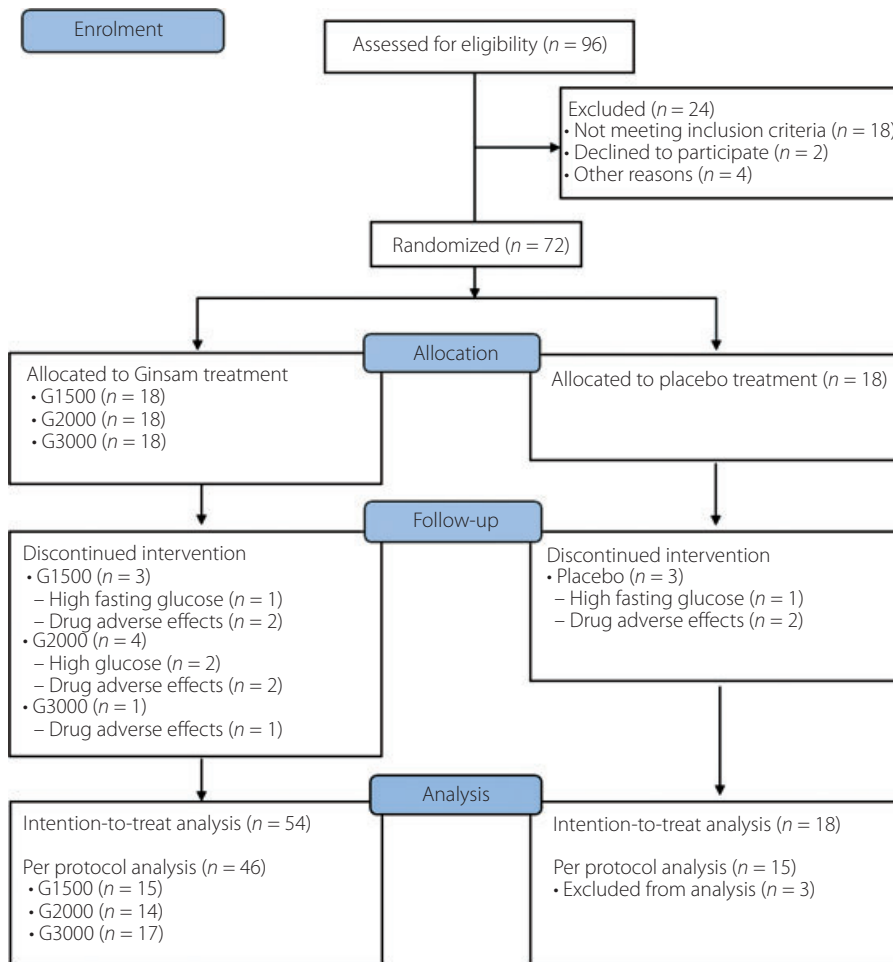


Figure 1 | Flow chart of enrolment of the study subjects.

Measurement of Biochemical Parameters

To evaluate the effects of ginsam on glucose metabolism, plasma glucose and insulin concentrations were measured after a 12-h fast, and all patients completed a 75-g OGTT. Plasma glucose concentration was measured using the glucose oxidase method. Plasma insulin concentration was measured by radioimmunoassay (Linco Research, St Charles, MO, USA). Plasma glucose concentration was also measured at 2 h after the 75-g OGTT. HbA_{1c} level was measured by ion-exchange high-performance liquid chromatography. The HOMA-IR, HOMA-B and QUICKI were calculated as described previously^{18,19}.

Measurement of Other Biomarkers Related to Glucose Metabolism: hsCRP, Adiponectin, TNF- α , IL-6 and Leptin Concentrations

High sensitivity CRP concentration was measured by immunonephelometry. Circulating adiponectin concentration was measured using an enzyme-linked immunosorbent assay kit (AdipoGen, Seoul, Korea). The intra- and interassay coefficient of variation was 3.3 and 7.4% in adiponectin. Plasma TNF- α ,

IL-6 and leptin concentrations were measured using multiplex kits (Linco Research).

Statistical Analyses

The present phase II study aimed to investigate the level of glucose lowering effects of ginsam without superiority or non-inferiority hypothesis testing for treatment differences among groups. A 95% confidence interval for the difference in HbA_{1c} levels after 8-week treatment with a total width of 0.8% of HbA_{1c} (absolute) based on previous studies^{10,15,20} was regarded as sufficient for this exploratory trial and would be obtained with 72 completed participants in the placebo and ginsam groups. We allocated 18 patients to the placebo group and 54 patients to the three ginsam groups ($n = 18$ each) without pre-specified confirmatory hypotheses. A withdrawal rate was assumed to be 15%. Both intention-to-treat and per protocol analyses were carried out for the efficacy analysis and safety profile.

Data are expressed as mean \pm SD and were analyzed using spss Windows version 14.0 (SPSS, Chicago, IL, USA). Changes

in parameters from the baseline values were evaluated using paired *t*-tests. The significance of differences in the changes in parameters between groups was evaluated using ANOVA and post-hoc testing. The percentages of patients achieving a reduction in the HbA_{1c} level of >0.5% and the frequency of AE were compared using the χ^2 test. *P*-values <0.05 were considered to be statistically significant.

RESULTS

A total of 72 patients with type 2 diabetes were randomly divided into four groups (ginsam 1500, 2000 and 3000 mg, and placebo, *n* = 18 each). Figure 1 shows the flow of enrolment and end-points of the study subjects. The baseline demographics

and disease characteristics were not significantly different between groups (Table 1). Medical history, use of other medications and lifestyles, such as smoking status, alcohol consumption and diet habit, were not different between the groups (data not shown). On average, patients in each group were moderately hyperglycemic (mean HbA_{1c} 7.6–7.8% [60–62 mmol/mol] for each group) at baseline.

The between-treatment difference in drug compliance was assessed for the ginsam and placebo groups. The percentage of pills consumed during the 8 weeks did not differ between groups: 96.4% in the ginsam group and 92.6% in the placebo group. The proportion of pills consumed also did not differ significantly among the three ginsam groups.

Table 1 | Baseline characteristics according to treatment group

	Placebo		Ginsam 1500 mg		Ginsam 2000 mg		Ginsam 3000 mg		<i>P</i> *
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age (years)	54.8	10.0	52.7	11.0	52.7	10.0	51.1	8.6	NS
Male <i>n</i> (%) [†]	11	61.1	9	50	11	61.1	13	72.2	NS
Duration of diabetes	2.4	2.7	2.7	2.9	3.7	3.7	2.7	2.9	NS
Height (cm)	163.7	8.3	163.0	7.5	165.4	6.5	166.2	6.8	NS
Weight (kg)	67.9	8.6	70.2	15.2	65.9	9.3	70.2	7.8	NS
SBP (mmHg)	125.9	16.0	125.2	9.8	126.2	12.3	122.9	13.0	NS
DBP (mmHg)	76.3	10.1	75.6	8.2	78.2	8.6	79.2	11.3	NS
BMI (kg/m ²)	25.3	1.9	26.3	4.8	24.0	2.6	25.4	2.7	NS
Waist circumference (cm)	89.9	6.7	91.6	9.8	86.3	8.8	88.8	7.0	NS
Fasting glucose (mmol/L)	8.25	1.80	9.15	2.24	9.54	1.96	8.95	1.49	NS
Postload 2-h glucose (mmol/l)	15.51	2.84	17.52	4.83	16.57	4.84	16.82	4.12	NS
Fasting insulin (pmol/L)	68.76	29.17	80.56	39.59	65.98	30.56	84.03	45.84	NS
HbA _{1c} (%)	7.6	0.4	7.8	1.3	7.8	1.2	7.7	0.8	NS
HbA _{1c} (mmol/mol)	60	7	62	12	62	13	61	9	NS
Total cholesterol (mmol/L)	5.04	0.80	5.68	1.06	5.31	1.07	5.23	0.78	NS
Triglyceride (mmol/L)	1.67	0.53	2.00	1.03	1.67	0.73	2.05	1.63	NS
HDL-cholesterol (mmol/L)	1.45	0.28	1.35	0.36	1.32	0.47	1.21	0.28	NS
LDL-cholesterol (mmol/L)	2.62	0.61	3.03	0.74	2.92	0.80	2.82	0.59	NS
AST (IU/L)	24.1	7.7	26.3	7.3	24.3	6.8	23.4	8.9	NS
ALT (IU/L)	26.4	12.5	33.2	11.8	27.2	10.2	27.0	13.7	NS
γ GT (IU/L)	44.1	35.9	55.5	38.5	43.2	36.5	37.9	17.0	NS
Creatinine (mg/dL)	1.02	0.19	0.98	0.21	0.92	0.17	0.96	0.08	NS
HOMA-IR	3.8	2.1	4.7	2.5	4.1	2.0	4.9	2.9	NS
HOMA-B	43.5	14.3	47.8	29.7	34.1	17.9	46.4	26.7	NS
QUICKI	0.54	0.07	0.51	0.05	0.53	0.06	0.51	0.07	NS
hsCRP (mg/L)	0.14	0.29	0.23	0.24	0.13	0.16	0.16	0.13	NS
TNF- α (pg/mL)	7.9	3.5	8.9	5.8	7.3	5.7	8.5	8.1	NS
IL-6 (pg/mL)	24.2	29.3	25.5	30.6	31.5	43.7	24.0	22.4	NS
Adiponectin (μ g/mL)	8.6	4.4	9.4	6.4	9.4	4.1	9.1	5.0	NS
Leptin (pg/mL)	9.2	11.8	9.5	9.3	7.7	5.1	8.7	11.0	NS
Antihypertensive med. [†]	3	16.7%	2	11.1%	3	16.7%	2	11.1%	NS
Lipid lowering med. [†]	2	11.1%	1	5.6%	2	11.1%	3	16.7%	NS

*Significant difference between groups by one-way ANOVA. [†]Data are *n* and %. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CRP, c-reactive protein; DBP, diastolic blood pressure; γ GT, γ -glutamyl transferase; HOMA-B, homeostasis model assessment for β -cell function; HOMA-IR, homeostasis model assessment for insulin resistance; IL-6, interleukin-6; med., medication; NS, not significant; QUICKI, quantitative insulin sensitivity check index; SBP, systolic blood pressure; TNF- α , tumor necrosis factor- α .

Primary End-point**HbA_{1c} Level**

For the primary end-point of the present study, the change in HbA_{1c} level significantly differed between the placebo and 1500 mg ginsam groups ($P = 0.021$ in the intention-to-treat analysis and $P = 0.014$ in the per protocol analysis), but not between the placebo and other ginsam groups (Figure 2). Within individual groups, treatment with ginsam for 8 weeks reduced the HbA_{1c} level significantly relative to the baseline values: in the intention-to-treat analysis, $-0.56 \pm 0.25\%$ in the 1500 mg group ($P = 0.034$), $-0.31 \pm 0.12\%$ in the 2000 mg group ($P = 0.042$) and $-0.29 \pm 0.11\%$ in the 3000 mg ginsam group ($P = 0.025$) compared with the placebo group ($-0.02 \pm 0.12\%$, $P = 0.267$). In the per protocol analysis, a similar trend was found with greater glucose lowering efficacy in the ginsam group: -0.59 ± 0.25 , -0.34 ± 0.12 and $-0.33 \pm 0.11\%$ in the 1500, 2000 and 3000 mg groups, respectively, and $-0.01 \pm 0.12\%$ in the placebo group. When one outlier who showed $\Delta\text{HbA}_{1c} > 1.5\%$ in the ginsam 1500 mg arm was excluded, ΔHbA_{1c} (%) decreased from 0.56 ± 0.25 to 0.45 ± 0.23 in this arm with borderline significance ($P = 0.087$). As a secondary analysis, when ΔHbA_{1c} was compared between placebo and combined ginsam groups, there was significant difference in ΔHbA_{1c} between the two arms irrespective of including the outlier: placebo vs combined ginsam groups with outlier, $-0.02 \pm 0.12\%$ vs $0.38 \pm 0.09\%$ and placebo vs combined ginsam group without outlier, $-0.02 \pm 0.12\%$ vs $0.36 \pm 0.07\%$, both $P < 0.01$.

Secondary End-Points**FPG and 2-h PG Concentrations**

FPG concentration tended to decrease after ginsam treatment. The mean changes in FPG concentration from baseline to 8 weeks were -0.12 ± 1.62 mmol/L ($P = 0.719$) in the placebo group and -1.19 ± 0.85 mmol/L ($P = 0.021$), -0.79 ± 1.28 mmol/L ($P = 0.094$), and -0.38 ± 0.91 mmol/L ($P = 0.119$) in the 1500, 2000 and 3000 mg ginsam groups, respectively. There was a statistical significance between the change in the placebo and 1500 mg ginsam groups ($P = 0.043$; Figure 2).

The mean changes in 2-h PG concentration from baseline to 8 weeks were -1.18 ± 1.62 mmol/L ($P = 0.262$) in the placebo group, and -2.32 ± 3.01 mmol/L ($P = 0.047$), -1.03 ± 2.36 mmol/L ($P = 0.179$) and -1.73 ± 2.79 mmol/L ($P = 0.054$) in the 1500, 2000 and 3000 mg ginsam groups, respectively. The changes in 2-h PG concentration did not differ significantly between the placebo and ginsam-treated groups.

Potency of the Glucose-lowering Effect (HbA_{1c} Level By >0.5%) and Changes in the Index of Insulin Resistance and β -Cell Function

The percentage of patients whose HbA_{1c} decreased by >0.5% differed significantly between the placebo group (11.1%) and the 1500 mg ginsam (27.8%) and 2000 mg ginsam (27.8%) groups, but not between the placebo and 3000 mg ginsam (16.7%) groups (Figure 2). However, the percentage of patients achieving a glycemic response, defined as a HbA_{1c} level of $\leq 7.0\%$ (53 mmol/mol) at 8 weeks, did not differ between groups. This

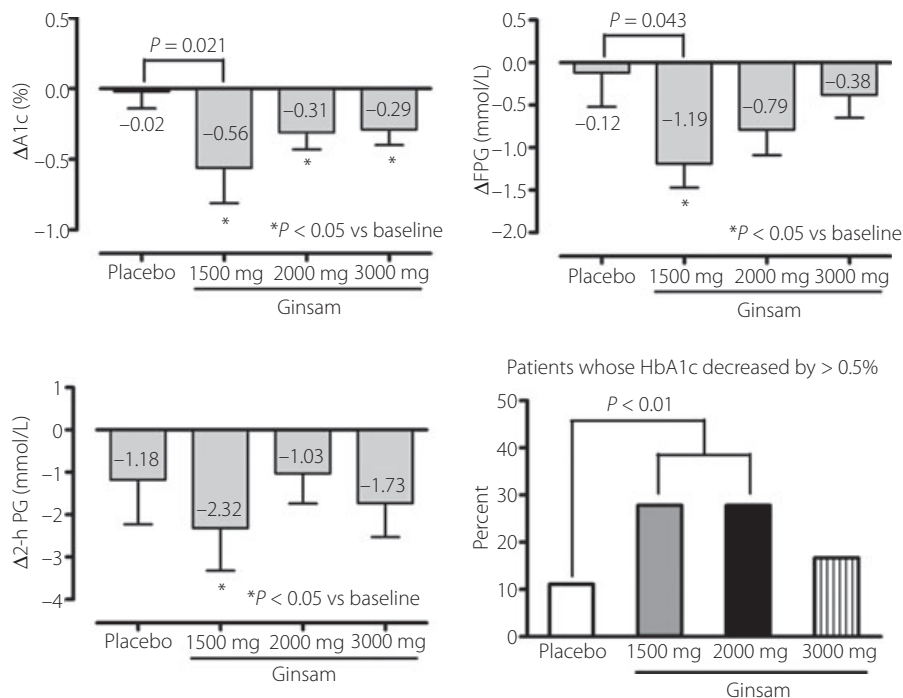


Figure 2 | Changes of HbA_{1c} level, and fasting and postload glucose concentration and percentage of patients whose HbA_{1c} decreased by >0.5% during 8 weeks of treatment with ginsam.

Table 2 | Changes of anthropometric and biochemical parameters after 8 weeks of Ginsam treatment

	Placebo		Ginsam 1500 mg		Ginsam 2000 mg		Ginsam 3000 mg		<i>P</i> *
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
ΔSBP (mmHg)	-0.55	12.33	1.22	10.91	1.55	14.18	-1.75	10.51	NS
ΔDBP (mmHg)	-1.45	6.74	1.56	7.04	3.27	5.62	-2.83	9.90	NS
ΔBMI (kg/m ²)	0.06	0.94	0.29	0.30	0.06	0.45	0.23	0.42	NS
ΔWaist circumference (cm)	0.50	2.12	0.79	1.20	0.89	3.12	-0.33	3.99	NS
ΔFasting glucose (mmol/L)	0.12	1.62	1.19	0.85	0.79	1.28	0.38	0.91	A
Δ2-h PG (mmol/L)	1.18	1.62	2.32	3.01	1.03	2.36	1.73	2.79	NS
ΔHbA _{1c} (%)	0.02	0.43	0.56	0.62	0.31	0.32	0.29	0.34	A
ΔInsulin (pmol/L)	-0.35	33.06	5.07	30.14	-5.49	22.71	-4.10	16.74	NS
ΔTotal cholesterol (mmol/L)	-0.05	0.88	0.37	0.72	0.18	0.74	0.24	0.69	NS
ΔTriglycerides (mmol/L)	-0.05	0.40	0.15	1.02	0.11	0.53	0.18	1.03	NS
ΔHDL-cholesterol (mmol/L)	0.04	0.19	0.01	0.18	0.01	0.12	0.04	0.12	NS
ΔLDL-cholesterol (mmol/L)	-0.06	0.61	0.24	0.37	0.17	0.42	0.25	0.67	NS
ΔAST (IU/L)	2.36	4.50	5.11	4.34	1.00	4.36	4.92	5.14	NS
ΔALT (IU/L)	3.91	6.12	8.89	10.24	2.09	6.80	7.38	11.67	NS
ΔγGT (IU/L)	2.27	14.04	15.33	30.98	5.00	11.09	-3.15	18.15	NS
ΔCreatinine (mg/dL)	0.08	0.02	0.12	0.09	-0.16	0.12	0.14	0.12	NS
ΔHOMA-IR	0.25	1.89	0.66	1.32	-0.24	2.20	-0.06	1.19	NS
ΔHOMA-B	-5.25	27.87	-2.87	26.14	-6.29	9.62	-4.84	10.24	NS
ΔQUICKI	0.01	0.07	-0.02	0.06	-0.01	0.04	0.01	0.03	NS
ΔhsCRP (mg/L)	-0.01	0.06	0.05	0.28	0.06	0.17	-0.01	0.09	NS
ΔTNF-α (pg/mL)	-0.09	3.21	2.48	2.32	1.73	1.80	2.20	3.42	A,C
ΔIL-6 (pg/mL)	1.72	10.41	10.11	12.83	8.44	19.19	7.06	14.91	NS
ΔAdiponectin (μg/mL)	-0.47	2.05	-0.50	2.27	-0.70	1.34	-1.19	3.74	NS
ΔLeptin (pg/mL)	0.67	2.54	0.18	2.38	0.38	2.76	-0.53	2.08	NS

*Statistical significance by ANOVA between groups. Post-hoc analysis by least-significant difference (mean difference between groups, $P < 0.05$ in all cases). A, placebo vs 1500 mg; ALT, alanine aminotransferase; AST aspartate aminotransferase; B, placebo vs 2000 mg; C, placebo vs 3000 mg; γGT, γ-glutamyl transferase; HOMA-B, homeostasis model assessment for β-cell function; HOMA-IR, homeostasis model assessment for insulin resistance; IL-6, interleukin-6; PG, postload glucose; QUICKI, quantitative insulin sensitivity check index; TNF-α, tumor necrosis factor-α.

result might be attributed to the differences in the baseline HbA_{1c} levels, albeit statistically non-significant. The changes in HOMA-B, HOMA-IR and QUICKI, which are indicators of insulin secretory function and insulin resistance, did not differ significantly between groups (Table 2).

Changes in Biomarkers (Concentrations of Adiponectin, hsCRP, TNF-α, IL-6 and Leptin) From Baseline

Adiponectin concentration did not change significantly during the 8 weeks in the placebo or ginsam groups. TNF-α concentration in all ginsam groups and IL-6 concentration in the 1500 mg ginsam group decreased significantly after 8 weeks ($P < 0.05$). TNF-α concentration after the 8-week treatment was significantly lower in the 1500 and 3000 mg ginsam groups than in the placebo group. The plasma concentrations of hsCRP and leptin did not change significantly after 8 weeks of treatment in any group (Table 2).

Other Parameters

Bodyweight, body mass index and waist circumference did not differ between groups, and did not change during the 8 weeks.

Low-density lipoprotein cholesterol concentration decreased slightly, by 0.24 ± 0.37 mmol/L in the 1500 mg ginsam group ($P = 0.089$). Other lipid concentrations did not change significantly after the 8 weeks in any group (Table 2).

Correlations Between Changes in HbA_{1c} Level and Biomarkers

Because TNF-α and IL-6 concentrations were decreased after ginsam treatment, correlation analysis was carried out to investigate the relationships between the changes in HbA_{1c} level and these markers. The change in HbA_{1c} level of ginsam treatment correlated positively and significantly with the changes in TNF-α and IL-6 concentrations (Figure 3).

Tolerability and Safety

Overview of AE

AE were reported by 11 (61.1%) patients treated with the placebo and by 36 (63.0%) patients treated with ginsam: 14 in the 1500 mg, 11 in the 2000 mg and 11 in the 3000 mg ginsam group. The most commonly reported AE were general weakness (16.7%) and gastrointestinal disturbance (11.1%) in the placebo group, and general weakness (16.7%), gastrointestinal

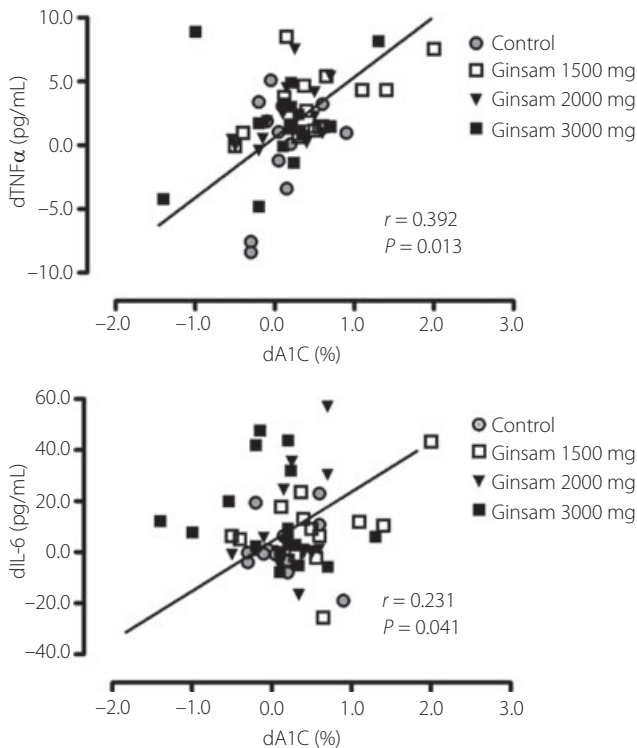


Figure 3 | Correlations between the changes of HbA_{1c} and the changes of tumor necrosis factor- α (TNF- α) or interleukin-6 (IL-6) levels. The changes of HbA_{1c} were positively and significantly correlated with changes of TNF- α and IL-6.

disturbance (9.3%), upper respiratory infection (9.3%), musculoskeletal pain (7.4%) and pruritus (3.7%) in the ginsam-treated groups (Table S1). The double-blind therapy was discontinued as a result of all-cause AE in five (9.3%) ginsam-treated patients and in two (11.1%) placebo-treated patients; the difference was not significant. No SAE were reported in any group, and no patient reported hypoglycemic symptoms during the study.

Blood Pressure and Biochemical Parameters

The changes in systolic and diastolic blood pressure did not differ significantly between groups. Within- and between-treatment differences in liver function, as assessed by AST, ALT and γ -glutamyl transferases levels, and in renal function, as assessed by serum creatinine concentration, were not significant.

DISCUSSION

In the present study, ginsam, which was produced by vinegar extraction from *P. ginseng* to yield high concentrations of ginsenoside Rg3, showed possible glucose-lowering effects in drug-naïve patients with type 2 diabetes. The percentage of patients achieving >0.5% HbA_{1c} reduction was greater in the ginsam-treated group than in the placebo group. This glucose-lowering effect was possibly attributable to the inflammatory process where TNF- α and IL-6 concentrations were decreased after

ginsam treatment, and their changes were correlated with the changes in HbA_{1c} level.

Various standardized formulas of ginseng products have been introduced⁴. Different preparation methods for processing ginseng products, and variable ages and species of ginseng contribute to the variability in the ginsenoside composition and the anti-hyperglycemic efficacy of individual ginseng products^{6,9,14,20–22}. Among the many bioactive compounds contained in ginseng, the most representative active compounds are ginseng-specific saponins (ginsenosides)⁸. Ginsenosides are comprised of a steroid skeleton and sugar moieties, and the type, number and position of the sugars determine its structure and function. Among the known species of ginsenosides, ginsenosides Rg1, Rh2, Rb1, Re and Rg3 have been reported to have glucose-lowering effects in animal studies^{10,13,23,24}. Recently, Reeds *et al.*²⁵ reported that ginsenoside Re therapy does not improve β -cell function or insulin sensitivity in overweight/obese subjects with impaired glucose tolerance or newly diagnosed diabetes. In the current study, we used ginsam, which was enriched with Rg3 and the main component of steam-treated ginseng (red ginseng) or acid-treated ginseng²⁶. In an animal study, treatment of ginsam improved the metabolic profile in high-fat fed ICR mice¹⁴. We reported recently that ginsam treatment decreased glucose excursion during the intraperitoneal glucose tolerance test by 21.5% in an obese insulin-resistant rat model¹⁵. These beneficial effects of ginsam were related to an increased GLUT4 protein level in skeletal muscle, and increased peroxisome proliferator-activated receptor- γ protein level and AMP-activated protein kinase phosphorylation in liver and skeletal muscle. Rg3 enhanced both basal and insulin-induced glucose uptake in a dose-dependent manner and increased the levels of phosphorylated IRS-1/Akt and GLUT4 mRNA¹².

Furthermore, there have been several studies documenting the role of Rg3 in improving pancreatic β -cell function. A group reported that Rg3 increased glucose-stimulated insulin secretion¹³, and another group showed that Rg3 suppressed palmitate-induced apoptosis of pancreatic β -cell lines²⁷.

Interestingly, the ginsam-induced improved glucose homeostasis was associated with decreased concentrations of pro-inflammatory cytokines, TNF- α and IL-6, in the current study. Many studies have provided evidence of a critical role of TNF- α and IL-6 in the pathogenesis of diabetes and its complications through impairment of insulin signaling^{28–30}, leading to a surge of interest in finding new antidiabetic agents that suppress the inflammatory pathway³¹. A recent study reported that a fermented form of *P. ginseng* protected against pancreatic β -cell damage by downregulating inducible nitric oxide synthase and TNF- α gene expression by blocking nuclear factor kappa B activities²². These data, along with the current study results, provide evidence for the anti-inflammatory and anti-oxidative effects of ginsam that contributed to improvement of glucose metabolism.

In the present study, treatment with ginsam for 8 weeks significantly reduced HbA_{1c} level by 0.29–0.56%, which was lower

than the potency of other oral antidiabetic agents proved in Korean drug-naïve type 2 diabetic patients³². Furthermore, a dose–response relationship was not found. The reason for the lack of a linear relationship is not entirely clear. Drug compliance did not differ significantly between groups. It is possible that the dose range studied was too high, as was the case in a previous study¹⁶ and that a threshold of around 1500 mg of ginsam might be the most effective in improving glucose homeostasis. Also, the 8-week treatment period might not have been long enough to assess the full effect of ginsam on glucose control.

Currently available oral antidiabetic drugs have a number of adverse effects, such as hypoglycemia, lactic acidosis and weight gain³³. In the present study, ginsam was well tolerated, as there were no treatment-related SAE and the frequency of side-effects did not differ significantly between the ginsam and placebo groups. The number of patients who stopped the study medication for any reason did not differ between the ginsam and placebo groups (9.3% vs 11.1%). In addition, treatment with ginsam was at least weight neutral and did not cause hypoglycemia. Furthermore, ginsam did not alter hepatic or renal functions and did not modify cardiovascular risk factors, such as blood pressure or lipid profile.

There were some limitations in the present study. First, the gold standard technique for evaluating pancreas β -cell function and insulin resistance, such as clamp study, were not used. Second, the study duration of 8 weeks did not allow assessment of long-term results. Given the positive impact of low dose ginsam, it is conceivable that longer-term ginsam use would result in a more durable glucose lowering effect. Third, just 18 patients were assigned to four respective arms, although 72 patients were enrolled as a whole. The relatively small number in each arm might be associated with weak significance. Finally, the baseline characteristics among the study groups were not strictly comparable, even though the differences were not statistically significant.

In conclusion, an 8-week treatment with 1500 mg ginsam moderately improved the HbA_{1c} level in type 2 diabetic patients with inadequate glycemic control. The present study suggests that 1500 mg ginsam might possibly be a viable option for glucose lowering in patients with diabetes who do not trust ‘Westernized’ medicine and would prefer to use botanical therapies without major side-effects, but future phase III clinical studies are needed.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 | All-cause adverse events *n* (%) occurring in patients receiving placebo or ginsam

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