

***Panax ginseng* has no effect on indices of glucose regulation following acute or chronic ingestion in healthy volunteers**

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In the absence of effective pharmacotherapy for diabetes there has been an increase in the use of, and research into, alternative treatment strategies. These include exercise, dietary interventions and the use of supplements including extracts of ginseng. Two separate, placebo-controlled, double-blind, cross-over studies investigating the effects of chronic ingestion of *Panax ginseng* (study 1 used G115, study 2 used Cheong Kwan Jang) on glycated Hb (HbA1c; study 1, *n* 18; study 2, *n* 11), fasting plasma insulin (study 1, *n* 17; study 2, *n* 12), fasting plasma glucose and postprandial response (following breakfast) (study 1, *n* 23; study 2, *n* 14) in healthy volunteers are reported. In both studies it was found that *Panax ginseng* had no effect on any gluco-regulatory parameter investigated. These results are not consistent with those reported for a diabetic sample (albeit using slightly different outcomes). These results would suggest that chronic use of *Panax ginseng* by non-diabetic individuals will have little long-term effect on glucose regulation. The benefits to glucose regulation associated with long-term ginseng use may only be present in populations with compromised glucose control; however, further research is needed to confirm such a speculation.

***Panax ginseng*: Glucose response: Insulin: Glycated Hb levels**

The increasing incidence of diabetes⁽¹⁾ is a global concern, especially when the available treatment appears to be insufficient to halt the disease progression and the majority of type 2 diabetes patients eventually require insulin therapy⁽²⁾. It is estimated that diabetes is likely to be the fifth leading cause of death globally⁽³⁾. These considerations have led to an increase in the use of, and research into, alternative treatment strategies, including exercise and dietary interventions. The latter include herbal supplements including extracts of ginseng.

The term 'ginseng' usually refers to the dried root of several species in the plant genus *Panax* (Araliaceae family). The two most common species are *Panax ginseng* (Asian ginseng) and *Panax quinquefolius* (American ginseng), both of which have documented acute hypoglycaemic effects^(4–15). The acute hypoglycaemic effects of *Panax quinquefolius* have been demonstrated in a series of randomised, placebo-controlled studies in diabetic and healthy human subjects. Compared with placebo, reductions in the blood glucose response to a 25 g (and 75 g⁽¹⁵⁾) glucose challenge have been reported during a 120 min oral glucose tolerance test in both diabetic patients who had ingested 3, 6 and 9 g^(9,10), and healthy participants administered 1, 2, 3 and 9 g *Panax quinquefolius*^(9,11,15). However, Sievenpiper *et al.*⁽¹⁶⁾ failed to report any hypoglycaemic effect of 6 g *Panax quinquefolius*,

administered 40 min before, or concurrently with, a 75 g glucose drink in twelve healthy volunteers. Additionally, Sievenpiper *et al.*⁽¹⁷⁾ reported that there was no effect of eight other widely used ginseng types (Sanchi, Siberian, American, Asian, Korean red, Japanese, wild American and Vietnamese) on indices of glycaemic control following a 75 g oral glucose tolerance test in healthy volunteers. However, an extract of *Panax ginseng* was associated with increased blood glucose levels and insulin response following the glucose load⁽¹⁷⁾. With regards to *Panax ginseng*, a further two studies have reported significant reductions in fasting blood glucose levels measured 1 h after a single dose of 200 and 400 mg in healthy volunteers but no effect on postprandial glucose (following a 25 g glucose drink) response^(13,14). While there are discrepancies between the findings of the acute studies, these may be attributable to differences in populations (healthy and diabetic), dietary states (fasting and postprandial) and ginseng types (Asian and American). Additionally, treatment doses, timing and the level of glucose loads have differed between studies. Nevertheless there is a growing consensus that both *Panax ginseng* and *Panax quinquefolius* are capable of acute glycaemic modulation in both healthy and diabetic populations.

In line with the acute effects briefly delineated earlier, ginseng may also be promising as a potential chronic treatment

Abbreviation: HbA1c, glycated Hb.

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in diabetes. A reduction in fasting blood glucose levels and glycosylated Hb (HbA1c; an index of blood glucose over the past month or so) were reported following 8 weeks of administration of 100 and 200 mg/d of an unspecified ginseng extract in eighteen participants with type 2 diabetes mellitus⁽¹⁸⁾. Similarly, Tetsutani *et al.*⁽⁸⁾ reported that 24 months of treatment with 3–4.5 g/d Korean red *Panax ginseng* decreased HbA1c in thirty-four type 2 diabetics compared with controls. With regards to *Panax quinquefolius*, a decrease in fasted blood glucose and HbA1c has been reported in twenty-four type 2 diabetic patients following 8 weeks of administration of 1 g of a proprietary ginseng extract, taken 40 min before each meal⁽¹⁰⁾. Similarly, Vuksan *et al.*⁽¹²⁾ reported improved glucose regulation following chronic supplementation with *Panax ginseng*. Nineteen well-controlled type 2 diabetes patients received *Panax ginseng* for 12 weeks. *Panax ginseng* (2 g) was ingested 40 min before each of three daily meals. Between-groups comparisons were made on eleven indices of glucose regulation, presented under three categories: (1) HbA1c; (2) fasting indices (fasting plasma glucose, fasting plasma insulin and homeostasis model assessment (HOMA)); and (3) postprandial response to a 75 g oral glucose tolerance test (mean plasma glucose, mean plasma insulin, peak plasma glucose, peak plasma insulin, plasma glucose area under the curve, plasma insulin area under the curve and oral glucose tolerance test-insulin sensitivity index). Results indicate that following 12 weeks of *Panax ginseng* supplementation there was no difference in HbA1c, fasting plasma glucose or peak plasma glucose. All other indices of glucose regulation that were measured were improved in the treatment group.

As with the series of acute studies it is of clinical interest to investigate the glycaemic effects following chronic ingestion of ginseng, in a healthy non-diabetic population. Additionally, given that no study to date has investigated the acute glycaemic effects beyond the clinically relevant 2 h post-dose measurement point, it is of interest to investigate ginseng's glycaemic effects beyond this point. Specifically, to investigate whether glucose levels continue to fall, beyond normoglycaemic levels, once they have returned to baseline levels.

The present paper reports, for the first time, the results from two double-blind, placebo-controlled, balanced, cross-over studies. These studies assessed the effects of 4 and 8 weeks of ingestion of two *Panax ginseng* extracts on indices of glycaemic regulation (HbA1c, fasting plasma insulin, fasting plasma glucose) and at 3 h post-breakfast, in healthy volunteers.

Participants and methods

Participants

Both study 1 and study 2 were approved by the Northumbria University Division of Psychology Ethics committee and conducted in accordance with the Declaration of Helsinki. Prior to participation each participant gave informed consent and completed a medical health questionnaire. All participants reported that they were in good health (free from heart disorders, respiratory disorders, high blood pressure, epilepsy, panic attacks and diabetes) and were not taking any illicit social drugs. Additionally, they were free from 'over-the-counter' or prescribed medications, with the exception, for some female

volunteers, of the contraceptive pill. Heavy smokers (more than ten cigarettes per day) were excluded from both studies. All participants fell within the normal healthy BMI range (participants who fell outside the normative range were excluded from the study). All participants fasted overnight and were alcohol- and caffeine-free for 12 h prior to, and during, assessment days. In both studies volunteers were paid £150 for participation. No participant took part in both studies.

Study 1. Thirteen female and twelve male volunteers, recruited through local media advertisements, participated in study 1. Due to a number of missing data points (blood could not be collected or finger prick analysis reported an error) the dataset was reduced to twenty-three (twelve males, eleven females; mean age 35.6 (SD 10.8) years) for finger prick blood glucose levels; reduced to eighteen (ten males, eight females; mean age 33.3 (SD 10.4) years) for HbA1c and further reduced to seventeen (eight males, nine females; mean age 32.8 (SD 9.7) years) for fasting plasma insulin. Treatment compliance was assessed through verbal communication: participants were asked to record any days that they forgot to take their dose. Two participants reported forgetting to take their dose when in the placebo condition. A further two participants reported that they forgot to take their dose when in the active treatment condition. One participant forgot to take day 14's treatment dose while the second forgot to take the treatment on day 6. All participants were blind to the treatment condition throughout the study and all were included in the analysis.

Study 2. Thirteen female and five male volunteers, recruited through local media advertisements, participated in study 2. Due to a number of missing data points (blood could not be collected or finger prick analysis reported an error) the dataset was reduced to fourteen (five males, nine females; mean age 38.4 (SD 10.6) years) for finger prick blood glucose levels; reduced to twelve (four males, eight females; mean age 40.75 (SD 9.64) years) for fasting plasma insulin and further reduced to eleven (three males, eight females; mean age 41.5 (SD 9.7) years) for HbA1c. Treatment compliance was assessed through verbal communication: participants were asked to record any days that they forgot to take their dose. One participant reported a failure to take one day's dose when in the active treatment condition (day 17 of the treatment regimen) due to unforeseen working commitments. Participants were blind to their treatment condition throughout the study and all participants were included in the analysis.

Physiological measures

Glycated Hb. A 2.5 ml venous blood sample was taken from the arm of each participant at the beginning of each testing day (days 1, 29, 57). Blood samples were collected in a monovette containing EDTA and whole blood was stored at -20°C prior to analysis. HbA1c levels were established using a Tosoh G7 HbA1c analyser. This system uses a cation exchange column to separate Hb components by different ionic charge. The various components of Hb, including A1c, are separated into six fractions and assayed.

Fasting plasma insulin. A 2.5 ml blood sample was taken from the arm of each participant at the beginning of each testing day (days 1, 29, 57). Blood samples were collected in a serum gel monovette and immediately centrifuged for

10 min at 3000 rpm at 7°C using an Allegra X-22R centrifuge supplied by Beckman Coulter. The resulting supernatant was poured off into an Eppendorf tube and kept at -20°C prior to analysis. Blood insulin levels were established using a solid-phase enzyme-amplified sensitivity immunoassay (Bio-Source INS-EASIA) performed on microtitre plates. The assay uses monoclonal antibodies directed against distinct epitopes of insulin.

Capillary finger prick blood samples. Capillary finger prick blood glucose was sampled pre-dose and 3 h post-dose on days 1, 29 and 57. Blood glucose levels were measured using a Reflotron Plus diagnostic machine and Reflotron test sticks, CV is 1.8% in the normal range and 2.5% in the normal range for repeatability (within-series imprecision) and reproducibility (day-to-day imprecision), respectively (Roche Diagnostics, Germany). The reliability of the test has previously been confirmed⁽¹⁹⁾.

Treatments. Active treatments and placebo capsules (study 1, containing soyabean oil, partly hydrogenated soyabean oil, yellow beeswax, lecithin, yellow iron oxide; study 2, information is not available), matched for size, colour, opacity and odour were provided by the manufacturers. Prior to the commencement of each study, a disinterested third party, who had no other involvement in the study, prepared the treatments for each individual participant (treatment order was counterbalanced and participants were randomly allocated to a treatment regimen) and sealed them in containers marked only with the participant code and study day numbers (1–29; 30–57). Each participant ingested two capsules every day for 57 d (on days 1, 29 and 57 treatments were ingested in the laboratory). The individual capsules contained either an inert placebo or 100 mg *Panax ginseng* extract G115 in study 1 (Pharmaton SA, Lugano, Switzerland) or 100 mg *Panax ginseng* extract in study 2 (Cheong Kwan Jang, Korea Ginseng Corporation, Seoul, Korea). Depending on the condition to which the participant was allocated, the combination of capsules treatments corresponded to a dose of

0 mg (placebo) or 200 mg G115 (study 1) or 200 mg Korean ginseng (study 2).

Procedure

In both study 1 and study 2 participants received each treatment (placebo and 200 mg *Panax ginseng*) for 57 d in total, with an intervening wash-out period of 27 d between treatments when all participants received placebo. Treatment order was counterbalanced across participants and they were randomly allocated to a treatment regimen. Capillary finger prick blood and venous whole blood (2 × 2.5 ml) was sampled on each study day (days 1, 29, 57), in both treatment regimens (placebo and 200 mg), in study 1 and study 2, immediately prior to the ingestion of that day's dose and then again 3 h post-dose (finger prick sample only). Before leaving the laboratory on each study day, participants were provided with a container containing treatments for each day (either days 2–28 or days 30–56) until the next laboratory visit. Treatments on days 1, 29 and 57 of each period were consumed in the laboratory. All participants were in an overnight fasted state during pre-dose blood sampling and each participant consumed an identical breakfast on each of their study days, immediately after treatment ingestion (see Fig. 1). Typical light breakfasts consisted of toast, cereal or fruit (self-selected by the participant) and varied between participants.

Statistics

All data were analysed using the Minitab statistical package version 13.1 (Minitab Ltd, Coventry, UK). Treatment effect on HbA1c and plasma insulin were investigated by two-way repeated measures ANOVA (treatment (placebo, 200 mg) × day (1, 29, 57)) to reveal any chronic effects. Treatment effects on capillary finger prick blood glucose levels were investigated by three-way repeated measures ANOVA (treatment (placebo, 200 mg) × day (1, 29, 57) × session

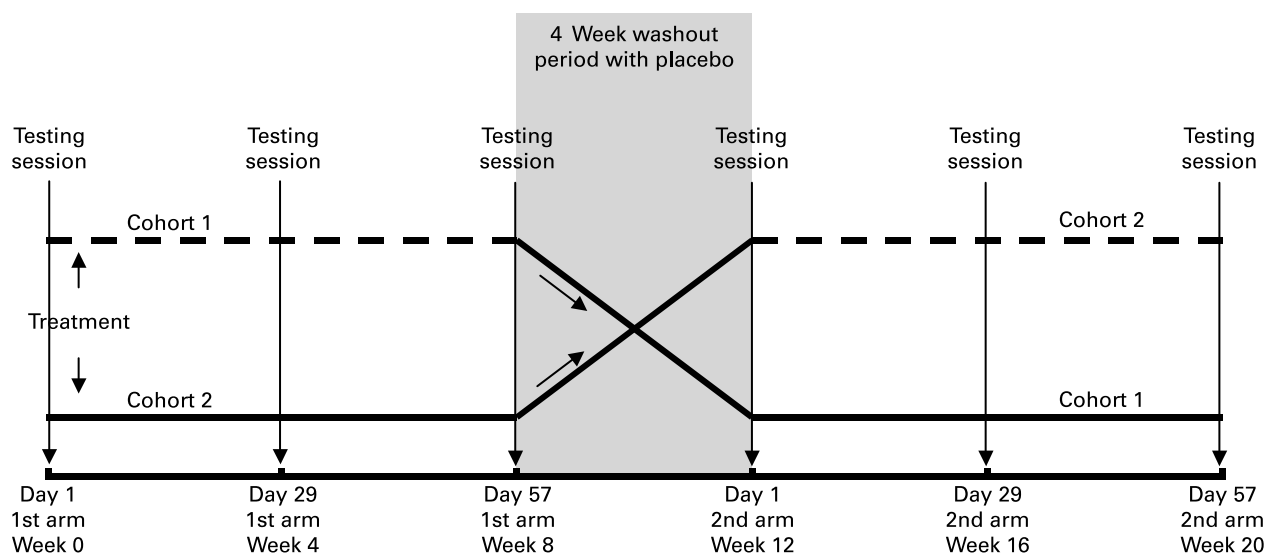


Fig. 1. Timelines of the study. Participants received either placebo (---) or 200 mg ginseng (—) during the first arm of the study (weeks 0–8), and the opposite treatment in the second arm (weeks 12–20). All participants received placebo during the washout period (beginning of week 9 to end of week 12). Testing days took place on days 1, 29 and 57 of each arm.

(pre, post)) to reveal any acute, chronic and superimposed (i.e. acute upon chronic) effect.

Results

Glycated Hb

There was no significant main effect of treatment or interaction with treatment revealed in either study 1 or study 2 (see Table 1).

Fasting plasma insulin

There was no significant main effect of treatment or interaction with treatment revealed in either study 1 or study 2 (see Table 1).

Capillary finger prick blood glucose

There was no significant main effect of treatment or significant interaction with treatment revealed in either study 1 or study 2 (see Table 2).

Discussion

To our knowledge, the present study is the first to assess the effect of chronic ingestion of *Panax ginseng* on indices of glucose regulation in healthy volunteers. The results show that 200 mg *Panax ginseng* from two different sources, ingested daily for 4 and 8 weeks, has no effect on indices of glucose regulation (HbA1c, fasting plasma insulin, fasting plasma glucose). The results also suggest that there is no effect at the acute 3 h measurement point that follows a light breakfast, measured 180 min after ginseng ingestion, in healthy volunteers.

To date there have been a number of studies that have investigated the glycaemic effects, following chronic ingestion, of different members of the genus *Panax* family in a diabetic population. However, only three studies^(8,10,12) give sufficient detail, relating to the extract and dose used, to allow discussion. Two of the three studies have utilised *Panax ginseng*. The results of the present study are at odds

with both of these previous studies. For example, in the first, Tetsutani *et al.*⁽⁸⁾ reported significant reductions in HbA1c following 3–4.5 g *Panax ginseng* administered for 24 months. In the second Vuksan *et al.*⁽¹²⁾ reported significant improvements in nine of the eleven indices of glucose regulation measured, following 12 weeks of *Panax ginseng* supplementation (6 g/d). Interestingly, the two indices that Vuksan failed to find improvements on (i.e. HbA1c and fasting blood glucose levels) are two of the four indices of glucose regulation measured in the present study (however, it should be noted that both previous studies utilised diabetic populations, therefore direct comparisons between the present study, utilising non-diabetics, and these previous studies are problematic). In the third study, Vuksan *et al.*⁽¹⁰⁾ reported the effect following 8-week administration of *Panax quinquefolius* (1 g/d) and reported significant reductions in HbA1c and fasting blood glucose levels (again comparisons are problematic as differences between ginseng type and the population studied may explain the different profile of results). Given the caution advised earlier, the most parsimonious explanation for the discrepancies between the present study and those reported in a diabetic population would be differences in study duration, the extract under investigation and differences in the population studied. Further research is needed to investigate these effects in a non-diabetic population. Additionally, caution is advised when interpreting the present results as there are a number of limitations; the present study had reduced sample size as a result of missing data; the storage of the blood samples (i.e. -20°C) is not recommended as the stability of the sample is questionable and finally there is an imbalance of the number of males and females in study 2.

The present study also allowed further consideration of the acute glycaemic effects of *Panax ginseng* ingestion that followed a light breakfast. The results revealed no difference between treatment and placebo, measured 180 min after ginseng ingestion. The rationale for this measurement point stems from an interest to investigate if the hypoglycaemic effects (previously reported) would persist beyond the clinically relevant 2 h measurement point. This is of interest as no study to date has investigated the glycaemic effects beyond this 2 h point. It is possible that ginseng continues to lower blood glucose levels past normoglycaemic levels

Table 1. Glycated Hb (HbA1c) and fasting plasma insulin levels following 29 and 57 d of consecutive ginseng ingestion (200 mg/d) for two different ginseng extracts in healthy volunteers*

(Mean values with their standard errors)

Treatment	Day 1		Day 29		Day 57		
	Mean	SE	Mean	SE	Mean	SE	
HbA1c (% of total)							
Study 1 (n 18)	Placebo	5.45	0.08	5.32	0.08	5.24	0.08
	200 mg	5.36	0.07	5.38	0.09	5.32	0.09
Study 2 (n 11)	Placebo	5.45	0.11	5.24	0.09	5.21	0.08
	200 mg	5.49	0.11	5.41	0.12	5.23	0.10
Plasma insulin ($\mu\text{IU/ml}$)							
Study 1 (n 17)	Placebo	10.51	0.98	13.85	1.36	13.66	0.94
	200 mg	11.03	0.73	12.93	2.04	14.13	2.90
Study 2 (n 12)	Placebo	13.99	1.53	13.12	0.94	13.57	1.63
	200 mg	13.98	1.16	14.57	1.09	13.12	0.81

* For details of subjects and procedures, see Participants and methods. Study 1 used G115 ginseng and study 2 used Cheong Kwan Jang ginseng.

Table 2. Blood glucose levels (mmol/l) following 29 and 57 d of consecutive ginseng ingestion (200 mg/d) are represented for two different ginseng extracts, in healthy volunteers*

(Mean values with their standard errors)

Study	Treatment	Day 1				Day 29				Day 57			
		Pre-dose		3 h post-dose		Pre-dose		3 h post-dose		Pre-dose		3 h post-dose	
		Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Study 1 (n 23)	Placebo	4.90	0.19	4.94	0.14	5.05	0.11	5.15	0.16	5.00	0.16	5.42	0.11
	200 mg	5.04	0.16	5.07	0.15	5.18	0.15	5.22	0.20	5.29	0.10	5.21	0.16
Study 2 (n 14)	Placebo	5.65	0.14	5.49	0.19	5.39	0.17	5.16	0.19	5.36	0.17	5.30	0.17
	200 mg	5.43	0.16	5.26	0.23	5.53	0.14	5.11	0.34	5.55	0.19	5.41	0.23

* For details of subjects and procedures, see Participants and methods. Study 1 used G115 ginseng and study 2 used Cheong Kwan Jang ginseng. Pre-dose values represent blood glucose levels following an overnight fast and measured prior to the ingestion of that day's ginseng dose. Post-dose values represent blood glucose levels measured 3 h post-dose. A light breakfast was consumed immediately following ginseng dose on each study day.

(normoglycaemic levels are typically reached by 120 min). As the present study is the first study to measure the acute gluco-regulatory effects of ginseng beyond this 2 h point it is not valid to compare results of the present study to those that have measured the glycaemic effect during an oral glucose tolerance test (incorporating the 2 h measurement point) and the fact that participants' blood glucose levels will have returned to normoglycaemic levels. Further research is needed.

The present results may give insight into the safety of *Panax ginseng* use in healthy non-diabetic populations. Despite there being no health risk associated with the acute postprandial hypoglycaemic properties of ginseng (these effects being considered advantageous in diabetic populations), there may be some concerns relating to the duration of these effects and further concerns when such products are ingested in a fasted state. One might assume that the actions of glucagon would counteract any further hypoglycaemic effect, once glucose levels have returned to normal levels following a challenge, at later time-points. However, such a control mechanism did not appear in a group of healthy volunteers whose fasted blood glucose level dropped by as much as 20%, when measured 120 min after *Panax ginseng* ingestion (no later time-points were measured)⁽¹³⁾. Therefore, the present results suggest that ginseng's acute hypoglycaemic effect does not continue once glucose levels have normalised, after consuming a light breakfast (obviously, we cannot comment if ginseng lowered blood glucose levels at earlier time-points and we cannot comment if this effect would be the same, if participants were fasted overnight). This is of particular interest as *Panax ginseng* is by far the most commonly consumed member of the genus, not only for its purported health benefits but also for its effect on human behaviour⁽²⁰⁾.

The mechanisms underlying ginseng's glycaemic effects are not clear at present. However, animal and human data would suggest three possible mechanisms that could potentially account for the modulation in blood glucose levels: (1) modulation of glucose uptake; (2) modulation of glucose disposal; (3) modulation of insulin secretion. For example, Lai *et al.*⁽²¹⁾ showed ginsenoside Rh₂ led to reductions in plasma glucose levels and an overexpression of the GLUT4 glucose transporter in rats. Wang *et al.*⁽²²⁾ provided evidence that ginseng increases aerobic glycolysis through enhancing the activities of citrate synthetase, malate dehydrogenase and succinate dehydrogenase, cytochrome oxidase (four

rate-limiting enzymes in aerobic glycolysis). Chung *et al.*⁽²³⁾ reported that 50 mg/kg aqueous *Panax ginseng* root body and rootlets administered for 28 d decreased the activity of the rate-limiting gluconeogenic enzyme glucose-6-phosphatase in liver preparations in diabetic mice by 46 and 20%. Liu *et al.*⁽²⁴⁾ provided evidence that the oral ingestion of *Panax ginseng* improved insulin sensitivity that resulted in the modulation (i.e. lowering) of circulating glucose levels.

In conclusion, the present study suggests that the chronic ingestion of *Panax ginseng* has no effect on indices of glucose regulation in a non-diabetic sample. Additionally, there was no difference in glucose levels when measured 180 min post-dose. Further research is needed.

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