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Short Communication

The glycaemic effects of single doses of *Panax ginseng* in young healthy volunteers

J. L. Reay, D. O. Kennedy and A. B. Scholey*

Human Cognitive Neuroscience Unit, Division of Psychology, Northumbria University, Newcastle upon Tyne NE1 8ST, UK

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The results of two acute placebo-controlled, double-blind cross-over studies assessing the effect of *Panax ginseng* (G115) on blood glucose levels are reported. In study 1, thirty participants received three treatments: placebo; 200 mg G115; 400 mg G115. In study 2, twenty-seven participants received four treatments: placebo (0 mg ginseng and 30 mg saccharin); ginseng (200 mg ginseng and 30 mg saccharin); placebo–glucose (0 mg ginseng and 25 g oral glucose); ginseng–glucose (200 mg ginseng and 25 g oral glucose). Blood glucose levels were measured at baseline (at 09.00 hours after an overnight fast) and then 60, 90 (study 1 only) and 120 min post-dose. Both studies demonstrated that G115 alone significantly lowers fasting blood glucose levels. Conversely, in study 2 there was a significant drink × ginseng interaction suggesting opposing glycaemic effects of ginseng under fasting and raised blood glucose conditions. These data have implications for the use of ginseng in individuals with poor gluco-regulation.

Panax: Ginseng: Acute: Placebo: Blood glucose: Hypoglycaemia: Healthy adults

The number of diagnosed diabetes sufferers continues to rise exponentially (Mokdad *et al.* 2003) and the currently available armamentarium is insufficient to halt the disease progression. The majority of type 2 diabetes patients eventually require insulin therapy (Turner *et al.* 2000), and it is estimated that diabetes is likely to be the fifth leading cause of death globally (Roglic *et al.* 2005). While the use of mainstream drugs is advocated by some physicians, many patients are more inclined toward the use of alternative therapies including food supplements and herbal medicines (Shane-McWorter, 2005). Despite a lack of evidence for their safety and efficacy, the use of herbal products increased substantially through the 1990s, with over 60% failing to report the use of these products to their physician (Eisenberg *et al.* 1998).

‘Ginseng’ usually refers to the dried root of several species in the plant genus *Panax* (Araliaceae family). The most widely used is *Panax ginseng* (G115), which is indigenous to the Far East. Other members of the genus include *Panax quinquefolius* (American ginseng), *Panax notoginseng* and *Panax japonicus*. Ginseng is known to have gluco-regulatory properties. For example, a decrease in fasting blood glucose and HbA1c was reported in type 2 diabetic patients following 8 weeks administration of a proprietary extract of *Panax quinquefolius*, taken 40 min before each meal (Vuksan *et al.* 2000b). Additionally, reductions in blood glucose levels were reported during a standard oral glucose tolerance test

in diabetic patients following 3, 6 and 9 g *Panax quinquefolius* and in healthy participants administered 1, 2 and 3 g (Vuksan *et al.* 2000a,b, 2001). With regard to G115, reduced fasting blood glucose levels and glycated Hb (HbA1c) were found following 8 weeks administration to type 2 diabetic patients (Sotaniemi *et al.* 1995). Similarly, 24 months of treatment with G115 decreased HbA1c in type 2 diabetics (Tetsutani *et al.* 2000). We report here the glycaemic results of two studies that assessed the effects of single doses of G115 on blood glucose levels in healthy volunteers.

Method

Two separate placebo-controlled, double-blind, crossover studies were undertaken in healthy young adults. All participants were recruited through university advertisement. Prior to participation each participant gave informed consent and completed a medical health questionnaire. All participants reported that they were in good health, and that they were free from heart disorders, high blood pressure, respiratory disorders, epilepsy, panic attacks and diabetes. Additionally, they reported being free from ‘over the-counter’ treatments, illicit social drugs and prescribed medications, with the exception, for some female volunteers, of the contraceptive pill. All participants self-reported they were in an overnight fasting state and were alcohol-free for at least 12 h prior to the 09.00

hours baseline blood glucose measurements (which were all consistent with expected overnight fasting blood glucose levels in healthy volunteers). Both studies were approved by the Northumbria University Division of Psychology Ethics Committee and conducted in accordance with the Declaration of Helsinki.

In study 1, sixteen female and fourteen male participants (mean age 22.6 (SD 5.46) years) received 200 mg ginseng, 400 mg ginseng and placebo on separate days. In study 2, ten female and seventeen male participants (mean age 21.89 (SD 4.64) years) received four treatments: placebo (0 mg G115 and 30 mg saccharin), ginseng (200 mg G115 and 30 mg saccharin), placebo–glucose (0 mg G115 and 25 g oral glucose) and ginseng–glucose (200 mg G115 and 25 g oral glucose) on separate days. Participants in the second study received their capsule treatment (200 mg G115 or 0 mg G115) at time-point zero and then 30 min later, a 200 ml drink (20 ml sugar-free fruit cordial and 180 ml tap water) containing 25 g glucose or 30 mg saccharin. The timing of administration of each treatment was selected on the basis that ginseng's gluco-regulatory effects are evident within 1 h of administration while glucose levels peak at around 30 min post-ingestion. In both studies, treatments were separated by a 7 d washout period and were counterbalanced across participants and days. Capillary blood glucose levels were measured at baseline then 60 min, 90 min (study 1 only) and 120 min post-dose (in study 2 the timings were calculated from the ingestion of the ginseng or placebo capsule treatment) utilising a Reflotron Plus diagnostic machine and test sticks (Roche Diagnostics, Mannheim, Germany). The reliability of the test has previously been confirmed (Price & Koller, 1988).

Results

Statistics

Prior to analysis of 'change from baseline' data, raw baseline scores for the three treatment conditions (placebo, 200 mg, 400 mg) in study 1 and for all four treatment conditions in study 2 (placebo, ginseng, placebo–glucose, ginseng–glucose)

were subject to one-way repeated measures ANOVA using the Minitab statistical package version 13.1 (Minitab Ltd, Coventry, UK).

'Change from baseline' post-dose blood glucose levels were analysed using the Minitab statistical package version 13.1. Following an initial repeated measures ANOVA (study 1, treatment \times time of blood sample; study 2, ginseng \times drink \times time of blood sample) *a priori* planned comparisons were made between placebo and each of the active treatments (200 and 400 mg G115) at each time-point utilising *t* tests with MS_{Error} as an error term (Keppel, 1991). To ensure the overall protection level against Type I error, comparisons were strictly planned prior to commencement of the study, only probabilities associated with planned comparisons were calculated, all planned comparisons were two-tailed.

Baseline

There were no significant differences in baseline blood glucose levels revealed in study 1 ($F_{(2,58)} 2.66, P=0.08$) nor study 2 ($F_{(3,78)} 2.25, P=0.09$) (see Table 1).

Study 1

The initial repeated measure ANOVA (treatment \times time of blood sample) revealed a significant main effect of treatment on blood glucose level ($F_{(2,116)} 3.59, P=0.034$), but there was no significant treatment \times time-point interaction ($F_{(4,116)} 1.49, P=0.210$). Planned comparisons comparing each treatment to placebo at each time-point revealed that there were significant reductions in blood glucose levels for both ginseng treatments at all post-dose time-points relative to placebo (Table 1): 200 mg led to reductions at 1 h post-dose ($t_{116} 3.31, P=0.001$), after 90 min ($t_{116} 3.65, P=0.0003$) and 120 min post-dose ($t_{116} 2.58, P=0.01$). The 400 mg treatment also led to reductions at 1 h post dose ($t_{116} 3.42, P=0.0007$), after 90 min ($t_{116} 3.57, P=0.0004$) and 120 min post-dose ($t_{116} 5.50, P=0.0000001$).

Table 1. The effects of *Panax ginseng* (G115) on capillary blood glucose levels in healthy human volunteers‡ (Mean values with their standard errors)

| | Pre-dose baseline blood glucose level (mmol/l) | | Post-dose change from baseline blood glucose level (mmol/l) | | | | | |
|-----------------------|--|-------|---|-------|-----------|-------|-----------|-------|
| | Mean | SEM | 60 min | | 90 min | | 120 min | |
| | | | Mean | SEM | Mean | SEM | Mean | SEM |
| Study 1 (n 30) | | | | | | | | |
| Placebo | 5.336 | 0.211 | -0.076 | 0.248 | 0.034 | 0.258 | 0.013 | 0.216 |
| 200 mg G115 | 5.681 | 0.159 | -0.646*** | 0.176 | -0.594*** | 0.198 | -0.432* | 0.182 |
| 400 mg G115 | 5.939 | 0.996 | -0.664*** | 0.214 | -0.580*** | 0.212 | -0.933*** | 0.213 |
| Study 2 (n 27) | | | | | | | | |
| Placebo | 5.229 | 0.125 | -0.198 | 0.126 | | | -0.721 | 0.114 |
| 200 mg G115 | 5.462 | 0.112 | -0.630††† | 0.096 | | | -0.708 | 0.121 |
| Glucose (25 g drink) | 5.338 | 0.153 | 1.739††† | 0.206 | | | -0.923 | 0.156 |
| G115–glucose | 5.077 | 0.122 | 1.980††† | 0.268 | | | -0.603 | 0.151 |

Mean values were significantly different from those of the study 1 placebo group: * $P<0.05$; *** $P<0.001$.

Mean values were significantly different from those of the study 2 placebo group: ††† $P<0.001$.

‡ For details of procedures, see p. 639.

Study 2

A repeated measure ANOVA (ginseng \times drink \times time of blood sample) revealed a significant ginseng \times drink interaction on capillary blood glucose levels ($F_{(1,26)} 5.26, P=0.03$). The pattern of results, taken across the two post-dose measurements, suggests that the co-administration of ginseng with glucose served to further increase blood glucose levels (mean of both time-points 0.688 mmol/l) as compared with glucose alone (mean 0.407 mmol/l). Conversely, in the absence of a glucose drink ginseng serves to further reduce blood glucose levels (mean -0.669 mmol/l) as compared with the saccharin condition (mean -0.458 mmol/l).

Planned comparisons, comparing each treatment with placebo at each time-point, revealed that the ingestion of oral glucose alone (placebo–glucose condition; $t_{26} 9.40, P<0.001$) and in combination with 200 mg ginseng (ginseng–glucose condition; $t_{26} 10.570, P<0.001$) led to significantly increased blood glucose levels at the 1 h post-dose measurement point compared with placebo (Table 1). There were no significant differences between the placebo–glucose and ginseng–glucose conditions on blood glucose levels. However, following the ingestion of ginseng alone (ginseng–placebo condition), blood glucose levels were significantly reduced 1 h post-dose ($t_{26} 2.096, P=0.046$).

Discussion

Both study 1 and study 2 demonstrated that a single acute dose of G115 can significantly lower blood glucose levels in healthy, overnight fasted volunteers. Additionally, study 2 revealed a significant interaction between the administration of 25 g oral glucose drink and 200 mg ginseng. This significant pattern of results suggests that in the absence of a glucose load (i.e. in overnight fasting participants) a single dose of G115 (200 mg) resulted in a post-dose fall in circulating blood glucose levels, relative to placebo. However, in the presence of elevated glucose levels following an oral glucose drink, the co-administration of ginseng was associated with further raised blood glucose levels, relative to the glucose condition, although no significant increase was revealed at any individual time-point on the planned comparisons, relative to the glucose condition. Both study 1 and study 2 are indicative of G115's gluco-modulating properties in young non-diabetic participants.

It should be noted that in both studies baseline differences were not significant; however, there was a trend for significant differences ($0.05 < P < 0.1$) in both studies. While it is feasible that this may have contributed to the magnitude of the treatment effects observed in study 1, where treatment effects tended to be in the opposite direction to initial condition effects, this was not the case for study 2. Therefore, it appears that the present data represent real physiological effects of G115 rather than a reflection of chance baseline differences between the conditions. Clearly further replication of the present findings are needed, as is more research directed at delineating the glycaemic properties of G115 in healthy and patient populations.

The present results are dissimilar to the recently reported hypoglycaemic effects of a different ginseng species, *Panax quinquefolius*, during standard oral glucose tolerance tests in

both diabetic and healthy participants (Vuksan *et al.* 2000a,b, 2001) and are inconsistent with two reports of G115 being associated with significantly increased blood glucose levels and insulin responses following a 75 g glucose load (Sievenpiper *et al.* 2003, 2004) suggesting that different *Panax* species produce differing glycaemic responses. With regard to American ginseng (*Panax quinquefolius*), Vuksan *et al.* (2000a) have suggested three possible mechanisms: modulation of glucose disposal, glucose transport or insulin secretion. The three are not mutually exclusive and the latter two may both be mediated by increased NO production (Roy *et al.* 1998; Spinas *et al.* 1998). The mechanisms responsible for the glycaemic effects of Korean ginseng reported here may reflect similar processes possibly with different levels of insulin receptor binding reversibility (although the biological plausibility of this speculative idea remains to be investigated). The exact processes affected by this herbal extract remain unknown and may reflect complex additive or synergistic effects on several physiological systems involved in gluco-regulation (see Scholey *et al.* 2005). Until further research has delineated the mechanisms underlying ginseng's gluco-regulatory effects, generalisations should not be made between the effects of different ginseng species. Sufferers from diabetes and similar conditions should exercise caution in the use of ginseng products.

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