North American Ginseng Exerts a Neutral Effect on Blood Pressure in Individuals With Hypertension

P. Mark Stavro, Minna Woo, Tibor F. Heim, Lawrence A. Leiter, Vladimir Vuksan

Abstract—An early observational study suggested that ginseng could elevate blood pressure. This caused concern because 4.5% of American adults use ginseng, with a popular choice being North American ginseng. To date, North American ginseng lacks hemodynamic evaluation; therefore, we conducted a randomized, double-blinded, controlled trial to investigate its effect on blood pressure in 16 hypertensive individuals (mean±SD age 61.1±8.1 years; systolic/diastolic blood pressure 132.4±12.8/83.3±8.1 mm Hg; 13 on antihypertensives). We used 6 batches of North American ginseng root that varied in quality and ginsenoside content, representing the spectrum of this ginseng on the market. On 8 mornings, each participant was fitted with an ambulatory blood pressure monitor, which measured blood pressure during a 30-minute baseline period. Each participant then consumed in a randomized and double-blind fashion 3 g of encapsulated treatment: placebo (on 2 mornings) or powdered North American ginseng (on 6 mornings). After treatment, blood pressure was measured every 10 minutes for 160 minutes, and its change at each post-treatment time point relative to baseline was determined per individual and averaged, and the mean was obtained for the overall 160-minute period. None of the North American ginsengs or their mean differed from placebo in their effect on overall (160 minutes) mean blood pressure change. None affected blood pressure versus placebo at the 10-minute intervals; but their mean versus placebo increased systolic and diastolic blood pressure at 140 and 160 minutes, respectively, and lowered diastolic blood pressure at 100 minutes. The findings together suggested that North American ginseng exerts a neutral acute effect on blood pressure in hypertensive individuals. (Hypertension. 2005;46:1-6.)

Key Words: clinical trials ■ blood pressure ■ hypertension, essential ■ ginsenoside ■ nutrition

Ginseng is an herb that grows in temperate regions of Asia and North America. Populations value its root for medicinal purposes, but there is suggestion that it might elevate blood pressure (BP). This is based on an observational study by Siegel published >25 years ago, which found that hypertension developed in 16 adults reporting the use of ginseng root. In response, medical commentators recommend that hypertensive individuals avoid ginseng.

More recently, animal studies and randomized controlled clinical trials (RCTs) show that Panax ginseng, the most consumed species of ginseng in the United States, exerts a neutral or lowering effect on BP. Although these outcomes contrast Siegel’s finding, it should be noted that they pertain to a single ginseng species. Another commonly consumed species of ginseng in the United States is P. quinquefolius, or North American ginseng (NAG), which ranks second to P. ginseng for use. Together, these species comprise most of the ginseng that ~9 million American adults consume annually. However, to date, the effect of NAG on BP is unknown and could be important to address because this herb is used widely and acts biologically different from other ginseng species.

The importance of determining the effect of NAG on BP also holds from a phytochemical perspective. All ginsengs contain a group of triterpene glycosides called ginsenosides, which show antihypertensive efficacy in animals. Because the content of NAG and profile of ginsenosides differs from P. ginseng, its potential effect on BP cannot be inferred from the latter and requires independent scrutiny. Also, batches of NAG may vary in their content of ginsenosides and may consequently yield inconsistent hemodynamic effects. Thus, to comprehensively determine the effect of NAG on BP, multiple batches need to be tested.

Therefore, we determined the acute effect of 6 batches of NAG (differing in quality and ginsenoside content) on BP in hypertensive individuals. The batches originated from 6 farms in Ontario and were chosen to represent the spectrum of NAG cultivated in this region, which supplies >60% of NAG worldwide. Accordingly, we were able to address whether different batches of the same ginseng species, varying in quality and phytochemistry, affected BP.
Methods

Participants

Nineteen individuals provided written informed consent to participate. Inclusion required them to be 18 to 75 years of age and have hypertension, as defined by the use of antihypertensives, or a seated systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg at each of 3 separate prestudy visits. Exclusion criteria included secondary hypertension, diabetes, kidney or liver disease, unstable angina, ginseng, or other herbal use in the previous 2 months or during the study, and body weight changes of > 2.2 kg between visits. Sixteen participants adhered to the study protocol, and their baseline characteristics are provided (Table 1). They included 12 males and 4 females with hypertension, with a mean ± SD age of 61.1 ± 8.1 years, body mass index of 30.4 ± 6.8 kg/m², and well-controlled office systolic/diastolic BP of 132.4 ± 12.2/83.3 ± 10.3 mm Hg; 13 of the participants were treated with antihypertensives. Their fasting serum glucose, estimated creatinine clearance, and liver function were normal. The research ethics board at St. Michael’s Hospital approved the study; also, the procedures followed were in accordance with the guidelines of St. Michael’s Hospital.

Treatments

We tested a 3-g dose of 2 identical cornstarch placebos and 6 batches of dried whole NAG root. Each batch consisted of 3- or 4-year-old dried whole NAG root. The batches were selected by the Ontario Ginseng Growers Association to represent the spectrum of NAG on the market; batches were chosen according to price, which was determined by age and appearance (and indicated by price). The absence of ginsenoside Rf, found in P. ginseng but not NAG, indicated NAG authenticity (Table 2). Each NAG root batch was ground into powder and packed into identical #00 (500 mg) capsules, as was placebo; NAG and placebo were encapsulated and coded by a person independent of the study.

Protocol

On 8 mornings (8 AM to 10 AM), participants arrived at our clinic fasted (10 to 12 hours) and off their antihypertensives (previous 12 to 24 hours). They had body weight measured, sat for 5 minutes, and then had office BP measured 3×. Next, they were fitted with an ambulatory BP monitor (ABPM) that took BP at 5-minute intervals for 30 minutes, totaling 7 measures; the mean of the latter 6 measurements was used as baseline BP. Then, in a double-blind and random sequence, they consumed 300 mL of water with 3 g of 1 of the 8 treatments; this represented time of 0 minutes. For the next 160 minutes, the ABPM measured BP at 10-minute intervals; immediately after the 60-minute measurement, a 356-mL (380 kcal) Ensure meal was provided after the 60-minute measurement. Accordingly, the effect of NAG on BP was determined during fasting and after a nutritionally complete breakfast, mimicking a typical morning. Each participant remained seated for the entire protocol and consumed 1 of either the 6 NAGs or 2 placebos per visit but consumed all treatments in total. Each visit was separated by a 7-day washout.

BP Measurement

Office BP measurements were performed as described previously. Briefly, 3 readings were obtained from the right arm of seated participants while their arm was supported at heart level; 1 trained observer took all measures and used a mercury sphygmomanometer (Baumanometer; W.A. Baum). For ABP measurements, participants were fitted with a SpaceLabs 90207 ABPM. The cuff was secured around the participant’s nondominant arm, and it remained there during the entire test. All measurements were taken while the participants were seated with their arm at heart level. Measurements were automatically repeated if an error occurred. The adult cuff and the large adult cuff were used for arm circumferences of 24 to 31 cm and 32 to 42 cm, respectively.

Study Outcomes and Analyses

For each NAG and placebo, the post-treatment change in systolic and diastolic BP as well as pulse pressure (systolic BP–diastolic BP) relative to baseline were calculated at 10-minute intervals per individual and averaged. Comparisons were made between the mean change associated with: (1) each NAG treatment, and (2) the mean of the 2 placebos at these intervals and the entire 160-minute post-treatment period. Repeated-measures ANOVA with the Tukey–Kramer multiple comparisons test assessed which treatments were different. Also, comparisons were made between the mean change associated with: (1) the mean of the 6 NAG treatments, and (2) the mean of the 2 placebos at the 10-minute intervals and for the entire

**TABLE 1. Baseline Characteristics of the 16 Participants**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males/females</td>
<td>12/4</td>
</tr>
<tr>
<td>Age (years)</td>
<td>61.1 ± 8.1</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>30.4 ± 6.8</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>132.4 ± 12.2</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>83.3 ± 10.3</td>
</tr>
<tr>
<td>Antihypertensive agents</td>
<td>13 Yes, 3 No</td>
</tr>
<tr>
<td>No. taking 1 agent/n = 2 Agents</td>
<td>7/6</td>
</tr>
<tr>
<td>No. taking specific agents</td>
<td>ACE (6)†, ARB (2)‡, BB (2)§, CCB (3)¶, D (6)#</td>
</tr>
<tr>
<td>Fasting serum glucose (mmol/L)</td>
<td>4.7 ± 0.4</td>
</tr>
<tr>
<td>Creatinine clearance (mL/min)</td>
<td>93.5 ± 28.5*</td>
</tr>
<tr>
<td>Alanine transferase (units)</td>
<td>20.9 ± 4.8</td>
</tr>
<tr>
<td>Aspartate acid transferase (units)</td>
<td>24.8 ± 5.3</td>
</tr>
</tbody>
</table>

Data expressed as mean ± SD.

*Estimated by the Cockcroft–Gault equation.

†ACE indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, β-blocker; CCB, calcium channel blocker; D, diuretic.

‡Ramipril n = 4; isosorbid n = 1; enalapril n = 1; telmisartan n = 2; †facebutolol n = 1; atenolol n = 1; ‡amiodipine n = 3; #hydrochlorothiazide n = 5; furosemide n = 1.

**TABLE 2. Quality Indicators and Ginsenoside Profile of the 6 NAG Batches That Were Cultivated on 6 Separate Farms**

<table>
<thead>
<tr>
<th>Quality Indicator</th>
<th>Farm A</th>
<th>Farm B</th>
<th>Farm C</th>
<th>Farm D</th>
<th>Farm E</th>
<th>Farm F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Price ($/kg)†</td>
<td>46</td>
<td>51</td>
<td>40</td>
<td>44</td>
<td>55</td>
<td>33</td>
</tr>
<tr>
<td>Ginsenoside</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (mg/g)</td>
<td>65.6</td>
<td>62.8</td>
<td>63.4</td>
<td>56.5</td>
<td>51.6</td>
<td>53.3</td>
</tr>
<tr>
<td>PPT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (mg/g)</td>
<td>18.3</td>
<td>16.0</td>
<td>15.0</td>
<td>16.0</td>
<td>14.0</td>
<td>13.8</td>
</tr>
<tr>
<td>Re (mg/g)</td>
<td>1.7</td>
<td>0.8</td>
<td>1.1</td>
<td>1.2</td>
<td>1.1</td>
<td>1.3</td>
</tr>
<tr>
<td>Rf (mg/g)</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Rb1 (mg/g)</td>
<td>16.7</td>
<td>15.2</td>
<td>13.9</td>
<td>14.8</td>
<td>12.9</td>
<td>12.5</td>
</tr>
<tr>
<td>Rb2 (mg/g)</td>
<td>40.9</td>
<td>41.5</td>
<td>41.9</td>
<td>33.3</td>
<td>32.5</td>
<td>32.9</td>
</tr>
<tr>
<td>Rd (mg/g)</td>
<td>0.6</td>
<td>0.4</td>
<td>0.4</td>
<td>0.6</td>
<td>0.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Rg1 (mg/g)</td>
<td>3.3</td>
<td>2.2</td>
<td>2.5</td>
<td>3.8</td>
<td>2.4</td>
<td>2.9</td>
</tr>
<tr>
<td>Rg2 (mg/g)</td>
<td>2.5</td>
<td>2.7</td>
<td>3.6</td>
<td>2.7</td>
<td>2.4</td>
<td>3.2</td>
</tr>
</tbody>
</table>

*Age represents the No. of years from seeding.
†Price is in Canadian dollars.
160-minute period after treatment. A paired t test was used to determine significant differences.

Ginsenoside Analysis

Each NAG batch had its ginsenoside content determined by high-performance liquid chromatography.17

Results

All participants followed the study protocol without difficulty and reported no side effects after consumption of the 6 NAG samples and 2 placebos. Each participant consumed the NAGs and placebos within the required time with all of the water. Also, all participants consumed the Ensure meal at 60 minutes within the required 10 minutes.

Body Weight and Medications

Two participants showed a body weight change >2.2 kg between visits, and another consumed multivitamins and other herbal products on the morning of visits; consequently, their data were excluded from analysis. Overall, the data of 16 participants were included in the analysis. 13 of these participants were on antihypertensives, and they held their antihypertensive types, doses, and times of consumption constant throughout the entire duration of the study (~8 weeks).

BP Changes After Consumption of American Ginseng and Placebo

No significant differences occurred between the 6 separate NAG- and placebo-associated mean changes in systolic BP, diastolic BP, and pulse pressure at each of the 10-minute intervals (data not shown). No significant differences occurred between the 6 NAG- and placebo-associated mean changes in systolic BP, diastolic BP, and pulse pressure for the entire 160-minute post-treatment period (Table 3). The mean±SEM change in systolic and diastolic BP relative to baseline after NAG consumption ranged from 1.3±1.0 to 4.8±1.7 mm Hg and −2.2±1.0 to −0.8±0.7 mm Hg, respectively; the changes in these parameters after placebo were 2.4±1.0 and −1.2±0.8 mm Hg, respectively. The mean±SEM change in pulse pressure relative to baseline after the consumption of NAG ranged from 2.0±0.9 to 6.0±1.0 mm Hg, and for placebo, it was 3.6±0.8 mm Hg. The mean±SEM change in pulse pressure between Farm A and Farm E was significantly different (2.0±0.9 versus 6.0±1.0 mm Hg; P<0.05). None of the baseline systolic BP, diastolic BP, and pulse pressure values associated with the treatments differed significantly.

BP Change for Average of All NAGs and Placebo

For systolic BP, there was a significant difference at the 160-minute time point between the average of 6 NAGs and placebo (NAG 1.6±1.1 mm Hg versus placebo −1.6±1.2 mm Hg; Figure, A). For diastolic BP, there was a significant difference at the 100-minute time point (NAG −5.4±0.9 mm Hg versus placebo −3.4±1.0 mm Hg) and the 140-minute time point (NAG −3.2±0.8 mm Hg versus placebo −4.8±1.1 mm Hg) between the average of 6 NAGs and placebo (Figure, B). Pulse pressure changes between the average of the 6 NAGs and placebo did not differ (Figure, C). There was no significant difference between the average of the 6 NAGs and placebo on total post-treatment change in systolic BP, diastolic BP, and pulse pressure (Table 3).

Ginsenoside Profile

All 6 NAG batches showed a characteristic profile and content of ginsenosides that had a protopanaxatriol (PPT) or protopanaxadiol (PPD) triterpene backbone. The ginsenoside content of the batches did not differ (Table 2). All samples were authentic P. quinquefolius L.

Discussion

We found that the consumption of NAG versus placebo caused an overall neutral effect on BP in hypertensive individuals. This was demonstrated with 6 batches of NAG that differed in quality and ginsenoside profile and that were cultivated on 6 different farms in Ontario. The conclusion that NAG exerted a neutral effect on BP was based on 2 observations. First, when the separate batches were compared...
with each other and placebo, or their mean was compared versus placebo, no difference in effect was seen on overall change in systolic or diastolic BP during the entire 160-minute post-treatment period (Table 3). Second, none of the individual NAG batches showed a significant effect on BP relative to each other or placebo at the 10-minute interval time points (data not shown). However, it should be noted that the mean of the 6 NAGs relative to placebo significantly increased systolic and diastolic BP at 160 and 140 minutes, respectively, and also significantly decreased diastolic BP at 100 minutes (Figure). However, these differences could be considered clinically insignificant because the overall change in BP with NAG did not differ from placebo for the entire 160-minute period.

The outcome of this study can be extrapolated to the majority of NAG root marketed worldwide. A few lines of reasoning support this. First, ~60% of NAG root marketed globally originates from Ontario. Second, our 6 batches were representative of the 180 NAG crops from Ontario, as determined by the Ginseng Growers Association of Ontario. The batches grew in various soils and were cultivated differently, which yielded batches of varying quality, indicated by price (Table 3). Third, the batches had a typical NAG ginsenoside profile, lacking ginsenoside Rf and containing a low PPT/PPD ginsenoside ratio. The findings of this study are significant in light of the form and dose of NAG used, as well as the study design used. We used whole dried root, which is the primary, or natural, form of NAG that cultivators sell to marketers and manufacturers. Specifically, we avoided using water, ethanol, or glycerin extracts of NAG, which would have contained only NAG compounds soluble within these solvents. This would have precluded accurate interpretation of the BP effect of NAG. Thus, we tested the whole root to evaluate its components within their native matrix.

We administered NAG at a dose of 3 g for the following rationales. First, traditional Chinese medicine has recommended that the therapeutic dose of ginseng ranges from 3 to 10 g. Second, 3 g was the average intake of ginseng associated with elevated BP in Siegel’s study. Therefore, to remain consistent with this literature, a 3-g dose was administered. Furthermore, our previous studies with P ginseng or NAG used a 3-g dose.

We used an acute study design, similar to the procedure applied to the evaluation of new antihypertensive agents. As well, given the uncertainty of the effect of NAG on BP, and in light of Siegel’s observational findings, we opted to use an acute rather than chronic model. Within this experimental design, the primary outcome was change in BP relative to baseline. As shown in the Figure, the consumption of NAG or
placebo was associated with a steady rise in BP until the 60-minute time point, which is typical for hypertensive individuals during their transition from sleep to wakefulness in the morning.\textsuperscript{27,28} Also, after the meal at 60 minutes, BP decreased, which commonly occurs in hypertensive individuals.\textsuperscript{29,30} Overall, NAG and placebo consumption similarly affected BP during the morning hours after waking and eating.

The effect of NAG and \textit{P ginseng} on BP can be compared. The latter exists in a dried or steamed form, and both have been tested for their effects on BP. In a recent RCT, an extract of dried \textit{P ginseng} acted neutrally on BP in healthy individuals.\textsuperscript{8} Because an extract was used, and no ginsenoside details were provided, the study cannot be accurately compared with the current study. As for steamed \textit{P ginseng},\textsuperscript{7} we previously showed it to lower BP in a similarly designed study to the current, with the primary difference being the type of ginseng tested and its ginsenoside profile. Because the ginsenosides are the only ginseng component shown to have antihypertensive activity,\textsuperscript{5,6} the differing profile of ginsenosides between the 2 ginsengs may have underpinned the unique BP effects. In particular, NAG lacks ginsenoside Rg\textsubscript{2}, which is the most potent vasodilating ginsenoside; steamed \textit{P ginseng} is the only marketed ginseng to contain this ginsenoside.\textsuperscript{31,32} Thus, its absence could partly explain the neutral effect of NAG on BP.

The potential for ginseng to cause adverse events and interact with drugs should be considered. Coon and Ernst systematically reviewed 146 clinical trials representing >8500 individual exposures to ginseng and found it to have the same adverse event profile as placebo.\textsuperscript{33} The most common events included headache, nausea, restlessness, and sleeplessness. In our studies, we have seen that ginseng has the same adverse event profile as placebo.\textsuperscript{10,23–25,34} Considering drug interactions, an RCT by Yuan et al.\textsuperscript{35} showed that ginseng can interfere with warfarin metabolism, whereas another RCT showed no effect on the metabolism of this drug.\textsuperscript{36} Overall, hypertensive individuals who choose to consume NAG should be aware of its neutral effect on BP, its overall safety, and its potential to interact with warfarin.

The current study was limited in 3 ways. First, only the acute effect of NAG on BP was measured. Second, although antihypertensives were not taken on the test mornings, they were taken 12 to 24 hours beforehand, and could have thus residually affected BP. Still, throughout the study period, participants held the type, dose, and timing of their antihypertensives constant; as well, each participant underwent testing at the same time at each of his/her 8 visits. Thus, the study was designed to ensure that each participant would possess very similar blood chemistry, namely the blood profile of antihypertensive compounds and their metabolites, at each of his/her 8 visits. A third limitation was the disproportionate number of females (n=4) to males (n=12), which precluded sex-related comparisons.

\section*{Perspectives}

The current study was the first to demonstrate the effect of NAG on BP. It showed that 6 representative batches of NAG, regardless of quality or ginsenoside profile, had a neutral effect on BP in hypertensive individuals. This widens our perspective on the topic of ginseng and BP, which commenced >25 years ago with an observational study that implicated ginseng in causing hypertension. Since then, animal studies have demonstrated that \textit{P ginseng} potently stimulates vasodilation and lowers BP, whereas clinical trials found it to act neutrally or beneficially on BP. Now, the clinical effect of NAG on BP is beginning to be unraveled. Future studies should determine the effect of chronic NAG consumption on long-term changes in BP before recommendations are formed for its use in hypertensive individuals. In summary, this study, together with the previous studies on \textit{P ginseng}, highlight the importance of ginseng species and the study design in determining the effect of ginseng on BP. Further understanding of the effect of ginseng on BP is necessary given the potential overlap between the 4.5% prevalence of ginseng use and the >20% prevalence of hypertension among American adults.

\section*{Acknowledgments}

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\section*{References}


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