Long-Term Intake of North American Ginseng Has No Effect on 24-Hour Blood Pressure and Renal Function

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

Abstract—Ginseng is consumed by 10% to 20% of adults in Asia and by up to 5% in Western countries. Despite observational evidence suggesting a link between its intake and the development of hypertension, there remains no long-term scrutiny for its effect on blood pressure (BP). We therefore undertook a randomized, placebo-controlled, double-blinded, crossover trial in 52 hypertensive individuals to determine the effect of 12-week North American ginseng intake on 24-hour BP; we also measured serum cystatin C as a marker of renal function. After a 4-week placebo run-in, we randomly assigned 52 participants to 3 g/day of ginseng or placebo for 12 weeks. This was followed by an 8-week washout and a subsequent 12-week period in which the opposite treatment was administered. At run-in and at weeks 0 and 12 of each treatment period, participants were fitted with an ambulatory BP monitor to assess 24-hour BP. The primary outcome was the treatment difference at week 12 in mean 24-hour systolic BP. Secondary outcomes were treatment differences at week 12 in other ambulatory BP parameters and serum cystatin C. Forty participants (77%) completed the trial, with 3 removed from main analysis (n=2, antihypertensive drug changes; n=1, incomplete ambulatory monitoring). In the remaining 37, 12-week ginseng treatment was associated with a neutral effect on all ambulatory BP parameters compared with placebo; an intention-to-treat analysis supported this. Ginseng did not affect serum cystatin C level. Overall, long-term ginseng use had no effect on 24-hour BP and renal function in hypertensive individuals. (Hypertension. 2006;47:791-796.)

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

Ginseng is an herb that populations have valued as a tonic since 25 A.D.1 It is also shown through randomized, controlled trials (RCTs) to improve glycemic control2 and cognitive function.3 In contrast, however, there is repeated mention in the medical literature that ginseng can elevate blood pressure (BP).4–6 This stems from an early observational study by Siegel7 that connected the self-reported use of adults in these regions are estimated to have hypertension,14 until such evaluations are undertaken, physicians will remain greatly limited in the advice they can provide to hypertensive individuals. Regarding ginseng use. There is potential for overlap between the prevalence of ginseng use and hypertension. Still, there remains no long-term RCT investigation of the effect of ginseng on BP, and until such evaluations are undertaken, physicians will remain greatly limited in the advice they can provide to hypertensive individuals regarding ginseng use.

Although many species of ginseng exist, Panax quinquefolius, or North American ginseng (NAG), and Panax ginseng together account for the majority of ginseng consumed worldwide. Recently, we demonstrated that single 3-g doses of NAG15 and P ginseng16 exert neutral and lowering effects on BP, respectively, for 160 minutes after intake. In the former study,15 the neutral effect on BP was comprehensively shown with 6 batches of NAG in hypertensive individuals. To add to this finding now, the long-term effect of NAG on BP would be of even greater significance, because long-term BP outcomes are associated with cardiovascular disease events.17,18 Also, because long-term BP outcomes might not necessarily be inferable from acute outcomes,19 we proceeded to address the effect of NAG on BP after 12 weeks of intake (defined as long-term relative to our acute studies). We measured 24-hour ambulatory BP (ABP), because it is a better determinant of cardiovascular risk than office BP, and it allows for an assessment of circadian BP changes.20,21 As well, for safety reasons, serum cystatin C was measured as a marker of glomerular filtration rate and an indicator of the effect of NAG on renal function.22

We determined here, through a single-center, randomized, controlled, double-blinded, crossover trial, the effect of 12-
week NAG intake on 24-hour ABP and renal function in hypertensive individuals. We used a single batch of NAG, which was representative of NAG on the world market and which was shown previously to exert a neutral effect on BP for 160 minutes after intake. Thus, this study provided, for the first time, insight into how long-term ginseng intake could affect both BP and renal function in humans.

Methods

Participants

The research ethics board at St Michael’s Hospital approved the study, and the procedures used were in accordance with institutional guidelines. Individuals were recruited through newspaper advertisements in Toronto and provided written informed consent to participate. Inclusion was an age of 18 to 85 years and hypertension as defined by the use of antihypertensive drugs or a seated office systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg at each of 3 prestudy visits. Exclusion was secondary hypertension, white-coat hypertension, diabetes, kidney/liver disease, unstable angina, ginseng use for 2 months before or during the study, or any changes in the type/dose of antihypertensive drugs 1 month before or during the study.

Overall, 37 (30 men and 7 women) hypertensive individuals were included in the main analysis. Their ethnicities included European-white (n=26), East-Asian (n=5), South-Asian (n=4), African-Caribbean (n=2), and Native-Canadian (n=1) individuals. At run-in they had a mean±SEM age of 58.4±1.6 years, body mass index of 28.6±0.9 kg/m², serum creatinine C of 0.97±0.03 mg/L, office systolic/diastolic BP of 130.2±2.4/85.8±1.6 mm Hg, and 24-hour systolic/diastolic BP of 131.6±1.9/81.1±1.5 mm Hg. Of the 37 individuals, 32 were taking antihypertensive agents (monotherapy, n=20; ≥2 agents, n=12), including angiotensin-converting enzyme inhibitors (n=16), angiotensin receptor blockers (n=5), β-blockers (n=7), calcium channel blockers (n=12), diuretics (n=8), and α-blockers (n=1). The run-in characteristics of the 37 individuals included in the main analysis did not significantly differ from those who withdrew or were removed from main analysis (n=15; data not shown).

Treatments and Protocol

In this single-center, randomized, placebo-controlled, double-blinded trial conducted between April 2001 and October 2003 (recruitment: April 2001 to May 2002; follow-up: May 2002 to October 2003), we sought to determine the effect of 12-week NAG intake on 24-hour BP. To do so, we used an AB/BA 2-treatment, 2-period crossover design with the treatment sequences being NAG-then-placebo and placebo-then-NAG. We tested a 3-g dose of com starch placebo and a single batch of 3-year-old dried NAG root from an Ontario farm. Its acute BP effects and ginsenoside profile have been described previously (where it was designated as NAG from Farm B). Briefly, the total ginsenoside content of NAG was 62.8 mg/g; as well, its authenticity was confirmed by GLC and HPLC analysis. We administered NAG and com starch as powders in identical blue-white 500 mg #00 capsules (with vanilla extract added to mask smell and taste), which were prepared by Sunny Crunch Foods Ltd (Markham, Ontario, Canada).

Caspase was packaged in identical bottles, with their contents known by 1 person independent of the conduct of the study. This person coded the treatment bottles, performed the blinding, and prepared a concealed allocation schedule that randomly assigned 2 treatment sequences (NAG-then-placebo and placebo-then-NAG) to a consecutive series of numbers in an order generated by a random-number table. The treatments were sealed in sequentially numbered bottles according to the allocation schedule. On enrollment, each participant was assigned to the next consecutive number, and at the start of each study period, a second person dispensed the participant’s corresponding bottles of treatment capsules. We instructed participants to consume a 3-g daily dose as 3 capsules between 7:00 AM and 9:00 AM and 3 between 7:00 PM and 9:00 PM, because preliminary evidence has suggested that ginsenosides remain in human plasma for ~12 hours. All of the study personnel (including those administering the treatments and those assessing the outcomes) and participants were blinded to treatment assignment for the duration of the study.

After screening, 52 individuals were deemed eligible, and 28 were randomly assigned to the NAG-then-placebo treatment sequence and 24 to the placebo-then-NAG treatment sequence. The protocol included: (1) a 4-week open-label placebo run-in, (2) a 12-week treatment period in which the first treatment of the assigned sequence was consumed, (3) an 8-week washout period with no treatment, and (4) a 12-week treatment period in which the second treatment of the assigned sequence was consumed. At the start of run-in, and at the start (week 0) and end (week 12) of each treatment period, participants arrived at our clinic between 8:00 AM and 9:00 AM (10 to 12 hours prior) and off their antihypertensives (8 hours prior). Initially, they had body weight assessed, blood samples drawn, and were fitted with an ABP monitor (ABPM) that was activated between 9:00 AM and 10:00 AM. Immediately after ABPM activation, each participant began his/her typical antihypertensive drug routine (we were, thus, able to ensure that antihypertensive drugs were taken according to the same schedule each time the ABPM was worn). Participants refrained from taking NAG or placebo capsules for the period that the ABPM was worn (≥24 hours). Participants were instructed to retire between 10:00 PM and 12:00 AM and to awaken between 6:00 AM and 8:00 AM. They also prepared a 24-hour diary detailing activity, sleep, and drug schedules.

Primary and Secondary Outcomes

The primary outcome was mean 24-hour ambulatory systolic BP at week 12. Secondary outcomes included mean 24-hour diastolic BP and pulse pressure (PP), as well as mean daytime and night systolic BP, diastolic BP, and PP at week 12, with daytime defined as 8:00 AM to 8:00 AM and nighttime as 12:00 AM to 6:00 AM. Additional secondary outcomes were serum creatin C (marker of kidney function) and body weight at week 12. To avoid multiplicity, no subgroup analyses or adjusted analyses were performed.

BP Measurement

Office BP (at recruitment and run-in) was measured 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 of the measures and used a mercury sphygmomanometer (Baumanometer, W.A. Baum). For ABP measurements, participants were fitted with a SpaceLabs 90207 ABPM (SpaceLabs), with the cuff secured on the nondominant arm for the entire ≥24-hour period (worn on the same arm for all of the visits). ABPM measurements occurred every 15 minutes from 7:00 AM to 9:00 PM inclusive and every 20 minutes from 10:00 PM to 6:00 AM inclusive, with a maximum of 87 successful readings for the 24-hour period. Measurements were automatically repeated if an error occurred. The adult and large cuffs were used for arm circumferences of 24 to 31 cm and 32 to 42 cm, respectively.

Cystatin C

All of the assays were performed in serum obtained from fasted participants. Specimens were stored at −70°C. Cystatin C was measured by a particle-enhanced immunonephelometric assay (N Latex Cystatin C, Dade Behring) with a nephelometer (BNII, Dade Behring).

Statistical Analyses

Based on previous findings, we speculated that the maximum difference in mean 24-hour systolic BP at week 12 between NAG and placebo would be 4.4 mm Hg. Accordingly, with an estimated SD of the between-treatment difference being 7.1 mm Hg and assuming a correlation coefficient of 0.80 between-treatment values at week 12, at a significance level (α) of 0.05 we calculated that 36
individuals were required to achieve the noted difference in mean 24-hour systolic BP compared with placebo with 80% power. Based on previous withdrawal rates of ~10% during study periods of 12 weeks,28 we calculated that the enrollment of 52 participants would yield 36 participants to a 36-week study period.

We conducted a main analysis, a secondary analysis, and an intention-to-treat analysis. The main analysis included participants who: (1) finished both treatment periods, (2) completed 24-hours of ABP monitoring for all of the visits, and (3) adhered to the study protocol and exclusion criteria (ie, no medication changes). Data from these participants underwent crossover analysis.23 According to the assumptions of this analysis, each parameter was first tested for the period and carryover effect. Then, for the 24-hour, 8:00 AM to 8:00 PM, and 12:00 AM to 6:00 AM periods, the independent and interactive effects of treatment (NAG and placebo), week (0 and 12), and time of day (hour) on ambulatory systolic BP, diastolic BP, and PP were assessed by repeated-measures GLM 2-way ANOVA. Significant treatment effects were additionally explored at weeks 0 and 12 with repeated-measures GLM-ANOVA. For cystatin C, the independent and interactive effects of treatment and week were assessed by repeated-measures GLM 2-way ANOVA. Significant treatment effects were additionally explored at weeks 0 and 12 with repeated-measures GLM-ANOVA. We assessed body weight by the same procedure.

The secondary analysis included participants who finished the first treatment period with complete 24-hour ABPM at weeks 0 and 12. This analysis followed a parallel design test in which a GLM 2-way ANOVA tested the independent and interactive effects of treatment (NAG versus placebo) and week (0 versus 12) on ABP during the first treatment period. Significant treatment effects were explored at these weeks with a GLM-ANOVA. The intention-to-treat analysis included all of the participants who finished both treatment periods with complete 24-hour ABPM, and their data underwent crossover analysis (as described for main analysis).23

All of the analyses were run with sex and age as covariates and were performed with the Number Cruncher Statistical Software 2000. Significance was set at α of 0.05 and was 2-sided. Values are expressed as mean±SEM.

Adequacy of Blinding
The adequacy of blinding was assessed according to participant responses when asked which treatment they believed they were taking (NAG, placebo, or uncertain). This question was asked after each treatment period by an individual independent of the conduct of the study.

Results
Subjects
Of the screened individuals (n=67), 52 proceeded through run-in and randomization. Among them, 12 (23%) withdrew: 8 from the NAG-then-placebo sequence (n=3, period 1; n=1, washout; n=4, period 2) and 4 from the placebo-then-NAG sequence (n=2, period 1; n=2, washout). Accordingly, 3 withdrew while taking NAG (n=1, diarrhea; n=1, headache; n=1, antihypertensive drug change), 6 while taking placebo (n=6, work schedule), and 4 during washout (n=3, work schedule; n=1, antihypertensive drug change). Also, 3 from the placebo-then-NAG sequence were not included in main analysis because of antihypertensive drug changes (n=2) and unsuccessful ABPM (n=1). Overall, 37 participants (71%) proceeded to main analysis.

Compliance and Blinding
Compliance was estimated by pill count (NAG: 91.7±2.3%; placebo: 93.6±1.9%; P=0.50). Evaluation of binding re-

### Mean 24-Hour, Daytime, and Night Ambulatory Systolic BP, Diastolic BP, and PP Before (Week 0) and After (Week 12) NAG and Placebo Intake in 37 Hypertensive Participants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment</th>
<th>Week 0 (n=37), mm Hg</th>
<th>P Value*</th>
<th>Week 12 (n=37), mm Hg</th>
<th>P Value*</th>
<th>Difference at Week 12 (NAG–Placebo 95% CI), mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-Hour systolic BP</td>
<td>NAG</td>
<td>129.6±1.8</td>
<td>0.56</td>
<td>130.9±2.0</td>
<td>0.99</td>
<td>(−2.4 to 2.4)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>130.4±1.9</td>
<td></td>
<td>130.9±1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime systolic BP†</td>
<td>NAG</td>
<td>135.1±2.0</td>
<td>0.83</td>
<td>136.6±2.1</td>
<td>0.64</td>
<td>(−2.0 to 3.3)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>135.9±2.0</td>
<td></td>
<td>136.0±2.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Night systolic BP†</td>
<td>NAG</td>
<td>118.3±1.7</td>
<td>0.25</td>
<td>120.8±1.9</td>
<td>0.59</td>
<td>(−3.9 to 2.2)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>120.1±2.1</td>
<td></td>
<td>121.6±1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-Hour diastolic BP</td>
<td>NAG</td>
<td>79.7±1.3</td>
<td>0.91</td>
<td>80.6±1.5</td>
<td>0.99</td>
<td>(−1.6 to 1.7)</td>
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<tr>
<td></td>
<td>Placebo</td>
<td>79.9±1.3</td>
<td></td>
<td>80.5±1.4</td>
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<td></td>
</tr>
<tr>
<td>Daytime diastolic BP†</td>
<td>NAG</td>
<td>84.6±1.5</td>
<td>0.93</td>
<td>84.9±1.5</td>
<td>0.79</td>
<td>(−1.6 to 2.0)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>84.6±1.5</td>
<td></td>
<td>84.7±1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Night diastolic BP†</td>
<td>NAG</td>
<td>71.4±1.3</td>
<td>0.63</td>
<td>73.4±1.6</td>
<td>0.94</td>
<td>(−2.3 to 2.2)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>72.4±1.4</td>
<td></td>
<td>73.4±1.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-Hour PP</td>
<td>NAG</td>
<td>49.8±1.6</td>
<td>0.27</td>
<td>50.3±1.6</td>
<td>0.94</td>
<td>(−1.5 to 1.4)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>50.4±1.5</td>
<td></td>
<td>50.4±1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime PP†</td>
<td>NAG</td>
<td>51.1±1.7</td>
<td>0.61</td>
<td>51.6±1.8</td>
<td>0.60</td>
<td>(−1.2 to 1.9)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>51.5±1.6</td>
<td></td>
<td>51.3±1.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Night PP‡</td>
<td>NAG</td>
<td>46.9±1.6</td>
<td>0.21</td>
<td>47.4±1.5</td>
<td>0.35</td>
<td>(−2.5 to 0.9)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>48.1±1.6</td>
<td></td>
<td>48.2±1.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Also shown are the 95% CIs for the treatment differences at week 12. Values are presented as mean±SEM.

*P values are for between-treatment comparisons at week 0 and at week 12.
†Daytime indicates the mean of the period 8:00 AM to 8:00 PM inclusive.
‡Night indicates the mean of the period 12:00 AM to 6:00 AM inclusive.
revealed that of the 40 participants who completed both treatment periods, only 16 expressed certainty of when (ie, indicated what period) they consumed NAG. Accordingly, 9 of 40 (22.5%) correctly predicted when they were on NAG, whereas 7 of 40 (17.5%) indicated they were on NAG when on placebo ($P=0.58$ for $\chi^2$ analysis).

**Main Analysis of BP, Cystatin C, and Body Weight**

There were no significant period or carryover effects on any of the measured parameters (BP, bodyweight, or cystatin C). For the BP parameters at week 0, mean values did not differ between NAG and placebo (Table). However, at 6:00 AM on week 0, the PP was significantly lower for NAG compared with placebo ($P<0.05$; Figure); there were no other mean hourly differences.

There was no significant effect of treatment on the primary outcome, mean 24-hour systolic BP, or on any secondary outcomes (ie, mean values at week 12 did not differ between NAG and placebo; Table); and there was no significant interaction among treatment, week, and/or hour. At 1:00 PM (13:00 hours), however, diastolic BP was significantly higher at week 12 for NAG compared with placebo (Figure). There were no other mean hourly differences.

Body weight did not differ between NAG and placebo at week 0 ($82.8\pm2.3$ versus $82.7\pm2.3$ kg, respectively; $P=0.86$; $n=37$) and at week 12 ($82.6\pm2.3$ versus $82.8\pm2.3$ kg, respectively; $P=0.47$; $n=37$). The serum level of cystatin C did not differ between NAG and placebo at week 0 ($0.97\pm0.03$ versus $0.98\pm0.03$ mg/L, respectively; $P=0.40$; $n=34$) and at week 12 ($1.00\pm0.03$ versus $0.90\pm0.03$ mg/L, respectively; $P=0.32$; $n=34$). A sufficient number of blood samples were obtained from only 34 participants for the measurement of serum cystatin C.

**Secondary Analysis**

The secondary analysis included the 39 participants who completed the entire study plus those who withdrew but completed the first treatment period ($n=7$). When their data were analyzed together in a parallel-design comparison of NAG ($n=25$) versus placebo ($n=21$) on all of the ABP parameters from treatment period 1, NAG showed no signif-
icant effect versus placebo on any parameter (results not shown).

**Intention-to-Treat Analysis**

Because 12 of the 52 randomized participants were lost to follow-up, and 1 had incomplete ABPM, the intention-to-treat analysis included 39 individuals. It was only performed for ABP and showed no significant effect of period, carryover, or treatment on any ABP parameter (results not shown).

**Discussion**

We showed here, for the first time in a long-term RCT, the effect of ginseng on BP and renal function. The ginseng used was NAG, which is a species native to North America that is used predominantly in Canada, the United States, and China. We found that its intake at 3 g/day for 12 weeks relative to placebo was associated with a neutral effect on BP in hypertensive individuals. This was shown in the main analysis by a lack of difference between NAG and placebo at 12 weeks for each of the mean 24-hour, daytime and night ABP parameters (Table), which was supported by an intention-to-treat analysis. Also, although there was an increase in diastolic BP by a lack of difference between NAG and placebo at 12 weeks and showed no significant effect of period, carryover, or treatment on any ABP parameter (results not shown).

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The current study had 3 limitations. First, 25% of the participants withdrew, and another 5% had their data removed from main analysis. We did, however, conduct a secondary analysis and intention-to-treat analysis to rectify this, and both showed identical outcomes to the main analysis. Second, whereas the antihypertensive-treated participants in the main analysis (n=32) held their antihypertensive type(s) and dose(s) constant for the entire study, their use of antihypertensives could have prevented an accurate interpretation of the effect of NAG on BP because of possible NAG–drug interactions. However, an objective here was to determine the effect of NAG on BP in a representative population of hypertensive individuals so that the findings could be extrapolated to such individuals. To add to the current findings, future studies should determine the effect of NAG on BP in untreated hypertensive or prehypertensive individuals to better understand the influence of NAG on BP in the absence of antihypertensive drugs.
Perspectives
The topic of ginseng and BP in humans commenced >25 years ago with an observational study that suggested a link between ginseng use and hypertension. Since then, 2 acute-duration RCTs found that NAG15 and 24-hour BP relative to placebo in a multiethnic, middle-to-older aged, hypertensive population. NAG also had no effect on BP.16 Overall, these findings widen the perspective on ginseng and BP and provide initial insight into the effect of ginseng on renal function. Future RCTs should evaluate additional doses of NAG that represent its range of intake in the general population. As well, the effect of P ginseng on BP should be determined through similar long-term RCTs, because it shows the potential to lower BP.16

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References
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