No Beneficial Effects of Pine Bark Extract on Cardiovascular Disease Risk Factors

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Background: Although modifiable cardiovascular disease risk factors are common, some patients eschew conventional drug treatments in favor of natural alternatives. Pine bark extract, a dietary supplement source of antioxidant oligomeric proanthocyanidin complexes, has multiple putative cardiovascular benefits. Studies published to date about the supplement have notable methodological limitations.

Methods: We randomized 130 individuals with increased cardiovascular disease risk to take 200 mg of a water-based extract of pine bark (n=64; Toyo-FVG, Toyo Bio-Pharma, Torrance, California; Shinyaku Co, Ltd, Saga, Japan; also marketed as Flavagenol in Japan) or placebo (n=66) once per day. Blood pressure, our primary outcome, and other cardiovascular disease risk factors were measured at baseline and at 6 and 12 weeks. Statistical analyses were conducted using regression models.

Results: Baseline characteristics did not differ between the study groups. Over the 12-week intervention, the sum of systolic and diastolic blood pressures decreased by 1.0 mm Hg (95% confidence interval, −4.2 to 2.1 mm Hg) in the pine bark extract–treated group and by 1.9 mm Hg (−5.5 to 1.7 mm Hg) in the placebo group (P=.87). Other outcomes were likewise not significantly different, including body mass index, lipid panel measures, liver transaminase test results, lipoprotein cholesterol particle size, and levels of insulin, lipoprotein(a), fasting glucose, and high-sensitivity C-reactive protein. There were no subgroups for whom intake of pine bark extract affected cardiovascular disease risk factors.

Conclusions: This pine bark extract (at a dosage of 200 mg/d) was safe but was not associated with improvement in cardiovascular disease risk factors. Although variations among participants, dosages, and chemical preparations could contribute to different findings compared with past studies, our results are consistent with a general failure of antioxidants to demonstrate cardiovascular benefits.

Trial Registration: clinicaltrials.gov Identifier: NCT00425945

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vide promising indications for benefits, other studies6,12,14,15 show limited or no improvement for these conditions. As with investigations of blood pressure, most of these studies were open label and did not have a placebo control group. Adequate testing for such a widely used dietary supplement requires rigorous placebo-controlled clinical trials. To further evaluate the cardiovascular benefits of pine bark extract, we investigated the efficacy of pine bark extract on blood pressure and other CVD risk factors. The primary hypothesis was that pine bark extract would lower blood pressure in a population of overweight and obese participants with baseline prehypertension or hypertension. We chose a population at risk of developing CVD and not taking antihypertensive medications who would be likely to seek dietary supplements as an alternative therapy.

METHODS

We conducted a randomized, placebo-controlled, double-blind, parallel-group clinical trial. A total of 130 overweight and obese adults with systolic blood pressure above that considered optimal (125-160 mm Hg) were enrolled between January 31, 2007, and May 31, 2008. Participants were randomly assigned on a 1:1 ratio to take 200 mg of a French maritime pine bark extract (Toyo-FVG, Toyo Bio-Pharma, Torrance, California; Toyo Shinyaku Co, Ltd, Saga, Japan; also marked as Flavagenol in Japan). Randomization was performed using the permuted block method (block size, 6) stratified by sex. Participants and all study staff (including clinicians) were blinded until study completion. Data were collected at baseline and at 6 and 12 weeks after randomization, with a limited 3-week visit to assess adverse events. Statistical analyses were conducted using regression models. The study protocol was approved by the Stanford University Institutional Review Board, Stanford, California.

Participants

Participants were recruited from the local community by radio and printed advertisements. Among 2411 individuals who completed the initial screen by telephone and online, 643 were identified who were not taking diabetes medication, hypertension medication, or any dietary supplements within the past month aside from the recommended daily value of multivitamins (Figure 1). These individuals were invited to attend clinical screening at the Stanford Prevention Research Center. The inclusion criteria were overweight or obesity class I (body mass index [BMI] calculated as weight in kilograms divided by height in meters squared, 25.0-34.9) and prehypertensive or hypertensive systolic blood pressure (125-160 mm Hg). Many participants had suboptimal lipoprotein profiles and high-sensitivity C-reactive protein levels, but those with fasting levels exceeding the following were excluded: 450 mg/dL for triglycerides, 126 mg/dL for blood glucose, or 200 mg/dL for low-density lipoprotein cholesterol (LDL-C) (to convert triglycerides level to millimoles per liter, multiply by 0.0113; glucose level to millimoles per liter, multiply by 0.0555; and cholesterol level to millimoles per liter, multiply by 0.0259). These measurements for eligibility screening were obtained by point-of-care testing (LDX and GDX analyzers; Cholestech Corporation, Hayward, California).10 Individuals eligible at clinical screening were invited to attend a study orientation session, during which informed consent was obtained. Randomization followed the completion of 2 baseline visits.

RANDOMIZATION

The study sponsor (Toyo Shinyaku Co, Ltd) provided the researchers with pine bark extract and placebo study tablets labeled “A” and “B.” Computer-generated, sex-stratified, block permutation lists were generated by the research analyst and were provided to the pharmacy staff. At the conclusion of the second baseline visit, pharmacy staff dispensed study tablet A or study tablet B accordingly. Participants were equally likely to be randomized to receive either study tablet. Pharmacy staff had no role in subject recruitment, assessment, or follow-up. Investigators and all study staff were blinded to treatment assignment until all study results were collected, at which time the study sponsor revealed which tablet, A or B, contained pine bark extract.

STUDY TABLETS AND ADHERENCE

Study tablets of pine bark extract contained 50 mg each and were vacuum packed in sachets with each containing 4 tablets (200 mg). This dosage was selected based on the midrange of administration in past studies and the OPC content of this pine bark extract compared with other formulations. This formulation of pine bark extract is extracted from the milled bark of Pinus pinaster (also known as Pinus maritime and Pinus maritimus) using heated water. The extract is concentrated by evaporation and according to the manufacturer contains approximately 40% proanthocyanidin oligomers (dimer, trimer, and tetramer), 42% other polyphenols, and 18% other substances. The extract is subsequently compounded with excipients of palatinit sugar, caramel, sucrose, fatty acid ester, and calcium stearate. The placebo tablets consisted of these same excipients. Participants in either study group were instructed to take 4 tablets at the same time each morning. Tablets were distributed at baseline and at 3 and 6 weeks. Adherence was tracked by counting returned tablets at 3, 6, and 12 weeks. Tablet counting was conducted by pharmacy staff, who had no direct patient contact. Participants were asked to refrain from changing their diet, los-
ing weight, and beginning new dietary supplements or medications during the study. Three-day food records were administered at baseline and at 12 weeks to monitor changes in diet, particularly intake of antioxidant-rich foods. Participants were queried about their use of dietary supplements and medications at screening and were asked to report any changes.

OUTCOMES

Two sets of resting blood pressure measurements, the primary outcome, were obtained over a 3-day interval at baseline and at 12 weeks, and a single set was obtained at 6 weeks. All blood pressures were measured by registered nurses trained in the study protocol using a blood pressure monitor (Dinamap; Critikon Corporation, Tampa, Florida). To obtain a resting blood pressure, participants sat quietly for 5 minutes before the first measurement. All measurements were obtained with participants in a seated position, with their feet and ankles uncrossed, using the right arm. At each clinic visit, 3 blood pressure measurements were obtained, with at least 1 minute elapsing between the first and second measurements and with at least 3 minutes elapsing between the second and third measurements. Blood pressure for a given time point (baseline, 6, and 12 weeks) was calculated by taking the mean of all readings after discarding the first reading of each day.

Fasting (≥10 hours) blood samples were collected once at 6 weeks and twice (with 3-5 days between tests) at baseline and at 12 weeks. Insulin, fasting glucose, and glycated hemoglobin levels were used to assess glucose metabolism. Lipid panel measurements (high-density lipoprotein cholesterol [HDL-C], LDL-C, and triglycerides) and lipoprotein cholesterol particle size results were used to assess plasma lipoprotein cholesterol profile. High-sensitivity C-reactive protein level was used as a measure of systemic inflammation. Alanine aminotransferase and aspartate aminotransferase levels assured product safety. Assessment of lipoprotein cholesterol particle size and levels of glycated hemoglobin, lipoprotein(a), and high-sensitivity C-reactive protein was conducted by an outside laboratory (Liposcience, Raleigh, North Carolina). All other tests were performed at Stanford Hospital and Clinics Laboratory. Both laboratories are regulated by the Clinical Laboratory Improvement Act.

Height was measured once at baseline to the nearest tenth of an inch using a wall-mounted stadiometer. Body weight was measured to the nearest tenth of a pound once at 6 weeks and on 2 different days at baseline and at 12 weeks using a calibrated balance scale. Waist circumference was measured to the nearest tenth of an inch in the horizontal plane around the abdomen at the level of minimal circumference.

Adverse events and adverse effects were assessed using a survey administered at 3, 6, and 12 weeks. The adverse events and adverse effects questionnaire asked about symptoms commonly reported in past studies of pine bark extract, hospital and emergency department visits, new diagnoses, and changes in existing diagnoses. Participants were instructed to contact study staff if they experienced adverse events between study visits. In addition, we monitored study data for elevated blood pressure, liver function test results, and levels of glucose, triglycerides, and LDL-C.

STATISTICAL ANALYSIS

Comparability of the pine bark extract and placebo groups on baseline demographic and clinical characteristics was assessed by t test for continuous variables and by Pearson product moment correlation χ² test for categorical variables. The primary outcome was the combined change in systolic and diastolic blood pressures from baseline to 12 weeks. We hypothesized that this sum would decrease by at least 7 mm Hg in the pine bark extract group relative to the placebo group after 12 weeks. After projecting 10% participant attrition over 12 weeks, a sample size of 130 participants (65 per study group) was calculated to provide 79% power for detecting an effect size of 0.5 (mean divided by standard deviation) at α = 0.05.

Following our a priori primary analysis plan, the effect of pine bark extract on the primary outcome, 12-week blood pressure change, was examined using a regression model with 12-week blood pressure change as the dependent variable and with baseline blood pressure as a covariate. Although demographic variables were not significantly different between groups at baseline, we evaluated them as covariates in this regression model.

None were included in the final models because they were not significant statistically at P < .05. Secondary outcomes were assessed using similar regression models. Changes in blood pressure and in secondary outcomes were analyzed at 6 weeks using this same method. Because the 6-week outcomes did not differ from those noted at 12 weeks, we present only our analysis of 12-week outcomes. We also analyzed the data on an intent-to-treat basis, with the last observation carried forward for participants with missing data at follow-up. As expected given limited loss to follow-up, the findings were almost identical and are not presented. Missing adherence data were conservatively calculated as if the participant had consumed no study tablets. All statistical tests were 2-tailed, and the threshold significance level was P < .05. Statistical analysis was conducted using commercially available software (SAS, version 9.1; SAS Institute Inc, Cary, North Carolina).

BASELINE DATA AND STUDY RETENTION

No significant differences were noted in the baseline characteristics of the pine bark extract group (n = 64) vs the placebo group (n = 66) (Table 1). Consistent with our recruitment of a population with blood pressures above the normal (120/80 mm Hg) range, the mean (SD) blood pressures at baseline were 132.6 (10.9)/78.6 (7.9) mm Hg for the pine bark extract group and 133.2 (10.9)/79.9 (7.7) mm Hg for the placebo group. Other mean levels were within normal or clinically acceptable ranges at baseline except for high-sensitivity C-reactive protein (2.6 [SD, 2.8] mg/L for the pine bark extract group and 2.6 [SD, 2.9] mg/L for the placebo group); C-reactive protein level to nanomoles per liter, multiply by 9.524).

Of 130 randomized participants, 7 participants (4 in the pine bark extract group and 3 in the placebo group) dropped out before the 6-week data collection point, and 2 participants in the placebo group dropped out after the 6-week data collection point, for a 93.1% retention rate (Figure 1). Of 4 participants in the pine bark extract group who dropped out, 2 were concerned about possible adverse effects of the supplement, 1 began a blood pressure medication, and 1 began cancer treatments. Of 5 participants in the placebo group who dropped out, 1 moved out of the area, 2 were concerned about the cost and time of traveling to study visits, and 2 were lost to follow-up.

STUDY TABLET AND DIET

The mean study tablet adherence rates were 90.1% in the pine bark extract group and 92.6% in the placebo group.
Failure to consume at least 50% of study tablets was equally likely in both groups (5% for both, \( P = .97 \)). We analyzed changes in multiple dietary variables between the 2 groups from baseline to 12 weeks, none of which were statistically significant except for potassium intake (75 mg in the pine bark extract group vs −293 mg in the placebo group, \( P = .03 \)). Intake of fruit (\( P = .24 \)) and vegetables (\( P = .16 \)), the primary dietary sources of antioxidants, did not change differentially between the groups.

**EFFECT OF PINE BARK EXTRACT ON BLOOD PRESSURE**

At 6 weeks, systolic and diastolic blood pressure changes were insignificant, with systolic plus diastolic blood pressure decreasing by 1.1 mm Hg in the intervention group and by 1.2 mm Hg in the placebo group (Figure 2). After 12 weeks, blood pressure changes from baseline remained nonsignificant (\( P = .87 \)). The pine bark extract group had a 0.1–mm Hg (95% confidence interval [CI], −2.2 to 2.0 mm Hg) decrease in systolic blood pressure and a 0.9–mm Hg (−2.2 to 0.4 mm Hg) decrease in diastolic blood pressure (total decrease in blood pressure, 1.0 mm Hg; −4.2 to 2.1 mm Hg) from baseline to 12 weeks (Figure 2 and Figure 3 and Figure 4). The placebo group had a 1.6–mm Hg (95% CI, −4.0 to 0.9 mm Hg) decrease in systolic blood pressure and a 0.35–mm Hg decrease in diastolic blood pressure.
SECONDARY OUTCOMES

Changes in secondary CVD risk factors from baseline to 12 weeks were assessed for glycemic metabolism, plasma lipoprotein cholesterol measures, systemic inflammation, and measures of adiposity. Differences from baseline to 12 weeks between the pine bark extract group and the placebo group did not reach statistical significance except for BMI, which increased in the pine bark extract group (from 28.4 to 28.3) (group change difference, 0.20; 95% Cl, 0.03-0.39; P = .02) (Table 2).

ADVERSE EFFECTS

Adverse events were reported by 43 participants in the pine bark extract group and by 42 participants in the placebo group and did not differ in severity or by specific symptom. At 6 weeks and at 12 weeks, participants’ reporting of specific symptoms was common and equally frequent in both groups. At 12 weeks, the most commonly reported symptoms were headache (45.5% in the pine bark extract group vs 45.2% in the placebo group), sleepiness (40.9% vs 45.2%), frequent urination (38.6% vs 31.0%), gastrointestinal tract discomfort (38.6% vs 35.7%), and insomnia (34.1% vs 31.0%). In the pine bark extract group, there was 1 hospitalization and no emergency department visits. In the placebo group, there were no hospitalizations and 2 emergency department visits. No significant differences were noted between the 2 groups in liver alanine aminotransferase or aspartate aminotransferase test results at 6 weeks or at 12 weeks (Table 2).

SUBGROUP ANALYSES

We assessed whether an effect of pine bark extract might be limited to particular participant subgroups because participant baseline variables were within the normal range for many outcomes. Analyses were performed for subgroups defined by sex, weight, BMI, waist circumference above and below the median for age, baseline systolic blood pressure of 130 mm Hg or higher, ratio of total cholesterol level to HDL-C level of 3.5 or higher, and levels of glucose, cholesterol, triglycerides, glycated hemoglobin, and high-sensitivity C-reactive protein. There were no significant differences in blood pressure among any subgroups, while sporadic statistically significant differences, as might be expected by chance, were found for other outcomes. Despite our extensive subgroup analysis, the only suggestion of an effect was for participants with baseline systolic blood pressure of 130 mm Hg or higher, among whom the mean (SD) lipoprotein(a) level decreased by 2 (10) nmol/L among 37 individuals in the pine bark extract group (baseline level, 37 nmol/L) and increased by 4 (10) nmol/L among 38 individuals in the placebo group (47 nmol/L).

Table 2. Net Change in Secondary Outcomes From Baseline to 6 Weeks and 12 Weeks

<table>
<thead>
<tr>
<th>Variable</th>
<th>Change (95% Confidence Interval)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol level, mg/dL</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3.3 (-5.4 to 12.0)</td>
</tr>
<tr>
<td>LDL</td>
<td>3.3 (-4.3 to 10.9)</td>
</tr>
<tr>
<td>HDL</td>
<td>0.1 (-2.1 to 2.4)</td>
</tr>
<tr>
<td>Triglycerides level, mg/dL</td>
<td>-7.5 (-35.8 to 20.9)</td>
</tr>
<tr>
<td>Particle size, nm³</td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td>-1.4 (-3.1 to 0.3)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0.1 (-0.1 to 0.3)</td>
</tr>
<tr>
<td>Lipoprotein(a) level, nmol/L</td>
<td>-3.2 (-6.8 to 0.5)</td>
</tr>
<tr>
<td>High-sensitivity C-reactive protein level, nmol/L</td>
<td>-1.4 (-3.1 to 0.3)</td>
</tr>
<tr>
<td>Body mass index, lb</td>
<td>0.0 (-0.2 to 0.2)</td>
</tr>
<tr>
<td>Weight, lb</td>
<td>-0.1 (-1.2 to 1.0)</td>
</tr>
<tr>
<td>Glucose level, mg/dL</td>
<td>-1.0 (-4.4 to 2.3)</td>
</tr>
<tr>
<td>Insulin level, µIU/mL</td>
<td>0.8 (-0.9 to 2.5)</td>
</tr>
<tr>
<td>Glycated hemoglobin level</td>
<td>0.0 (-0.1 to 0.1)</td>
</tr>
<tr>
<td>% of total hemoglobin</td>
<td></td>
</tr>
<tr>
<td>Aminotransferase level, U/L</td>
<td></td>
</tr>
<tr>
<td>Alanine</td>
<td>3.8 (-1.6 to 9.3)</td>
</tr>
<tr>
<td>Aspartate</td>
<td>-1.3 (-3.4 to 0.8)</td>
</tr>
</tbody>
</table>

Abbreviations: C, cholesterol; ellipsis, not applicable; HDL, high-density lipoprotein; LDL, low-density lipoprotein. SI conversion factors: To convert aminotransferase level to microkats per liter, multiply by 0.0167; cholesterol level to millimoles per liter, multiply by 0.0259; C-reactive protein level to nanomoles per liter, multiply by 0.143; glucose level to millimoles per liter, multiply by 0.0556; glycated hemoglobin level to proportion of total hemoglobin, multiply by 0.01; pounds to kilograms, multiply by 0.45; and triglycerides level to millimoles per liter, multiply by 0.0113.

a Calculated as (follow-up minus baseline for the pine bark extract group) minus (follow-up minus baseline for the placebo group).

b Assessed only at baseline and 12 weeks.

c Lipoprotein(a) level is expressed in nanomoles per liter. A level of 75 nmol/L approximates the 75th percentile for this test in the general US population.

Our objective was to determine the effects of pine bark extract on blood pressure and other CVD risk factors in...
overweight and obese adults with higher-than-optimal systolic blood pressure. The study used a randomized, placebo-controlled, double-blind clinical trial design and achieved a sample size larger than most previous studies of pine bark extract. No significant effects on blood pressure, plasma lipoprotein cholesterol profile, glycemic metabolism, or inflammatory markers were observed between the pine bark extract group and the placebo group. Furthermore, when we limited our analysis to subgroups with more extreme values of numerous risk factors, we also failed to detect an effect of this pine bark extract (at 200 mg/d) on outcomes.

Our findings are consistent with a growing body of observational and clinical trial evidence that dietary supplements, particularly antioxidant supplementation, do not have a beneficial effect on heart disease. Vivekananthan et al performed a meta-analysis of large randomized clinical trials of vitamin E and beta carotene treatment and showed that they were ineffective for CVD prevention. In addition, the Women’s Health Initiative followed up 161,000 women for 7.9 years, and observation data showed no association between multivitamin use and CVD. Clinical, observational, and meta-analysis studies also showed that megadoses of vitamins were nonprotective against various cancers. Some studies also link antioxidant supplement use to increased mortality risk.

Several studies reported that pine bark extract decreases blood pressure. Shand et al observed a decrease of 7 mm Hg in systolic plus diastolic blood pressures combined for 24 participants taking pine bark extract (480 mg/d) for 12 weeks, while Hosseini et al noted a decrease in systolic blood pressure for 11 participants taking pine bark extract (200 mg/d) for 8 weeks. However, both of these studies lacked a comparison control group. In a randomized clinical trial, Liu et al found that participants with hypertension taking pine bark extract (100 mg/d) required lower doses of nifedipine to obtain normal blood pressure but did not test the effect of pine bark extract in the absence of conventional medications. In the largest randomized clinical trial to date focused on pine bark extract and blood pressure, we found that this supplement did not lower blood pressure among overweight and obese participants with prehypertension or stage 1 hypertension.

Trials of pine bark extract have shown decreases in LDL-C level, while equal numbers of trials, including ours, reported no significant benefits of pine bark extract on LDL-C level. Devaraj et al observed an increase in HDL-C level with pine bark extract but no effect on triglycerides level. Two other studies showed no effect of pine bark extract on HDL-C level. Our subgroup analyses of individuals with elevated baseline glucose and plasma lipid levels provide additional evidence that the pine bark extract evaluated herein does not improve these CVD risk factors.

Our study has several strengths. It is the largest study to date of pine bark extract and CVD risk factors. It used a rigorous randomized controlled trial method, while most other studies of pine bark extract were open label and lacked clear data collection techniques. Our study controlled for lifestyle effects by instructing participants to maintain their baseline dietary and physical activity patterns and by assessing these potential confounders at baseline and at the end of the study. In addition, although there were no previous safety concerns about pine bark extract, this study contributes to evidence about the safety of pine bark extract, including its effect on liver function.

There are several limitations of the study. While the percentage of OPCs in the pine bark extract evaluated herein is comparable to that of other commercially available pine bark extracts, there are variations in monomer, dimer, and trimer chemical components of pine bark extracts with similar percentages of OPCs. This may account for variations in physiologic effects among different pine bark extract preparations and among antioxidants in general. Hence, study findings about this pine bark extract (at 200 mg/d) may not be fully applicable to other pine bark extracts or to antioxidant dietary supplements in general. This study exemplifies the challenge faced by researchers studying dietary supplements with chemical constituents that are not easily standardized.

Furthermore, past studies have shown decreases in CVD risk factors when pine bark extract was tested as an adjunct to conventional pharmacologic treatment. In contrast, we evaluated the effects of pine bark extract as a solitary therapy, a design more likely to isolate the effect of pine bark extract. In addition, we recognize that a substantial portion of our study population had baseline lipid panel and lipoprotein profile values within a normal range or an acceptable range. Nevertheless, we still would have expected improvement in CVD risk factors given the putative biologic mechanism of antioxidants. Exploratory analyses of subgroups with elevated risk factor values also failed to reveal any CVD risk factor improvement.

In conclusion, the pine bark extract (200 mg/d) tested in this study for 12 weeks among an overweight and obese population with elevated blood pressure and other CVD risk factors was safe but did not improve blood pressure or various other CVD risk factors. In addition, no benefit was noted for subpopulations with baseline values higher than median risk. Although a different dosage or formulation might produce different results, our findings argue against recommending this pine bark extract to improve CVD risk factors.

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