WELCOME!

UNDERSTANDING PINE BARK EXTRACT as an ALTERNATIVE TREATMENT (UPBEAT)

ORIENTATION FOR ANTIOXIDANT STUDY
Agenda

- Short presentation about the study
- Break for additional questions
- Understand and sign consent forms
- Schedule your visits

Inside your packet:

- Study staff contact information
- Two consent forms (one copy is for our records)
- 3-day food record + tips sheet
- Demographics form
- Appointment slip
- Calendar with sample visit
Objectives of Presentation

- What is interesting about pine bark extract?
- Who are we?
- Why are you here?
- What are you committing to?
- What are your rights as a participant?

- SIGN YOU UP!
History of Pine Bark

- Pine bark has been used as a food, tea, and medicine by Native American tribes for thousands of years.

- The extract was discovered by Jacques Masquelier of the University of Bordeaux, France in 1947.

- He read about a winter expedition in New York where a group of men survived by drinking tea made from pine bark.

- The extract contains natural compounds called OPCs (oligomeric proanthocyanidin complexes).

- Also found in common foods: grape seeds, wine, cranberries, apples, pears, and pomegranates.

- Potent antioxidants that may provide cardiovascular benefits.
Health Benefits of Pine Bark

- Shand and others (2003) – 480mg/day pine bark extract for 12 weeks
  - 7mmHg decrease in blood pressure
  - Significant decrease in BMI and % body fat

- Liu and others (2004) – 100mg/day pine bark extract for 12 weeks
  - 35 mg/dl decrease in blood glucose levels
  - Reduced the need for blood pressure medications

- Davaraj and others (2002) – 150mg/day pine bark extract for 6 weeks
  - 7% decrease in LDL levels
  - 14.5% increase in HDL levels

- Petrassi and others (2000) – 200 to 300mg/day pine bark extract
  - Improved circulation, less edema of the legs
Other possible benefits:


- Pine bark **relieves menstrual cramps** – Kohama (2004).

But…

- Previous studies are flawed because they:
  - Lacked a control group
  - Lacked randomization
  - Lacked enough participants
  - Had poorly defined outcomes
  - Lacked correct statistical analyses

- By filling a knowledge gap, this study will provide important answers to both consumers and health professionals
PART A:
WHAT YOU MUST KNOW ABOUT THE STUDY
35-year history of research into the effects of:

- Nutrition
- Physical Activity
- Smoking Cessation
- Health Behaviors

On heart disease, cancer, diabetes, bone health, and other conditions
Your Research Team

Randall S. Stafford, MD, PhD – Principal Investigator
Rebecca Drieling, MMQ – Research Director
Christopher Gardner, PhD – Co-Investigator
Jun Ma, MD, RD, PhD – Co-Investigator
Heather Klaftenegger – Research Assistant
Alexis Fields – Undergraduate Research Intern

Program on Prevention Outcomes and Practices
Purpose of Our Project

- Evaluate the effect of pine bark extract (Flavangenol®) on cardiovascular risk factors including:
  - Blood Pressure
  - Blood Sugar Levels
  - Cholesterol Levels
  - Body Weight
  - Markers of Systemic Inflammation
- Confirm the safety of pine bark
Eligibility Criteria

- **Inclusion**
  - For age 18-34 years systolic blood pressure (SBP) between 125 and 140 mmHg
  - For age > 35 years, SBP between 125 and 159 mmHg
  - Body mass index (BMI) 25.0 to 34.9

- **Exclusion**
  - Diastolic Blood Pressure (DBP) ≥ 100 mmHg
  - Triglycerides (TG) ≥ 450 mg/dL
  - Low Density Lipoprotein (LDL) ≥ 200 mg/dL
  - Fasting blood glucose (FBG) ≥ 126 mg/dL
Warning levels that may require checking with your physician

- **For age < 70 years:**
  - Systolic Blood Pressure ≥ 145 mmHg
  - Diastolic Blood Pressure ≥ 95 mmHg
  - Low Density Lipoprotein (LDL) ≥ 170 mg/dL
  - Triglycerides (TG) ≥ 300 mg/dL or
  - Fasting blood glucose (FBG) ≥ 110 mg/dL

- **For age > 70 years:**
  - Systolic Blood Pressure > 140 mmHg
  - Diastolic Blood Pressure > 90 mmHg and/or
  - Low Density Lipoprotein (LDL) > 150 mg/dL
Other Considerations

- Agree to refrain from taking medications that affect blood pressure, blood sugar or weight through the end of a 12 week follow up.

- Agree to discontinue the use of supplements that are not vitamins or minerals for 12 weeks and go through a 4 week wash-out period before enrollment.

- Agree to reduce the amount of vitamins and minerals to 200% or less of the daily value.
Study Design

Randomization

Pine Bark Supplement, $n = 65$ (200mg/day)

Placebo, $n = 65$ (0mg/day)

Total of 130 individuals in the study

Assigned by “CHANCE” NOT BY CHOICE

No bias of who gets what treatment

50 – 50 CHANCE

65 individuals – Pine Bark supplement
65 individuals – placebo (control) group

NEITHER YOU OR THE STUDY STAFF WILL KNOW WHICH GROUP YOU ARE IN
## Procedures

### 1. Tablets

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<th>6</th>
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<td>Week</td>
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Procedures: 1. Tablets

- Will pick up supplement and/or drop off left over tablets at the General Clinical Research Center at the following visits:
  - Baseline
  - 3 weeks
  - 6 weeks
  - 12 weeks

- Take 4 Study Tablets Once a Day in the Morning. Total of 200 mg of Pine Bark Extract per day

- Expect to have extra tablets when you drop them off.

- Make sure to bring them or bring the empty baggie if all tablets are gone!
## Procedures

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1. Tablets

![Increase arrows]

2. Blood Pressure

![Increase arrows]
Procedures: 2. Blood Pressure

- Primary outcome of the study

- Will be measured before collection of blood samples:
  
  Twice at Baseline (3 to 7 days apart)
  Once at 6 weeks
  Twice at 12 weeks (3 to 7 days apart)

- Resting Blood Pressure
  
  If you feel rushed at your clinic visit, please ask your Nurse for a few extra minutes to relax.
Procedures: Other Measurements

- Weight
- Waist circumference

These Measurements will be measured:
Twice at Baseline Visits (3 to 7 days apart)
Once at 6 weeks
Twice at 12 weeks (3 to 7 days apart)
# Procedures

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1. Tablets

2. Blood Pressure

3. Blood Sampling
Procedures: 3. Blood Sampling

- Blood samples will be obtained after an 8 hour fast (e.g. from 10:00pm to 6:00am)

- 5 blood samples over 12 weeks:
  - Twice at Baseline (3 to 7 days apart)
  - Once at 6 weeks
  - Twice at 12 weeks (3 to 7 days apart)

- Blood samples will be 20 cc’s (approximately 1 ½ tablespoons)

- Visits start at 7:30am Monday – Friday

- General Clinical Research Center (GCRC), Stanford Hospital
**Measurements from blood:**

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<tr>
<th>Blood Glucose</th>
<th>Fasting blood glucose</th>
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<td>Hemoglobin A1C</td>
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<td>Fasting insulin</td>
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<td>Cholesterol and</td>
<td>Lipid Panel</td>
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<td>Inflammation</td>
<td>Low density lipoprotein particle size</td>
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<td></td>
<td>Lipoprotein A</td>
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<td></td>
<td>C-Reactive protein</td>
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<tr>
<td>Liver Function</td>
<td>Aspartate aminotransferase (AST)</td>
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<td>Alanine Aminotransferase (ALT)</td>
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You will receive your results at the end of the study.
All laboratory measures are free!!!
A value of more than $400 per blood draw.
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Procedures: 4. Questionnaires

- General Information / Demographics
  - Complete during orientation meeting

- 3-Day Food Records
  - Record items consumed on a single day for 3 separate days
  - Can but do not have to be consecutive days
  - Must include two weekdays and one weekend day
  - Read instructions and include brand name and size of foods
    - Bring completed form to 2nd study visit
    - We will mail you the second Food Record at 9 weeks
    - Bring second completed form to 5th study visit

- Adverse Symptoms
  - Complete at 3rd visit, 4th visit, 5th visit, and 6th visit
## Procedures

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Procedures: 5. Compensation

- Total of $100 in compensation intended to partially compensate you for your inconvenience and efforts.

- Compensation Provided as Visa Gift Cards
  - Redeemable anywhere that you can use a credit card
  - Far more convenient than payment by check or cash

- Compensation Schedule
  - Initial $25 mailed to you after visit 2
  - Additional $30 mailed to you after visit 4
  - Additional $45 mailed to you after visit 6
  - Total $100
Time Commitment

This DOES NOT include YOUR TRAVEL TIME to the Stanford campus

- **Visit 1:** 25 to 30 minutes
  - Blood sampling and other measurements

- **Visit 2:** 40 to 60 minutes (visits before 8:00am may take longer)
  - Bring completed 3-Day Food Record
  - Blood sampling, other measurements, receive study tablets
  - Compensation: $25 gift card

- **Visit 3:** 15 to 20 minutes
  - Exchange study tablets and complete adverse events form
Time Commitment

- Visit 4: 30 to 40 minutes
  - Blood sampling, other measurements, exchange study tablets, and complete adverse events form
  - Compensation: $30 gift card

- Visit 5: 25 to 30 minutes
  - Bring completed 3-Day Food Record
  - Blood sampling, other measurements, and complete adverse events form

- Visit 6: 25-30 minutes
  - Blood sampling, other measurements, return study tablets, and complete adverse events form
  - Compensation: $45 gift card
Time Commitment

- **Take study tablets:**
  - 1 minute each day to take study tablets with a non-alcoholic beverage of your choice

- **3-Day food records**
  - Must include two weekdays and one weekend day (they can, but do not have to be consecutive days)
  - 45 to 60 minutes prior to the 2nd visit and prior to the 5th visit
  - Bring to visit 2 and visit 5

- **Using your Visa gift cards**
  - 5-30 minutes on each of three occasions
Potential Benefits

- Improvement in blood pressure (?)
- Other cardiovascular health benefits (?)
  (glucose and cholesterol levels, weight, inflammatory markers)
- Free physiological and laboratory measurements
- Knowledge about cardiovascular risk factors, nutrition, and health

WE CANNOT AND DO NOT GUARANTEE OR PROMISE THAT YOU WILL RECEIVE ANY BENEFITS FROM THIS STUDY
Potential Risks and Discomforts

- Blood Sampling
  - Discomfort from needle, possible bruising

- Potential side effects from supplement:
  - gastrointestinal discomfort
  - nausea
  - dizziness
  - headache
  - sleepiness
  - urinary retention
  - urinary frequency
  - constipation
  - increased perspiration
Costs and Funding Source

- No cost to you for your participation

- All study costs are funded by Toyo Shinyaku Co., Ltd.

- You will obtain free information about your lab test results at the end of the study

- Compensation of $100
  (plus parking permits totaling $25 in value)
PART B: GENERAL INFORMATION ABOUT BEING A RESEARCH PARTICIPANT
Participation in Other Studies

Allowed only if informed approval is obtained from the investigators of both projects
Women of Childbearing Age

- You can’t be in this study if you are pregnant or lactating
- You should not join this study if you are planning to become pregnant in the next year
- Any nutritional supplement may involve unforeseen risks to you and your unborn fetus
Blood: Sampling and Storage Issues

- No genetic testing
- No development of commercial products
- No use of samples without your permission
- Any extra blood will be discarded
Right to Refuse or Withdraw

- Your participation in this research study is entirely voluntary – you may choose to withdraw at ANY TIME (and this decision will not affect your medical/health care)

- There are several reasons for which you may be withdrawn from the study:
  - Failure to follow instructions
  - Continuation determined to be harmful to you
  - You need treatment not provided by study
  - Study is cancelled
  - Other administrative reasons
  - Unanticipated circumstances
Personal Health Information (PHI)

- Name
- Phone number
- Address
- Date of birth

- All PHI and clinical information will be destroyed after 6 years.

- Your data will not be published

- Your identity will not be revealed
Confidentiality/Anonymity

- You will be assigned a second ID number
- Your data will be kept in a locked room or in the case of electronic files, in a password protected manner
- Absolute confidentiality cannot be guaranteed

Patient information may be provided to Federal and other regulatory agencies as required
Alternatives

- Nutrition – Low sodium diet, plant based diet, weight loss
  - Talk to a Registered Dietitian

- Prescription Medications –
  - Talk to your physician regarding whether it is reasonable for you to participate in this study
Financial Interest Disclosure

- No Conflict of Interest

- Neither the investigators nor Stanford University have stock or investment interests in Toyo Shinyaku Co., Ltd.
Call the Principal Investigator:

Randall S. Stafford, MD, PhD
(650) 724-2400
Complications

Administrative Panel on Human Subjects in Medical Research
Stanford University
Stanford, CA 94305-501

Call: (650) 723-5244
New Information

- You will be informed if new information arises
Human Subjects Bill of Rights

- See Page 12 of Your Consent Form
THANK YOU!

FOR ATTENDING THE UPBEAT STUDY ORIENTATION