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!**

BACKGROUND

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 **improves migraine headaches –** Kaiser Permanente Dept. of Neurology (2006).
- Pine bark **reduces asthma** and improves lung function – Hosseini (2001), Lau (2004).
- Pine bark **improves vessel function** in patients with chronic venous insufficiency – Cesarone (2006).
- Pine bark **reduces symptoms of ADHD** in children – Trebaticka (2006).
- Pine bark **relieves menstrual cramps** – Kohama (2004).
- Pine bark **improves sexual function** in men with erectile dysfunction – Stanislavov (2003).

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

Stanford

Prevention

Research

Center

- 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

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

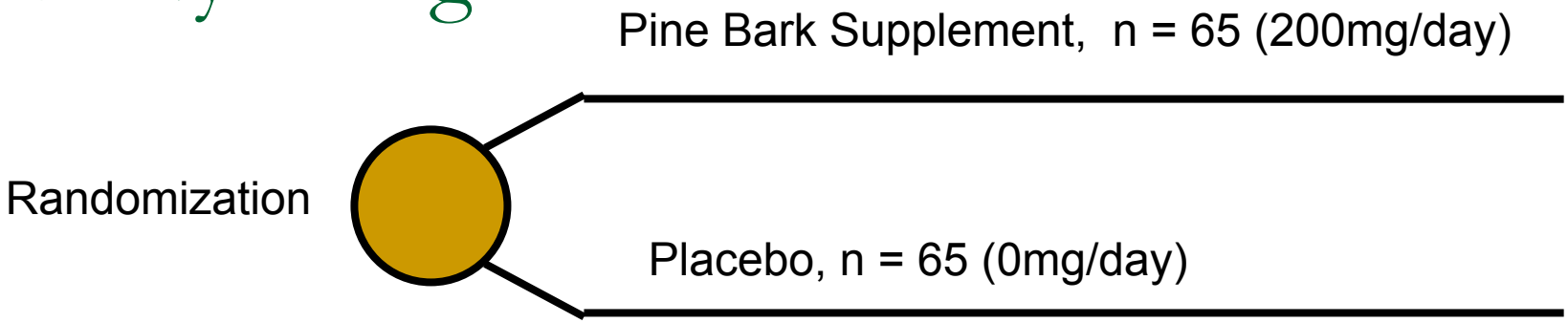
- **For age < 70 years:**
  - Systolic Blood Pressure ≥ 145 mmHg
  - Diastolic Blood Pressure ≥ 95 mmHg
  - Low Density Lipoprotein (LDL) ≥ 170 mg/dL
  - Triglycerides (TG) ≥ 300 mg/dL or
  - Fasting blood glucose (FBG) ≥ 110 mg/dL

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



Total of 130 individuals in the study

Assigned by “CHANCE” NOT BY CHOICE

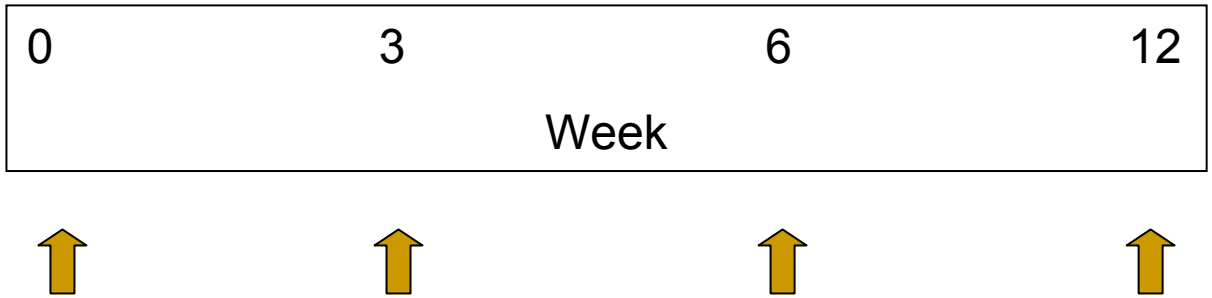
No bias of who gets what treatment

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

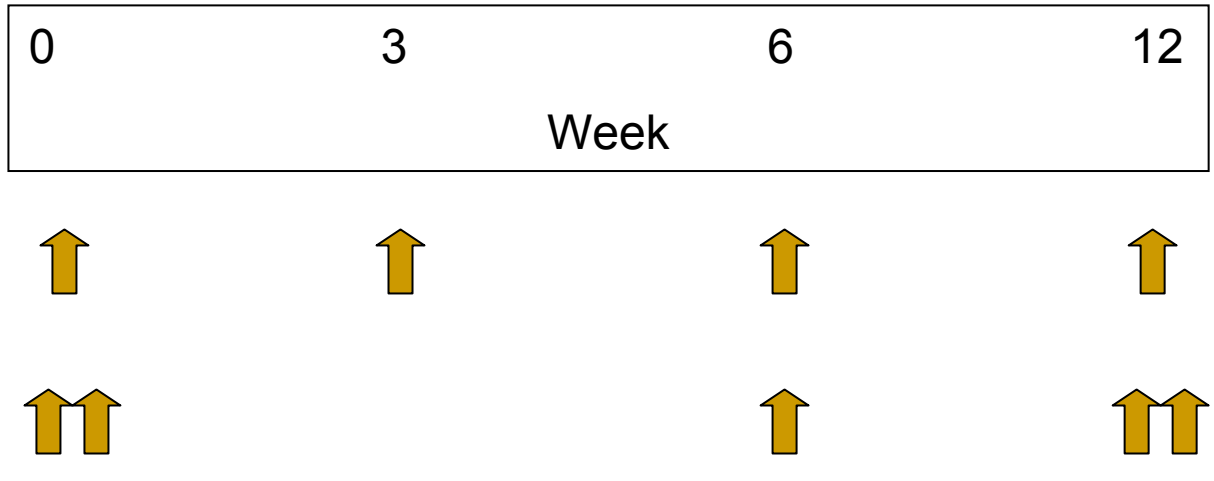


1. **Tablets**

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



1. Tablets

2. Blood Pressure

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

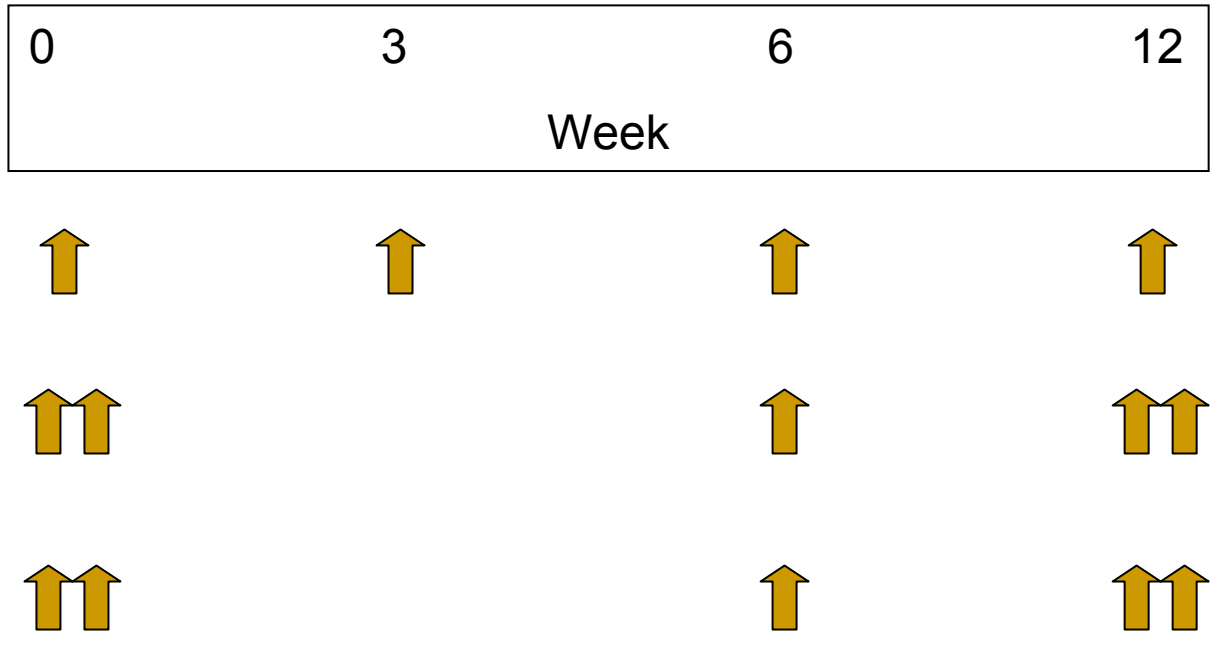
- Weight
- Waist circumference
- These Measurements will be measured:

  Twice at Baseline Visits (3 to 7 days apart)

  Once at 6 weeks

  Twice at 12 weeks (3 to 7 days apart)

Procedures



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:

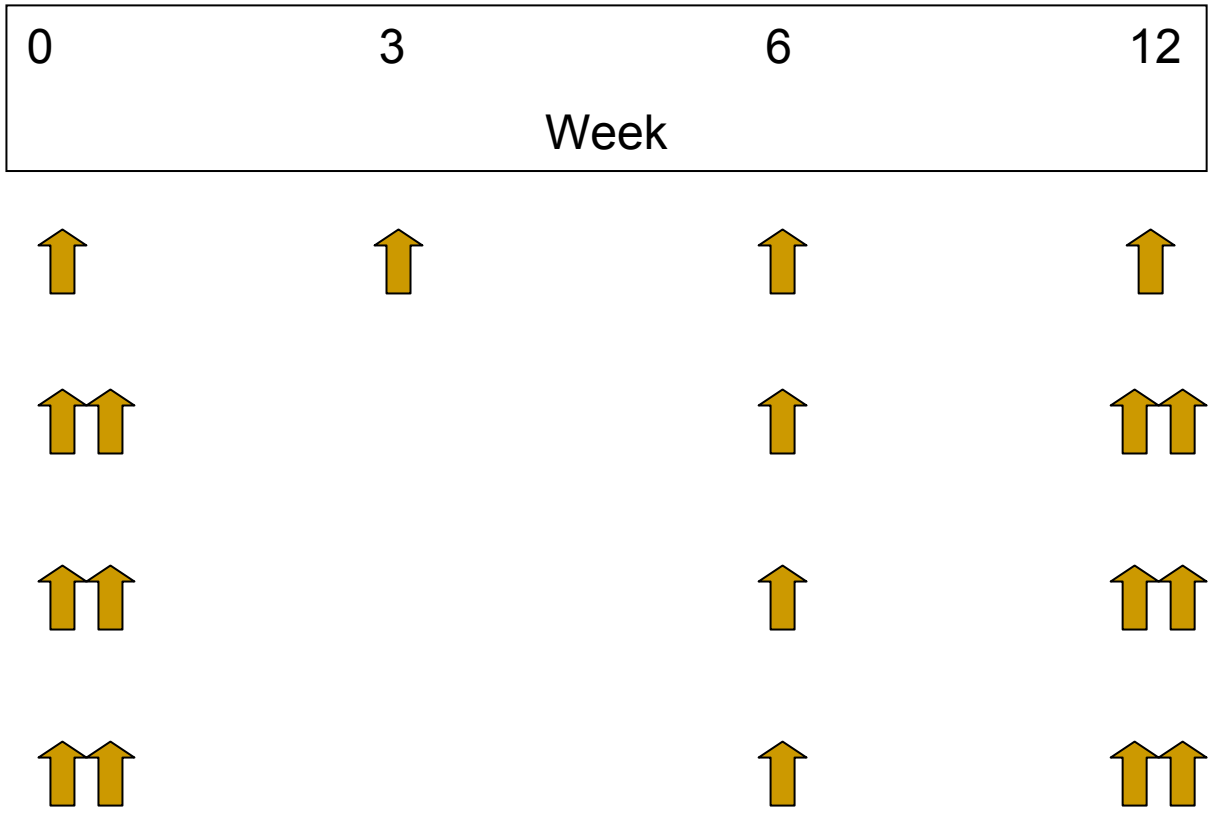
Blood Glucose	Fasting blood glucose
	Hemoglobin A1C
	Fasting insulin
Cholesterol and Inflammation	Lipid Panel
	Low density lipoprotein particle size
	Lipoprotein A
	C-Reactive protein
Liver Function	Aspartate aminotransferase (AST)
	Alanine Aminotransferase (ALT)

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.

Procedures


0
3
6
12
Week
1. Tablets
2. Blood Pressure
3. Blood Sampling
4. Questionnaires

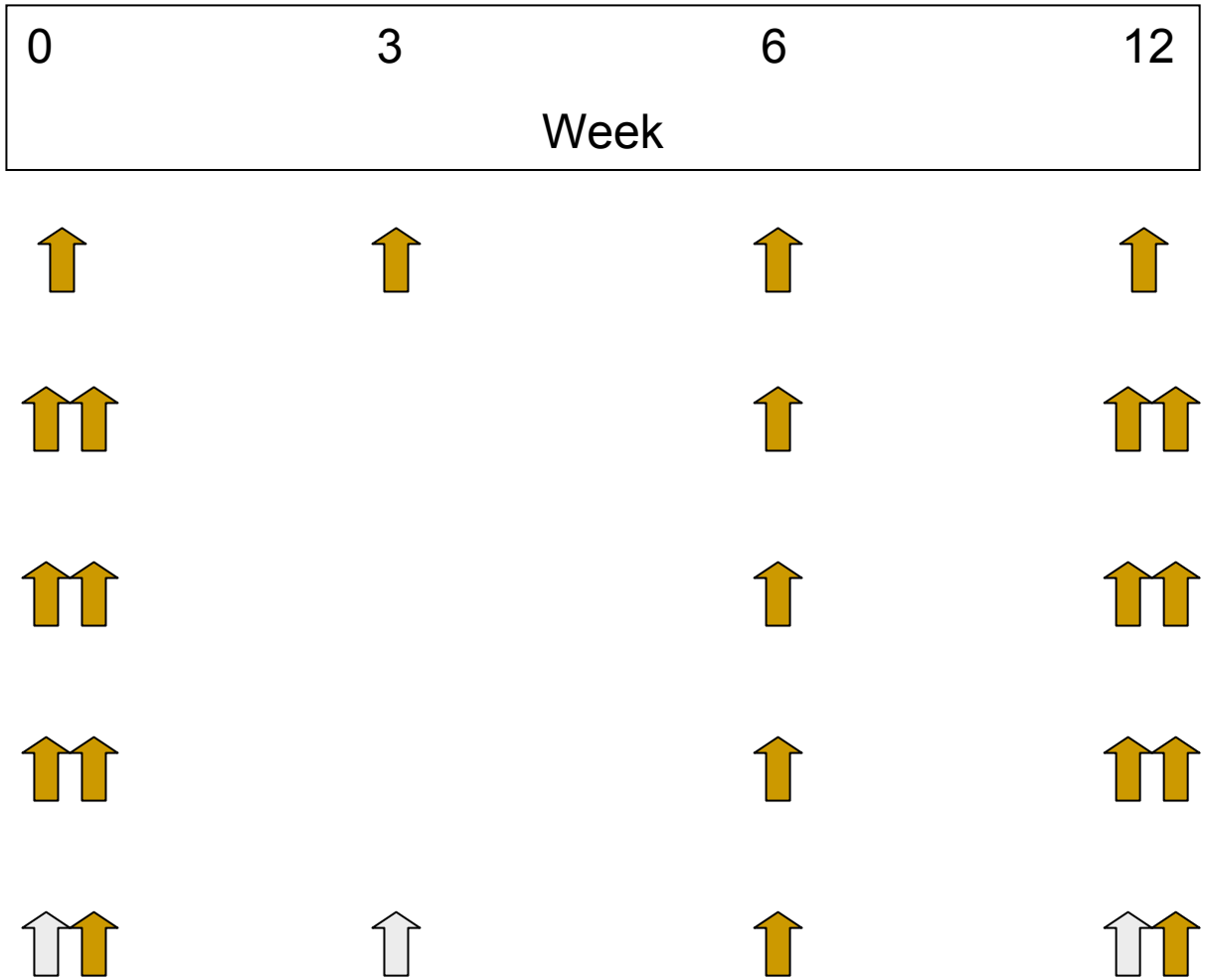
Procedures: 4. Questionnaires

- 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


0
3
6
12
Week
1. Tablets
2. Blood Pressure
3. Blood Sampling
4. Questionnaires
5. Compensation

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.

Questions

- 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