Consent to Participate in Research

Study Title: Effects of Freeze Dried Strawberry Powder Supplementation on Vascular Function, Blood Markers of Cardiovascular Risk, and the Gut Microbiome

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Sponsor: California Strawberry Commission

Summary of the research

This is a consent form for participation in a research study. Your participation in this research study is voluntary. It contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to ask questions before making your decision whether or not to participate.

You are being asked to participate in a study of freeze dried strawberry supplementation. The purpose of this study is investigate the potential health benefits of consuming freeze dried strawberry powder on cardiovascular disease (CVD) risk factors, such as bad cholesterol and high blood pressure. The study will take approximately 16-20 weeks total and will require daily consumption of strawberry or placebo powders. You will also be asked to provide blood and fecal samples, and undergo noninvasive measurements of your blood pressure. The total time commitment (including testing visits and supplement pick-ups) will be approximately 8 hours total over the 16-20 weeks. There is minimal risk from study procedures, and you will receive no direct benefit from your participation. Your participation in this research study is voluntary and can be discontinued at any time.

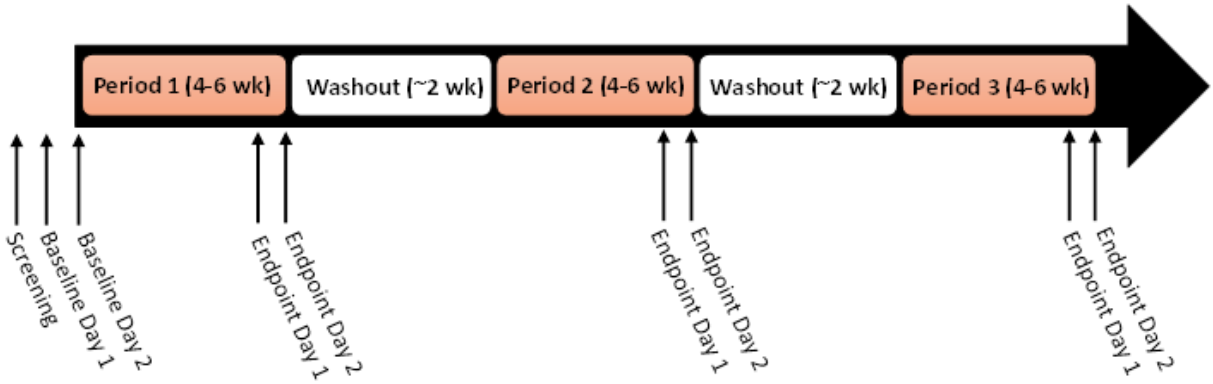
Why is this study being done?

Some studies of strawberries have reported reductions in risk factors for cardiovascular disease (CVD). This research is being done to find out the effect of a freeze dried strawberry powder on blood lipids, the health of your blood vessels, the gut microbiome, and other important cardiovascular disease (CVD) risk factors.

What will happen if I take part in this study?

General Overview of the Study

If you agree to participate in this study, your commitment would consist of three 4-6 week long treatment periods separated by an approximately two week long break between periods. Each of the 3 treatments (a higher dose of freeze dried strawberry powder, a lower dose of freeze dried strawberry powder, and a placebo powder) will be provided as ~40 g (~1.4 ounces) packages that are to be consumed daily. You should mix the powder into water and consume it in between meals rather than with food. You may consume the powder all at once or divide your dose throughout the day (e.g. ½ between breakfast and lunch, and ½ between lunch and dinner). The higher dose of freeze dried strawberry powder provides 40 g of freeze dried strawberries, which is equivalent to ~3 servings of fresh strawberries. The lower dose of freeze dried strawberry powder provides 13 g of freeze dried strawberries and is equivalent to ~1 serving of fresh strawberries. The placebo powder is matched so that it will have a similar taste and appearance to the freeze dried strawberry powder. You will be randomly assigned to the order in which you receive the two freeze dried strawberry doses and placebo, and your treatment order may be different from that of other participants. This assignment is done in a way that is similar to flipping a coin – we use a computer program to assign the order of treatments that you will receive.



During each treatment period, you will be required to avoid consuming any other foods or drinks that contain strawberries and other berries. You will be required to pick up your treatments every two weeks at the University of Arizona Collaboratory for Metabolic Disease Prevention and Treatment, and we will record your weight at this visit. In addition, you will be required to complete a log of your daily treatment powder intake. This is **not a weight-loss study,** so you must try to keep your body weight constant and your exercise level consistent throughout the entire study.

Screening Visit Procedures

If you decide to participate in the study and are considered eligible after the telephone screening, you will be further screened to determine your eligibility during a visit to the University of Arizona Collaboratory. The visit will consist of filling out forms (informed consent, medical history, personal information); measuring height and weight so that your body mass index (BMI) can be calculated; and measuring blood pressure (BP). If it is determined that you are still eligible after these measurements, a blood sample will be taken from your arm or hand for common blood tests (including a complete blood cell count, measures of liver and kidney function, and a blood fat panel) to determine your health status (approximately 15 mls of blood or ~1 tablespoon will be taken). You will feel a small pinch or discomfort when the needle is inserted. If the initial blood draw is unsuccessful, it may need to be repeated, with your permission. In addition, if you take thyroid medication you must provide the results of a current (within 6 months) thyroid lab test. If you do not have results, an extra 3.5 ml (0.2 Tbsp) of blood will be taken to conduct a thyroid test. If you are female of childbearing potential, you will be given a urine pregnancy test. You will be contacted within 3-5 days with the results of the screening bloodwork. The study investigators will review all of the screening data, and if you are still eligible for the study, you will be contacted to schedule your start date and baseline visit appointments. There will be no charge for the screening blood work or measurements, and you will receive these results. If you agree to participate in this study, you are also agreeing to check with the study staff before participating in any other research studies so that the study coordinator can determine if it is alright for you to participate. Also, you will only be included in this study if you agree to refrain from donating blood within 2 weeks of study test visits.

Baseline and Endpoint Testing Procedures

- Blood sampling: **Prior to having your blood taken, you cannot consume any food or drink except water for 12 hours and cannot drink alcohol for 48 hours. You also cannot engage in vigorous physical activity 12 hours prior to having your blood taken**. In addition to the blood taken at screening, three blood samples will also be taken at

baseline and the end of each test period (for a total of 12 times after screening). On two consecutive days, a blood sample will be taken from your arm after a twelve hour fast (consumption of no food or drinks except water). If the initial blood draw is unsuccessful it may need to be repeated, with your permission. Approximately 65 ml (~2 oz) of blood will be collected at baseline and at the end of each treatment period, on two separate days. Over the 16-20-week study, blood will be taken 12 times, with a total amount of ~260 mL (~ 9 oz), in addition to the blood that is taken for screening tests prior to the study (~15 mL, one tablespoon). A typical American Red Cross blood donation is 1 pint (~473 ml) per 8 weeks. Blood samples will be frozen and analyzed at the end of the study (once all participants have completed the study). The results of the study will only be available at the end of the entire study (which may take more than a year). Your blood may be tested for the following: blood fats (total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides), blood sugar (glucose, insulin), markers of inflammation, and strawberry bioactives. If you are a female of childbearing potential, you will be asked to provide a urine sample for pregnancy testing at baseline and at the end of each treatment period. If you become pregnant, you cannot continue your participation in the study. Your weight will also be measured at these visits.

- Pulse Wave Analysis (PWA) and Pulse Wave Velocity (PWV): On one of the consecutive testing days at baseline and the end of each supplementation period, you will also undergo tests that measure your blood pressure and pulse waveforms. These tests will be performed following the fasting blood sample. Pre-menopausal women will also be scheduled for these tests within the first 7 days of starting their menstrual period. The PWA measurement is very similar to a routine blood pressure measurement. Prior to the measurement, you will be asked to sit quietly with your feet flat on the floor for at least 5 minutes. A blood pressure cuff will be placed on your upper arm. The cuff will inflate, then deflate for 5 seconds, and then partially re-inflate. It is important that you remain quiet and still during this measurement. The procedure will be repeated twice, for a total of 3 measurements, with about 1 minute of rest between each. Repeated measurements are used to increase accuracy. For the PWV measurement, we will ask you to lay flat on a hospital bed without a pillow. A blood pressure cuff will be placed on your upper leg. We will gently place a hand-held sensor against an artery in your neck. This will measure the pressure waves of the blood in your artery. Once a good waveform is obtained, the blood pressure cuff on your leg will inflate to measure the pressure waveforms in that artery. Having these simultaneous measurements allows the device to calculate the speed at which blood is traveling through your arteries. The

PWV test will also be performed three times with about one minute between measurements.

How long will I be in this study?

If you agree to take part, it will take you about 16-20 weeks to complete this research study. Your participation in the study will consist of 3 treatment phases, each lasting 4-6 weeks and separated by a ~2 week compliance break. The total time for study visits at the Collaboratory, after initial screening, is approximately 480 minutes or 8 hours. Times may vary and pre-menopausal women will require an additional 5 minutes for a urine pregnancy test at screening, baseline, and the end of each treatment period. The following is an estimate of the amount of time participants will spend in study activities:

Screening appointment

- Forms, blood pressure, weight, height, and blood draw: 45- 60 minutes
- Pregnancy testing (pre-menopausal females only): 5 minutes

Baseline (prior to treatment 1)

- Day 1
  - Blood draw and weight: 15 minutes
  - PWA/PWV testing, followed by blood draw: 45 minutes
  - Pregnancy testing (pre-menopausal females only): 5 min minutes
- Day 2
  - Blood draw: 15 minutes

End of treatment periods 1, 2, and 3

- Day 1
  - Blood draw and weight: 15 minutes
  - PWA/PWV testing, followed by blood draw: 45 minutes
  - Pregnancy testing (females only): 5 minutes
- Day 2
  - Blood draw: 15 minutes

Bi-weekly visits to pick up treatments: 15 minutes/visit (~90 minutes)
At home: completing daily consumption logs (~15 minutes total)

Total time commitment (including supplement pick-ups) is ~8 hours.

How many people will take part in this study?

Approximately 50 people will take part in this research study.

What benefits can I expect from being in this study?

No benefit from participation in this study is guaranteed. There is growing interest in defining dietary patterns that can prevent the development of CVD risk. You will contribute to research that will advance our knowledge of the potential benefits of strawberry consumption with regard to CVD risk factors such as LDL cholesterol and blood pressure. You will receive screening laboratory analysis, including a complete blood cell count, measures of liver and kidney function, and blood fat values, at no cost to you. The final results of the study will not be available until all of the analyses are completed, which may take more than a year.

What risks, side effects or discomforts can I expect from being in the study?

Study treatments: You should not participate in this study if you have any sensitivity strawberries. The freeze dried strawberry and placebo powders are provided by the California Strawberry Commission. It is unlikely that you will experience any discomfort with the addition of the powder to your diet. However, you may have an unknown sensitivity to strawberries that causes you to experience headaches or GI (stomach) upset such as stomachache, diarrhea, or gas. You should report any adverse reactions to study personnel.

Blood Sampling: Blood draws often cause mild pain, swelling, or bleeding. There may be some bruising (blood under the surface of the skin), which will be minimized by pressing on the site after the needle is removed. There is also a slight chance of infection, dizziness, or fainting. These risks will be minimized, and most likely eliminated, by having trained medical staff draw the blood in a clinical setting using sterile supplies. If dizziness or fainting occurs, the symptoms will be alleviated by having you lie flat with your feet raised. The medical staff will also ask you to remain at the clinic until your blood pressure has been checked and you are cleared from any further risk.

Pulse Wave Analysis (PWA) and Pulse Wave Velocity (PWV): There are no known risks associated with these measurements. The sensation of pressure from the blood pressure cuff or hand-held probe may be uncomfortable. There is a possibility of red blotching or mild bruising (petechiae) appearing on the skin above and below the location of the blood pressure cuff. Studies indicate that the occurrence of petechiae is rare (occurring in less than ½ of 1% of patients), and it is typically not uncomfortable and does not require treatment.

There is a risk of loss of confidentiality if your information or your identity is obtained by someone other than the investigators, but precautions will be taken to prevent this from happening.

What other choices do I have if I do not take part in this study?

Your participation is voluntary. You may refuse to participate in this study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your usual benefits. Your decision will not affect your future relationship with The University of Arizona. If you are a student or employee at the University of Arizona, your decision will not affect your grades or employment status.

When may participation in the study be stopped?

Your participation in this study is voluntary. A participant may be withdrawn from the study at any time, either at the investigator's discretion or the participant's request. If you choose to stop your participation in the study, there is no consequence for doing so. Please inform study personnel of your decision in a timely manner. The person in charge of the research study can remove you from the research study without your approval. Possible reasons for removal include non-compliance with study protocol. Successful completion of this study depends on the total cooperation of the participants. If you cannot comply with study procedures (such as consuming the intervention or attending clinic visits), you will be asked to leave the study. Every effort will be made to give you a chance to comply with the study requirements, but if you do not follow the study protocol described above, you may be dropped from the study. In addition, please advise us of any medical events (such as illness, injury, surgery, etc.) that arise during the course of the study. Depending on the event, we may require you to obtain medical clearance before continuing with the study. Some medications may also interfere with our study outcomes so please inform us of any medication changes.

What happens if I am injured because I took part in this study?

Side effects (injury) can happen in any research study. These effects may not be your fault or the fault of the researcher involved. Known side effects have been described in this consent form. However, side effects that are not currently known may happen and require care. In the unlikely event that you become injured, medical care is available. If you suffer an injury from participating in this study, you should seek treatment. If you experience an injury or adverse event, please call Dr. Chesney Richter at 520-621-5382 immediately. The University of Arizona has no funds set aside for the payment of treatment expenses for this study. This, however, does not waive your rights in the event of negligence.

You will be provided with any new information that develops during the course of the research that may affect your decision whether or not to continue participation in the study.

What are the costs of taking part in this study?

Other than time and transportation, participants will not bear any additional costs due to their participation in this research study.

Will I be paid for taking part in this study?

For your time and participation in the study you will receive monetary compensation of $200.00, prorated and paid as follows:

Completion of first study period and endpoint testing: $50
Completion of second study period and endpoint testing: $75
Completion of third study period and endpoint testing: $75
Total for completion of the study = $200

Compensation for participation in a research study is considered taxable income for you. We are required to obtain your name, address, and Social Security number for federal tax reporting purposes. If your compensation for this research study or a combination of research studies is $600 or more in a calendar year (January to December), you will receive an IRS Form 1099 to report on your taxes.

Will my data or specimens be stored for future research?

In the main part of this study, we are collecting blood and fecal samples from you. There may be some specimens remaining after the study is complete. If you are willing to allow the remaining specimens to be used for future research studies, you must specify your consent below. Leftover samples will be labeled with a code number and stored in Dr. Skulas-Ray's locked laboratory.

If you agree, the samples may be used for other research after this study is over. These future studies may be helpful in understanding cardiovascular disease. It is unlikely that these studies will have a direct benefit to you. Neither your doctor nor you will receive results of these future research tests, nor will the results be put in your health record. Sometimes samples are used for genetic research about diseases that are passed on in families. Even if your sample(s) are used for this kind of research, the results will not be put in your health record. It is possible that your blood might be used to develop products or tests that could be patented and

licensed. There are no plans to provide financial compensation to you should this occur. If you have any questions, you should contact a member of the research team.

The length of time that leftover samples may be used is unknown. Consent for future use of your remaining samples is entirely voluntary and may be withdrawn at any time. If you decide now that your samples can be kept for research, you can change your mind at any time. Contact the study investigators to tell them you do not want your samples to be used, and they will no longer be used for research. However, we will not be able to identify your samples after we destroy the code break that links your name to your study ID number (6 years after study completion). If your samples have already been used for research it will not be possible to get them back. If it is still possible to identify your samples, any unused blood samples will be destroyed and not used for future research studies.

Please read each sentence below and think about your choice. After reading each sentence, initial on the line for "Yes" or "No." You can participate in the main portion of the study without consenting to the storage and use of leftover samples. If you have any questions, please ask the study investigators.

1. Your sample*[s]* may be stored and used for future research studies to learn about, prevent, treat, or cure cardiovascular disease and other health problems.

   _____ Yes _____ No

2. Your sample*[s]* may be shared with other investigators/groups without any identifying information.

   _____ Yes _____ No

3. Study investigators may contact you in the future to ask about taking part additional research studies.

   _____ Yes _____ No

Will my specimens be sold for commercial profits?

Specimens may be used in this research or other research, and shared with other organizations. You will not share in any commercial value or other compensation from products developed using the information/specimens.

Will I hear back on any results that directly impact me?

You will receive screening laboratory analysis, including a complete blood cell count, measures of liver and kidney function, and blood fat values, at no cost to you. You will not receive any clinically relevant results discovered about you and/or the general subject population.

Will Whole Genome Sequencing be done with my specimen?

To our knowledge at this time, whole genome sequencing will not be done.

Will my study-related information be shared, disclosed, and kept confidential?

All efforts will be made to limit the use and sharing of your personal research information to people who have a need to review this information. NO personal information will be kept with any sample. You will be assigned a study ID# and only the Principal Investigators and Study Coordinators will have access to the ID# assignments with the study files. Your research records will be labeled with your unique ID number and no names will be used. All records associated with your participation in the study will be subject to the usual confidentiality standards applicable to medical records and will be kept in a locked file at the PI's research office or in a password protected electronic file. Your research samples will be labeled with your unique ID number and they will be stored in locked freezers at the Collaboratory and in 313 Shantz Building. They will be maintained until three years after the date from when the study is published, and then destroyed unless you give permission for us to keep your blood samples for future use (see end of document).

In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Efforts will be made to keep your study-related information confidential. However, there may be circumstances where this information must be released.

Also, your records may be reviewed by the following groups:

- The University of Arizona Institutional Review Board
- Office for Human Research Protections or other federal, state, or international regulatory agencies
- The sponsor supporting the study, their agents or study monitors

Some of these records could contain information that personally identifies you. Reasonable efforts will be made to keep the personal information in your research record private. However, absolute confidentiality cannot be guaranteed.

Who can answer my questions about this study?

If at any time you feel you have had a research-related injury, or for questions, concerns, or complaints about the study you may contact **Dr. Chesney Richter at 520-621-5382**.

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, you may contact the Human Subjects Protection Program at 520-626-6721 or online at http://rgw.arizona.edu/compliance/human-subjects-protection-program.

If you are injured as a result of participating in this study or for questions about a study-related injury, you may contact **Dr. Chesney Richter at 520-621-5382**.

An Institutional Review Board responsible for human subjects research at The University of Arizona reviewed this research project and found it to be acceptable, according to applicable state and federal regulations and University policies designed to protect the rights and welfare of participants in research.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Signing the consent form

I have read (or someone has read to me) this form, and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study and I authorize the use and/or disclosure of my PHI. I am not giving up any legal rights by signing this form. I will be given a signed copy of this form.

Printed name of subject	Signature of subject	Date

Investigator/Research Staff

I have explained the research to the participant or the participant's representative before requesting the signature(s) above. There are no blanks in this document. A signed copy of this form has been given to the participant or to the participant's representative.

Printed name of person obtaining consent	Signature of person obtaining consent	Date