Safety and Pharmacokinetics of an Extract of Naringenin

Clinical Trials Identifier: NCT03582553

Date: 12-2-2019

Pennington Biomedical IRB FWA 00006218
Approved May 7, 2018

KEY INFORMATION CONSENT
TO PARTICIPATE IN A RESEARCH STUDY FOR AN ADULT
INFORMED CONSENT - PART IA
COHORT 1

Title of Study: Clinical Safety and Pharmacokinetic Evaluation of Naringenin: Single Dose Escalation Randomized Double Blind Controlled Trial

Study Sponsor: Louisiana Clinical and Translational Science Center (LA CaTS)

Principal Investigator: Candida Rebello, Ph.D. **Office:** (225)763-3159

1- What you should know about a research study
We give you this key information section of the consent form so that you may read and understand the reasons why you might or might not want to participate in the research. Your participation is voluntary.

2- What is the purpose of this study?
The purpose of this study is to determine the safety and tolerability of naringenin which is a substance found in citrus fruits such as oranges, grapefruits, and limes. The naringenin that will be tested in this study is extracted from oranges. Naringenin is a dietary supplement that is marketed in the United States.

3- What are the possible risks and discomforts?
There is a possibility of pain, bruising, or infection at the site of the needle insertion for the IV line. Trained personnel minimize this risk.

There are no known risks from consuming naringenin with the exception that it could interfere with certain medications. Therefore, we ask that you inform us if you are taking any medications.

Since naringenin is a substance found in citrus foods (such as oranges, lemons, grapefruit, and tomatoes) it could cause an allergic reaction in people who have citrus allergies. Therefore, we ask that you inform us if you have citrus allergies.

The amount of naringenin found in oranges varies. The dose of150 mg naringenin could be found in approximately four to 12 oranges. The investigators will consider the results of your blood tests as well as any adverse events you may experience. You will receive the 300 mg dose only if you tolerate the 150 mg dose of naringenin.

4- What are the possible benefits?
We cannot promise any benefits from your being in the study.

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5- If you do not want to take part in the study, are there other choices?

You have the choice at any time not to participate in this research study. If you choose not to participate, any health benefits to which you are entitled will not be affected in any way.

6- What will happen if you take part in this study?

After passing the screening, you will have six study visits all at the Pennington Center. On one occasion you will have a 13 hour visit at our inpatient unit. During this time blood will be collected for testing 8-10 times through an IV line placed in your arm. At 3 visits you will be asked to consume either:

1. Capsules containing naringenin extracted from oranges.
2. Capsules containing cellulose a filler commonly used in dietary supplements (placebo).

However, to optimize the study results, you will not be told which of the two types of pills you have been given at each visit. Whether you receive naringenin or the placebo is determined through a procedure similar to drawing numbers from a hat. The doses being tested are 150 mg and 300 mg. You will be given the 300 mg dose if you are able to tolerate the 150 mg dose.

The study will take place over a period of six months. Your expected time in this study will be six to eight weeks.

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CONSENT TO PARTICIPATE IN A RESEARCH STUDY FOR AN ADULT
INFORMED CONSENT - PART IB
COHORT 1

Title of Study: Clinical Safety and Pharmacokinetic Evaluation of Naringenin: Single Dose Escalation Randomized Double Blind Controlled Trial

Study Sponsor: Louisiana Clinical and Translational Science Center (LA CaTS)

What you should know about a research study

- We give you this consent form so that you may read about the purpose, risks and benefits of this research study.
- The main goal of research studies is to gain knowledge that may help people in the future.
- You have the right to refuse to take part, or agree to take part now and change your mind later on.
- Please review this consent form carefully and ask any questions before you make a decision.
- Your participation is voluntary.
- By signing this consent form, you agree to participate in the study as it is described.

1- Who is doing the study?

Principal Investigator:	Candida Rebello, Ph.D., R.D., LDN 225-763-3159
Medical Investigator:	Frank Greenway, M.D. 225-763-2576 24-hr. Emergency Phone Nos.: (Weekdays 7:00 a.m.-4:30 p.m.) (225) 765-4644 (After 4:30 p.m. and Weekends)
Co-Investigators:	Leanne Redman, Ph.D. Eric Ravussin, Ph.D. Juan Lertora, M.D., Ph.D.,

Dr. Candida Rebello directs this study, which is under the medical supervision of Dr. Frank Greenway. We expect about 18 people from one site will be enrolled in this study. The study will take place over a period of six months. Your expected time in this study will be two months. This is a Pennington Biomedical Research Center study.

2- Where is the study being conducted?

This study takes place at the Pennington Biomedical Research Center.

3- What is the purpose of this study?

The purpose of this study is to determine the safety and tolerability of naringenin which is a substance found in citrus fruits such as oranges, grapefruits, and limes. The naringenin that will be tested in this study is extracted from oranges. Naringenin is a dietary supplement that is marketed in the United States.

4- Who is eligible to participate in the study?

Inclusion Criteria

- Have a body mass index (BMI) in the range 20 kg/m^2 to 35 kg/m^2 (a number calculated from your height and weight).
- Are ≥ 18 years of age
- Have no evidence of diabetes (fasting blood sugar <126 mg/dL)
- Willing to refrain from consuming citrus fruits in any form and tomato products for 36 hours prior to each test day.

You may not qualify for this study based on other eligibility criteria not listed. The study coordinator will go over this information in detail.

5- What will happen to you if you take part in the study?

After passing the screening, your participation in the research study will be 6 to 8 weeks. You will have six study visits all at the Pennington Center. On one occasion you will have a 13 hour visit at our inpatient unit. During this time blood will be collected for testing which is explained later in this consent. At 3 visits you will be asked to consume either:

1. Capsules containing 150 mg naringenin extracted from oranges.
2. Capsules containing 300 mg naringenin extracted from oranges
3. Capsules containing cellulose, a filler commonly used in dietary supplements (placebo).

You will be given the two doses of naringenin and the placebo, each at separate visits. However, to optimize the study results, you will not be told which of the three types of capsules you have been given at each visit. Whether you receive naringenin or the placebo at each visit is determined through a procedure similar to drawing numbers from a hat. You will be given the 300 mg dose if you are able to tolerate the 150 mg dose.

CLINIC VISITS

Please note that all times provided for procedures are the total times for each clinic visit and are approximations that may vary depending on circumstances. The following chart shows what will happen at each study visit:

Summary of Study Visits and Procedures							
	Screening	Visit 1a	Visit 1b	Visit 2a	Visit 2b	Visit 3a	Visit 3b
Consent	x						
Height	x						
Weight	x	x		x		x	
Blood Pressure/Pulse/Temperature	x	x		x		x	
Medical History Questionnaire	x						
Pregnancy Test (Urine)*	x						
Recording of Medications	x						
Blood Collection for Health Measures	x						
Adverse Events		x	x	x	x	x	x
Blood Collection for Measurement of Naringenin (study supplement)			x				x
Blood Collection for Measurement of Naringenin (study supplement) 4 hours After Dose						x	
Blood Collection for Health Measures (0 hr)		x		x		x	
Blood Collection for Health Measures (24 hrs later)			x		x		x
Naringenin Administration (study supplement)		x		x		x	
IV Placement		x					
Blood Collection at 0, 2, 3, 3.5, 4, 4.5, 6, 8, and 12 hours After Dose		x					
* Women of Child bearing potential							

Screening Visit (1½ hours)

Before visit, fast for at least 8 hours, which means eat or drink nothing except water

We ask you to report to the Pennington Biomedical Clinic in the morning following an overnight fast (except for water) that began no later than 8 hours prior to the study appointment. If you agree to the procedures by signing the consent form the following tests, measurements, and procedures will be performed:

- Brief personal and family medical history.
- Height, weight, vital signs (blood pressure, pulse, and temperature).
- Recording of medication use.
- Collection of urine specimen for urine analysis to test for pregnancy (for women only).
- Drawing of blood (less than 1.5 tablespoons) to measure your electrolytes (for example, salts), cholesterol, triglycerides, iron, immune cell function, glucose and other standard health measures

After this visit, if you meet the inclusion/exclusion criteria you will be contacted by the study coordinator. You will have six study visits at the Pennington Center. There will be two visits back to back 3 different times with at least one week in between.

The coordinator will provide you with a list of foods that you should avoid for 36 hours prior to each test day.

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Visit 1a (13 hours)

Before visit, fast for at least 8 hours, which means eat or drink nothing except water

To start the study, you will visit the Pennington Biomedical clinic in the morning following an overnight fast (except for water) that began no later than 8 hours prior to the study appointment. We will perform the following tests and measurements:

- Weight, vital signs (blood pressure, pulse, and temperature).
- Blood will be drawn (less than 1.5 tablespoons) to assess standard health measures.
- You will be asked to swallow a capsule containing 150 mg of naringenin or placebo.
- An IV line will be placed in your arm to obtain blood samples eight times for testing the amount of naringenin in your blood. The total amount drawn is about two tablespoons. You will be provided a meal five hours after you take the naringenin dose, and at the end of the blood draws.
- You will be asked about any adverse events.

Visit 1b (½ hour)

Before visit, fast for at least 8 hours, which means eat or drink nothing except water

- This visit will take place the morning after Visit 1a.
- Blood will be drawn (less than 1.5 tablespoons) to assess standard health measures, and for measurement of naringenin levels.
- You will be asked about any adverse events from consuming naringenin.

Visit 2a (½ hour)

Before visit, fast for at least 8 hours, which means eat or drink nothing except water

We ask you to report to the Pennington Biomedical clinic in the morning following an overnight fast (except for water) that began no later than 8 hours prior to the study appointment. We will perform the following tests and measurements:

- Weight and vital signs (blood pressure, pulse, and temperature).
- Blood will be drawn (less than 1.5 tablespoons) to assess standard health measures.
- You will be asked to swallow capsules containing 150 mg or 300 mg of naringenin, or you will receive a placebo.
- You will be asked about any adverse events.

Visit 2b (½ hour)

Before visit, fast for at least 8 hours, which means eat or drink nothing except water

- This visit will take place the morning after Visit 2a.
- Blood will be drawn (less than 1.5 tablespoons) to assess standard health measures.
- You will be asked about any adverse events from consuming naringenin.

Visit 3a (5 hours)

Before visit, fast for at least 8 hours, which means eat or drink nothing except water

We ask you to report to the Pennington Biomedical clinic in the morning following an overnight fast (except for water) that began no later than 8 hours prior to the study appointment. We will perform the following tests and measurements:

- Weight and vital signs (blood pressure, pulse, and temperature).
- Blood will be drawn (less than 1.5 tablespoons) to assess standard health measures.
- You will be asked to swallow capsules containing 300 mg of naringenin or placebo.
- Blood will be drawn four hours after dose (less than 1 teaspoon) for measurement of naringenin.
- You will be asked about any adverse events.

Visit 3b (½ hour)

Before visit, fast for at least 8 hours, which means eat or drink nothing except water

- This visit will take place the morning after Visit 3a.
- Blood will be drawn (less than 1.5 tablespoons) to assess standard health measures, and for measurement of naringenin levels.
- You will be asked about any adverse events from consuming naringenin.

DESCRIPTION OF PROCEDURES

Blood Collection for Health Measures

To determine the safety of naringenin, blood will be drawn (1.5 tablespoons) before you swallow each dose of naringenin, or placebo. You will return 24 hours later (the next morning) and blood will be drawn (2 tablespoons) to repeat the safety testing, and to measure naringenin levels.

Adverse Events

You will be asked about any medical problems you may have experienced since your participation in this study.

Pharmacokinetic Testing

To understand the movement of naringenin through the body, blood will be drawn (less than 1 teaspoon) prior to receiving the dose of naringenin and at specific times (2, 3, 3.5, 4, 4.5, 6, 8, and12 hours) for a total of approximately two tablespoons of blood. An intravenous (IV) line will be placed in your arm vein for blood draw purposes and will remain there throughout the testing. **During your IV procedure, a small amount of your own blood (less than 1 teaspoon) will immediately be returned into your vein through the IV after each specimen is collected.**

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6- What are the possible risks and discomforts?

Blood Draw

There is a possibility of infection and/or pain and bruising at the vein on your arm where the needle is inserted. Aseptic (sterile) technique and trained personnel minimize these risks.

IV Procedure

There is a possibility of pain, bruising, or infection at the site of the needle insertion for the IV line. Trained personnel minimize this risk.

Study Supplement

There are no known risks from consuming naringenin with the exception that it could interfere with certain medications. Therefore, we ask that you inform us if you are taking any medications.

Citrus Allergies

Since naringenin is a substance found in citrus foods (such as oranges, lemons, grapefruit, and tomatoes) it could cause an allergic reaction in people who have citrus allergies. Therefore, we ask that you inform us if you have citrus allergies.

Other Food Allergies

Because of the way our meals are prepared for research, and the possibility that the ingredients in the foods we get from commercial vendors could change at any time without our knowledge, it cannot be guaranteed that allergens will be identified and removed from the foods used in our research studies. If you have a food allergy, and you are participating in a study where foods are provided, there is a risk that you could have an allergic reaction. All participants with known life-threatening food allergies must inform staff of their allergies.

Adverse Events

The amount of naringenin found in oranges varies. The dose of150 mg naringenin could be found in approximately four to 12 oranges. The investigators will consider the results of your blood tests as well as any adverse events you may experience. You will receive the 300 mg dose only if you tolerate the 150 mg dose of naringenin.

In addition to the risks listed above, you may experience a previously unknown risk or side effect.

7- What are the possible benefits?

We cannot promise any benefits from your being in the study. If you take part in this study, you may help others in the future.

8- If you do not want to take part in the study, are there other choices?

You have the choice at any time not to participate in this research study. If you choose not to participate, any health benefits to which you are entitled will not be affected in any way.

9- If you have any questions or problems, whom can you call?

If you have any questions about your rights as a research volunteer, you should call the Institutional Review Board Office at 225-763-2693 or the Executive Director of Pennington Biomedical at 225-763-2513. If you have any questions about the research study, contact Dr. Candida Rebello at 225-763-3159. If you think you have a research-related injury or medical illness, you should call Dr. Frank Greenway at 225-763-2578 during regular working hours. After working hours and on weekends you should call the answering service at 225-765-4644. The on-call physician will respond to your call.

10- What information will be kept private?

Every effort will be made to maintain the confidentiality of your study records. However, someone from the Food and Drug Administration, the National Institutes of Health, or the Pennington Biomedical Research Center, may inspect and/or copy the medical records related to the study. Results of the study may be published; however, we will keep your name and other identifying information private. Other than as set forth above, your identity will remain confidential unless disclosure is required by law.

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.

11- Can your taking part in the study end early?

Dr. Candida Rebello, Dr. Frank Greenway, or the study sponsor can withdraw you from the study for any reason or for no reason. You may withdraw from the study at any time without penalty; however, all data Pennington Biomedical has previously collected cannot be removed from the study. Possible reasons for withdrawal include an inability to comply with the study requirements or medical concerns that would make continued participation not in your best interests. The sponsor of the study may end the study early.

12- What if information becomes available that might affect your decision to stay in the study?

During the course of this study there may be new findings from this or other research which may affect your willingness to continue participation. Information concerning any such new findings will be provided to you. In this study, you will be informed of any clinically relevant research that may be discovered.

13- What charges will you have to pay?

None

14- What payment will you receive?

If you agree to take part, we will compensate you $225 for completion of the study. If your participation ends early you will be compensated based on the following completed visits, $100 for completion of Visits 1a and 1b and $125 on completion of Visits 3a and 3b. You will not be compensated for the screening visit. Your check will be requested from the LSU payroll department when you complete the study or at the appropriate milestone if you are compensated during the course of the study. It usually takes about 3-4 weeks for it to arrive at Pennington Biomedical Research Center.

Payments may only be made to U.S. citizens, legal resident aliens, and those who have a work eligible visa. You will need to provide your social security number to receive payment.

You are subject to a 1099 for receiving compensation. Payments in excess of $600 per calendar year are considered taxable income. If you will be paid more than $600, Pennington Biomedical/LSU will report this income to the IRS.

Non-US citizens are subject to having taxes withheld from payment and will need a passport, visa and 1-94 for payment to be processed.

15- Will you be compensated for a study-related injury or medical illness?

No form of compensation for medical treatment or for other damages (i.e., lost wages, time lost from work, etc.) is available from the Pennington Biomedical Research Center. In the event of injury or medical illness resulting from the research procedures in which you participate, you will be referred to a treatment facility. Medical treatment may be provided at your expense or at the expense of your health care insurer (e.g., Medicare, Medicaid, Blue Cross-Blue Shield, Dental Insurer, etc.) which may or may not provide coverage. The Pennington Biomedical Research Center is a research facility and provides medical treatment only as part of research protocols. Should you require ongoing medical treatments, they must be provided by community physicians and hospitals.

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16- Signatures

The study has been discussed with me and all my questions have been answered. I understand that additional questions regarding the study should be directed to the study investigators. I agree with the terms above and acknowledge that I will be given a copy of this signed consent form.

With my signature, I also acknowledge that I have been given either today or in the past a copy of the Notice of Privacy Practices for Protected Health Information.

_____
Printed Name of Volunteer

_____ _____
Signature of Volunteer Date

_____
Printed Name of Person Administering Informed Consent

_____ _____
Signature of Person Administering Informed Consent Date

Candida Rebello, Ph.D.
Principal Investigator

Frank Greenway, M.D.
Medical Investigator

Pennington Biomedical IRB FWA 00006218
Approved May 7, 2018

KEY INFORMATION CONSENT
TO PARTICIPATE IN A RESEARCH STUDY FOR AN ADULT
INFORMED CONSENT - PART IA
COHORT 2

Title of Study: Clinical Safety and Pharmacokinetic Evaluation of Naringenin: Single Dose Escalation Randomized Double Blind Controlled Trial

Study Sponsor: Louisiana Clinical and Translational Science Center (LA CaTS)

Principal Investigator: Candida Rebello, Ph.D. **Office:** (225)763-3159

1- What you should know about a research study
We give you this key information section of the consent form so that you may read and understand the reasons why you might or might not want to participate in the research. Your participation is voluntary.

2- What is the purpose of this study?
The purpose of this study is to determine the safety and tolerability of naringenin which is a substance found in citrus fruits such as oranges, grapefruits, and limes. The naringenin that will be tested in this study is extracted from oranges. Naringenin is a dietary supplement that is marketed in the United States.

3- What are the possible risks and discomforts?
There is a possibility of pain, bruising, or infection at the site of the needle insertion for the IV line. Trained personnel minimize this risk.

There are no known risks from consuming naringenin with the exception that it could interfere with certain medications. Therefore, we ask that you inform us if you are taking any medications.

Since naringenin is a substance found in citrus foods (such as oranges, lemons, grapefruit, and tomatoes) it could cause an allergic reaction in people who have citrus allergies. Therefore, we ask that you inform us if you have citrus allergies.

The amount of naringenin found in oranges varies. The dose of 600 mg naringenin could be found in approximately 16 to 48 oranges. The investigators will consider the results of your blood tests as well as any adverse events you may experience. You will receive the 900 mg dose only if you tolerate the 150 mg dose of naringenin.

4- What are the possible benefits?
We cannot promise any benefits from your being in the study.

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5- If you do not want to take part in the study, are there other choices?

You have the choice at any time not to participate in this research study. If you choose not to participate, any health benefits to which you are entitled will not be affected in any way.

6- What will happen if you take part in this study?

After passing the screening, you will have six study visits all at the Pennington Center. On one occasion you will have a 13 hour visit at our inpatient unit. During this time blood will be collected for testing which is explained later in this consent. At 3 visits you will be asked to consume either:

1. Capsules containing naringenin extracted from oranges.
2. Capsules containing cellulose, a filler commonly used in dietary supplements (placebo).

However, to optimize the study results, you will not be told which of the two types of pills you have been given at each visit. Whether you receive naringenin or the placebo is determined through a procedure similar to drawing numbers from a hat. The doses being tested are 600 mg and 900 mg. You will be given the 900 mg dose if you are able to tolerate the 600 mg dose.

The study will take place over a period of six months. Your expected time in this study will be six to eight weeks.

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CONSENT TO PARTICIPATE IN A RESEARCH STUDY FOR AN ADULT
INFORMED CONSENT - PART IB
COHORT 2

Title of Study: Clinical Safety and Pharmacokinetic Evaluation of Naringenin: Single Dose Escalation Randomized Double Blind Controlled Trial

Study Sponsor: Louisiana Clinical and Translational Science Center (LA CaTS)

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- The main goal of research studies is to gain knowledge that may help people in the future.
- You have the right to refuse to take part, or agree to take part now and change your mind later on.
- Please review this consent form carefully and ask any questions before you make a decision.
- Your participation is voluntary.
- By signing this consent form, you agree to participate in the study as it is described.

1- Who is doing the study?

Principal Investigator: Candida Rebello, Ph.D., R.D., LDN
225-763-3159

Medical Investigator: Frank Greenway, M.D.
225-763-2576
24-hr. Emergency Phone Nos.:
(Weekdays 7:00 a.m.-4:30 p.m.)
(225) 765-4644 (After 4:30 p.m. and Weekends)

Co-Investigators: Leanne Redman, Ph.D.
Eric Ravussin, Ph.D.
Juan Lertora, M.D., Ph.D.,

Dr. Candida Rebello directs this study, which is under the medical supervision of Dr. Frank Greenway. We expect about 18 people from one site will be enrolled in this study. The study will take place over a period of six months. Your expected time in this study will be two months. This is a Pennington Biomedical Research Center study.

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4- Who is eligible to participate in the study?

Inclusion Criteria

- Have a body mass index (BMI) in the range 20 kg/m^2 to 35 kg/m^2 (a number calculated from your height and weight).
- Are ≥ 18 years of age
- Have no evidence of diabetes (fasting blood sugar <126 mg/dL)
- Willing to refrain from consuming citrus fruits in any form and tomato products for 36 hours prior to each test day.

You may not qualify for this study based on other eligibility criteria not listed. The study coordinator will go over this information in detail.

5- What will happen to you if you take part in the study?

After passing the screening, your participation in the research study will be 6 to 8 weeks. You will have six study visits all at the Pennington Center. On one occasion you will have a 13 hour visit at our inpatient unit. During this time blood will be collected for testing which is explained later in this consent. At each visit you will be asked to consume either:

1. Capsules containing 600 mg naringenin extracted from oranges.
2. Capsules containing 900 mg naringenin extracted from oranges.
3. Capsules containing cellulose, a filler commonly used in dietary supplements (placebo).

You will be given two doses of naringenin and the placebo, each at separate visits. However, to optimize the study results, you will not be told which of the three types of capsules you have been given at each visit. Whether you receive naringenin or the placebo is determined through a procedure similar to drawing numbers from a hat. You will be given the 900 mg dose if you are able to tolerate the 600 mg dose.

CLINIC VISITS

Please note that all times provided for procedures are the total times for each clinic visit and are approximations that may vary depending on circumstances. The following chart shows what will happen at each study visit:

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Summary of Study Visits and Procedures							
	Screening	Visit 1a	Visit 1b	Visit 2a	Visit 2b	Visit 3a	Visit 3b
Consent	x						
Height	x						
Weight	x	x		x		x	
Blood Pressure/Pulse/Temperature	x	x		x		x	
Medical History Questionnaire	x						
Pregnancy Test (Urine)*	x						
Recording of Medications	x						
Blood Collection for Health Measures	x						
Adverse Events		x	x	x	x	x	x
Blood Collection for Measurement of Naringenin (study supplement)			x				x
Blood Collection for Measurement of Naringenin (study supplement) 4 hours After Dose						x	
Blood Collection for Health Measures (0 hr)		x		x		x	
Blood Collection for Health Measures (24 hrs later)			x		x		x
Naringenin Administration (study supplement)		x		x		x	
IV Placement		x					
Blood Collection at 0, 2, 3, 3.5, 4, 4.5, 6, 8, and 12 hours After Dose		x					
* Women of Child bearing potential							

Screening Visit (1½ hours)

Before visit, fast for at least 8 hours, which means eat or drink nothing except water

We ask you to report to the Pennington Biomedical Clinic in the morning following an overnight fast (except for water) that began no later than 8 hours prior to the study appointment. If you agree to the procedures by signing the consent form the following tests, measurements, and procedures will be performed:

- Brief personal and family medical history.
- Height, weight, vital signs (blood pressure, pulse, and temperature).
- Recording of medication use.
- Collection of urine specimen for urine analysis to test for pregnancy (for women only).
- Drawing of blood (less than 1.5 tablespoons) to measure your electrolytes (for example, salts), cholesterol, triglycerides, iron, immune cell function, glucose and other standard health measures

After this visit, if you meet the inclusion/exclusion criteria you will be contacted by the study coordinator. You will have six study visits at the Pennington Center. There will be two visits back to back 3 different times with at least one week in between.

The coordinator will provide you with a list of foods that you should avoid for 36 hours prior to each test day.

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Visit 1a (13 hours)

Before visit, fast for at least 8 hours, which means eat or drink nothing except water

To start the study, you will visit the Pennington Biomedical clinic in the morning following an overnight fast (except for water) that began no later than 8 hours prior to the study appointment. We will perform the following tests and measurements:

- Weight, vital signs (blood pressure, pulse, and temperature).
- Blood will be drawn (less than 1.5 tablespoons) to assess standard health measures.
- You will be asked to swallow capsules containing 600 mg of naringenin or placebo.
- An IV line will be placed in your arm to obtain blood samples eight times for testing the amount of naringenin in your blood. The total amount drawn is about two tablespoons. You will be provided a meal five hours after you take the naringenin dose, and at the end of the blood draws.
- You will be asked about any adverse events.

Visit 1b (½ hour)

Before visit, fast for at least 8 hours, which means eat or drink nothing except water

- This visit will take place the morning after Visit 1a.
- Blood will be drawn (less than 1.5 tablespoons) to assess standard health measures, and for measurement of naringenin levels.
- You will be asked about any adverse events from consuming naringenin.

Visit 2a (½ hour)

Before visit, fast for at least 8 hours, which means eat or drink nothing except water

We ask you to report to the Pennington Biomedical clinic in the morning following an overnight fast (except for water) that began no later than 8 hours prior to the study appointment. We will perform the following tests and measurements:

- Weight and vital signs (blood pressure, pulse, and temperature).
- Blood will be drawn (less than 1.5 tablespoons) to assess standard health measures.
- You will be asked to swallow capsules containing 600 mg or 900 mg of naringenin, or you will receive a placebo.
- You will be asked about any adverse events.

Visit 2b (½ hour)

Before visit, fast for at least 8 hours, which means eat or drink nothing except water

- This visit will take place the morning after Visit 2a.
- Blood will be drawn (less than 1.5 tablespoons) to assess standard health measures.
- You will be asked about any adverse events from consuming naringenin.

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Visit 3a (5 hours)

Before visit, fast for at least 8 hours, which means eat or drink nothing except water

We ask you to report to the Pennington Biomedical clinic in the morning following an overnight fast (except for water) that began no later than 8 hours prior to the study appointment. We will perform the following tests and measurements:

- Weight and vital signs (blood pressure, pulse, and temperature).
- Blood will be drawn (less than 1.5 tablespoons) to assess standard health measures.
- You will be asked to swallow capsules containing 900 mg of naringenin or placebo.
- Blood will be drawn four hours after dose (less than 1 teaspoon) for measurement of naringenin.
- You will be asked about any adverse events.

Visit 3b (½ hour)

Before visit, fast for at least 8 hours, which means eat or drink nothing except water

- This visit will take place the morning after Visit 3a.
- Blood will be drawn (less than 1.5 tablespoons) to assess standard health measures, and for measurement of naringenin levels.
- When you return the next morning, you will be asked about any adverse events.

DESCRIPTION OF PROCEDURES

Blood Collection for Health Measures

To determine the safety of naringenin, blood will be drawn (1.5 tablespoons) before you swallow each dose of naringenin, or placebo. You will return 24 hours later (the next morning) and blood will be drawn (2 tablespoons) to repeat the safety testing, and to measure naringenin levels.

Adverse Events

You will be asked about any medical problems you may have experienced since your participation in this study.

Pharmacokinetic Testing:

To understand the movement of naringenin through the body, blood will be drawn (less than 1 teaspoon) prior to receiving the dose of naringenin and at specific times (2, 3, 3.5, 4, 4.5, 6, 8, and12 hours) for a total of approximately two tablespoons of blood. An intravenous (IV) line will be placed in your arm vein for blood draw purposes and will remain there throughout the testing. **During your IV procedure, a small amount of your own blood (less than 1 teaspoon) will immediately be returned into your vein through the IV after each specimen is collected.**

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6- What are the possible risks and discomforts?

Blood Draw

There is a possibility of infection and/or pain and bruising at the vein on your arm where the needle is inserted. Aseptic (sterile) technique and trained personnel minimize these risks.

IV Procedure

There is a possibility of pain, bruising, or infection at the site of the needle insertion for the IV line. Trained personnel minimize this risk.

Study Supplement

There are no known risks from consuming naringenin with the exception that it could interfere with certain medications. Therefore, we ask that you inform us if you are taking any medications.

Citrus Allergies

Since naringenin is a substance found in citrus foods (such as oranges, lemons, grapefruit, and tomatoes) it could cause an allergic reaction in people who have citrus allergies. Therefore, we ask that you inform us if you have citrus allergies.

Other Food Allergies

Because of the way our meals are prepared for research, and the possibility that the ingredients in the foods we get from commercial vendors could change at any time without our knowledge, it cannot be guaranteed that allergens will be identified and removed from the foods used in our research studies. If you have a food allergy, and you are participating in a study where foods are provided, there is a risk that you could have an allergic reaction. All participants with known life-threatening food allergies must inform staff of their allergies.

Adverse Events

The amount of naringenin found in oranges varies. The dose of 600 mg naringenin could be found in approximately 16 to 48 oranges. The investigators will consider the results of your blood tests as well as any adverse events you may experience. You will receive the 900 mg dose only if you tolerate the 600 mg dose of naringenin.

In addition to the risks listed above, you may experience a previously unknown risk or side effect.

7- What are the possible benefits?

We cannot promise any benefits from your being in the study. If you take part in this study, you may help others in the future.

8- If you do not want to take part in the study, are there other choices?

You have the choice at any time not to participate in this research study. If you choose not to participate, any health benefits to which you are entitled will not be affected in any way.

9- If you have any questions or problems, whom can you call?

If you have any questions about your rights as a research volunteer, you should call the Institutional Review Board Office at 225-763-2693 or the Executive Director of Pennington Biomedical at 225-763-2513. If you have any questions about the research study, contact Dr. Candida Rebello at 225-763-3159. If you think you have a research-related injury or medical illness, you should call Dr. Frank Greenway at 225-763-2578 during regular working hours. After working hours and on weekends you should call the answering service at 225-765-4644. The on-call physician will respond to your call.

10- What information will be kept private?

Every effort will be made to maintain the confidentiality of your study records. However, someone from the Food and Drug Administration, the National Institutes of Health, or the Pennington Biomedical Research Center, may inspect and/or copy the medical records related to the study. Results of the study may be published; however, we will keep your name and other identifying information private. Other than as set forth above, your identity will remain confidential unless disclosure is required by law.

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.

11- Can your taking part in the study end early?

Dr. Candida Rebello, Dr. Frank Greenway, or the study sponsor can withdraw you from the study for any reason or for no reason. You may withdraw from the study at any time without penalty; however, all data Pennington Biomedical has previously collected cannot be removed from the study. Possible reasons for withdrawal include an inability to comply with the study requirements or medical concerns that would make continued participation not in your best interests. The sponsor of the study may end the study early.

12- What if information becomes available that might affect your decision to stay in the study?

During the course of this study there may be new findings from this or other research which may affect your willingness to continue participation. Information concerning any such new findings will be provided to you. In this study, you will be informed of any clinically relevant research that may be discovered.

13- What charges will you have to pay?

None

14- What payment will you receive?

If you agree to take part, we will compensate you $225 for completion of the study. If your participation ends early you will be compensated based on the following completed visits, $100 for completion of Visits 1a and 1b and $125 on completion of Visits 3a and 3b. You will not be compensated for the screening visit. Your check will be requested from the LSU payroll department when you complete the study or at the appropriate milestone if you are compensated during the course of the study. It usually takes about 3-4 weeks for it to arrive at Pennington Biomedical Research Center.

Payments may only be made to U.S. citizens, legal resident aliens, and those who have a work eligible visa. You will need to provide your social security number to receive payment.

You are subject to a 1099 for receiving compensation. Payments in excess of $600 per calendar year are considered taxable income. If you will be paid more than $600, Pennington Biomedical/LSU will report this income to the IRS.

Non-US citizens are subject to having taxes withheld from payment and will need a passport, visa and 1-94 for payment to be processed.

15- Will you be compensated for a study-related injury or medical illness?

No form of compensation for medical treatment or for other damages (i.e., lost wages, time lost from work, etc.) is available from the Pennington Biomedical Research Center. In the event of injury or medical illness resulting from the research procedures in which you participate, you will be referred to a treatment facility. Medical treatment may be provided at your expense or at the expense of your health care insurer (e.g., Medicare, Medicaid, Blue Cross-Blue Shield, Dental Insurer, etc.) which may or may not provide coverage. The Pennington Biomedical Research Center is a research facility and provides medical treatment only as part of research protocols. Should you require ongoing medical treatments, they must be provided by community physicians and hospitals.

16- Signatures

The study has been discussed with me and all my questions have been answered. I understand that additional questions regarding the study should be directed to the study investigators. I agree with the terms above and acknowledge that I will be given a copy of this signed consent form.

With my signature, I also acknowledge that I have been given either today or in the past a copy of the Notice of Privacy Practices for Protected Health Information.

_____
Printed Name of Volunteer

_____ _____
Signature of Volunteer Date

_____
Printed Name of Person Administering Informed Consent

_____ _____
Signature of Person Administering Informed Consent Date

Candida Rebello, Ph.D.
Principal Investigator

Frank Greenway, M.D.
Medical Investigator