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Safety and Pharmacokinetics of Naringenin: A Randomized, Controlled, Single Ascending Dose, Clinical Trial

Candida J. Rebello,

Pharmacology Clinical Trials, Pennington Biomedical Research Center (PBRC), Baton Rouge, Louisiana

Robbie A. Beyl,

Biostatistics, PBRC, Baton Rouge, Louisiana

Juan J. L. Lertora,

Clinical Pharmacology, PBRC, Baton Rouge, Louisiana

Frank L. Greenway,

Pharmacology Clinical Trials, Pennington Biomedical Research Center (PBRC), Baton Rouge, Louisiana

Eric Ravussin,

Human Translational Physiology, PBRC, Baton Rouge, Louisiana

David M. Ribnicky,

Rutgers University Botanical Center, New Jersey

Alexander Poulev,

Rutgers University Botanical Center, New Jersey

Brandon J. Kennedy,

Department of Chemistry, University of Tennessee, Knoxville, Tennessee

Hector F. Castro,

Department of Chemistry, University of Tennessee, Knoxville, Tennessee

Biological and Small Molecule Chemistry Core, University of Tennessee, Knoxville, Tennessee

Shawn R. Campagna,

Department of Chemistry, University of Tennessee, Knoxville, Tennessee

Biological and Small Molecule Chemistry Core, University of Tennessee, Knoxville, Tennessee

Ann A. Coulter,

Pharmacology Clinical Trials, Pennington Biomedical Research Center (PBRC), Baton Rouge, Louisiana

Leanne M. Redman

Reproductive Endocrinology, PBRC, Baton Rouge, Louisiana

Corresponding Author Candida Rebello, Pharmacology Clinical Trials, Pennington Biomedical Research Center, 6400 Perkins Road, Baton Rouge, LA 70808. Telephone: 225-2882411, Candida.Rebello@pbrc.edu.

Rutgers University Botanical Center, New Jersey

Abstract

Aims—This study evaluated the safety and pharmacokinetics of naringenin in healthy adults, consuming a whole orange (*Citrus Sinensis*) extract.

Methods—In a single ascending dose randomized crossover trial, 18 adults ingested 150mg (NAR150), 300mg (NAR300), 600mg (NAR600), and 900mg (NAR900) doses of naringenin or placebo. Each dose or placebo was followed by a wash-out period of at least one week. Blood safety markers were evaluated pre-dose and 24 hours post-dose. Adverse events were recorded. Serum naringenin concentrations were measured before and over 24 hours following ingestion of placebo, NAR150, and NAR600. Four and 24-hour serum measurements were obtained after placebo, NAR300, and NAR900 ingestion. Data were analyzed using a mixed effects linear model.

Results—There were no relevant adverse events or changes in blood safety markers following ingestion of all naringenin doses. The pharmacokinetic parameters were: Maximal concentration: $15.76 \pm 7.88 \mu\text{M}$ (NAR150) and $48.45 \pm 7.88 \mu\text{M}$ (NAR600); Time to peak: $3.17 \pm 0.74 \text{h}$ (NAR150) and $2.41 \pm 0.74 \text{h}$ (NAR600); Area under the 24-hour concentration-time curve: $67.61 \pm 24.36 \mu\text{M} \times \text{h}$ (NAR150) and $199.06 \pm 24.36 \mu\text{M} \times \text{h}$ (NAR600); and Apparent oral clearance: $10.21 \pm 2.34 \text{L/h}$ (NAR150) and $13.70 \pm 2.34 \text{L/h}$ (NAR 600). Naringenin half-life was 3.0h (NAR150) and 2.65h (NAR600). After NAR300 ingestion, serum concentrations were $10.67 \pm 5.74 \mu\text{M}$ (4h) and $0.35 \pm 0.30 \mu\text{M}$ (24h). After NAR900 ingestion, serum concentrations were $43.11 \pm 5.26 \mu\text{M}$ (4h) and $0.24 \pm 0.30 \mu\text{M}$ (24h).

Conclusions—Ingestion of 150 to 900mg doses of naringenin is safe in healthy adults, and serum concentrations are proportional to the dose administered. Since naringenin ($8 \mu\text{M}$) is effective in primary human adipocytes, ingestion of 300mg naringenin twice/day will likely elicit a physiologic effect.

Introduction

Dietary flavonoids are polyphenolic compounds present in many commonly consumed plant foods ¹. Naringenin belongs to a subgroup of flavonoids known as flavanones, and is found predominantly in citrus fruits and tomato ^{2,3}. The therapeutic potential of naringenin in modulating glucose and lipid metabolism has garnered substantial interest. In rodent studies and in vitro models, naringenin reduces diet-induced weight gain and improves glucose and lipid metabolism ⁴⁻⁷. Although most of the effects of naringenin have been shown in the liver, muscle, and islet cells, increases in energy expenditure and activation of brown fat have been demonstrated in mice fed a high-fat diet supplemented with naringenin ⁸. Our in vitro studies in differentiated human subcutaneous adipose-derived stem cells from overweight and obese female donors ⁹ show that naringenin stimulates mRNA and protein expression of uncoupling protein 1 (UCP1), glucose transporter type 4 (GLUT4), and carbohydrate responsive element binding protein (ChREBP), key determinants of thermogenesis, whole body insulin sensitivity, and glucose homeostasis ^{10,11}. In prospective studies, high flavanone intake from oranges and grapefruits is associated with a cardioprotective effect, particularly, a reduction in the risk of ischemic stroke ¹²⁻¹⁴.

Flavanones occur naturally as glycosides which means that they are bound to different sugars. Hydrolysis of the sugar moieties from the flavanone glycosides naringin and narirutin by colonic bacteria releases the aglycone naringenin, and this is the rate-limiting step in the absorption of naringenin¹⁵. After absorption, flavonoids are rapidly conjugated in the intestines or liver and appear in circulation as glucuronides or sulphoglucuronides^{16–18}. Ingestion of naringin or narirutin in 400 mL to 1L of orange juice, or segments from one medium fresh orange produce < 1 μ M of naringenin in circulation^{15,16,19,20}, far short of the 8–10 μ M concentration found to elicit physiologic effects in human adipocytes⁹. Therefore, we conducted a Phase 1 study in healthy adults to evaluate the safety, tolerability, and pharmacokinetics of naringenin in the free aglycone form, which can be readily absorbed from the small intestine.

Grapefruit juice has been shown to increase the oral availability of certain drugs. The interaction with grapefruit causes an inhibition of first pass metabolism of the drug mainly catalyzed by an intestinal cytochrome P450 (CYP) 3A4^{21,22}. Furanocoumarin derivatives isolated from grapefruit were identified as the clinically active constituents responsible for the inhibition²³. Moreover, it was determined that naringin and naringenin are not the primary inhibitors in grapefruit juice²⁴. While grapefruit contains a high content of furanocoumarin derivatives, sweet oranges contain a very small amount of these derivatives²⁵. An extract was prepared from whole sweet oranges (*Citrus Sinensis*) and we hypothesized that oral administration of the whole orange extract which contained naringenin along with its native plant material would enhance its bioavailability in humans. We evaluated the safety and tolerability of single ascending doses of naringenin in healthy adults and determined its pharmacokinetic profile in serum.

Methods

Study Design

Subjects were enrolled in a placebo-controlled, double-blind, single ascending dose crossover trial to determine the safety, tolerability, and pharmacokinetics of naringenin at the Pennington Biomedical Research Center (PBRC). The maximum recommended starting dose for naringenin was estimated at approximately 135 mg since no adverse events were reported at this dose in a previous study²⁶. Due to the short elimination half-life ($T_{1/2}$) of naringenin delivered in the free aglycone form ($T_{1/2}$ = 2.31 $\pm$ 0.4 h)²⁶, we hypothesized that multiple dosing up to 600 mg would be necessary for effective duration of action. The dose escalation scheme recommended for first in human studies is rapid dose escalation initially (maximum recommended starting dose [MRSD] x 2) until the estimated effective dose (600 mg) is reached and then at a more cautious escalation (for example, MRSD x 1.5)²⁷. Therefore, we evaluated the safety of 150, 300, 600, and 900 mg doses of naringenin. Each 150 mg dose capsule (NAR 150) contained 536 mg of the extract (28% naringenin, determined in quantitative analysis). The 300 mg (NAR 300), 600 mg (NAR 600), and 900 mg (NAR 900) naringenin doses were provided in two, four, and six capsules respectively. The placebo capsules contained microcrystalline cellulose and were similar in appearance.

The study design is represented in Table 1. Nine subjects were enrolled in each of two cohorts. Each subject in the cohorts was randomly assigned one of the relevant treatment

sequences in order of enrollment. For example, the first three enrolled subjects in Cohort 1 were each randomly assigned to one of three distinct treatment sequences (Sequence 1, 2, or 3), as were enrollees 4–6 and 7–9. As a result, three subjects in each cohort were randomly assigned to each of the three treatment sequences.

To maintain the blind, all subjects in Cohort 1 received two capsules at each visit which comprised either two placebo capsules, one placebo and one NAR 150 capsule or two NAR 150 capsules depending on the randomization sequence. A similar process was employed in Cohort 2 and each subject received six capsules at each visit. Capsules were dispensed by the PBRC pharmacist according to the randomization scheme prepared by the study biostatistician. All other study staff and investigators were blinded to the treatment assignment. Each treatment was followed by a washout period of at least one week. The study was approved by the Institutional Review Board of PBRC. All procedures were in accordance with PBRC's ethical standards. Subjects provided written informed consent. The trial was registered on [ClinicaTrials.gov](https://www.clinicaltrials.gov) with registration number [NCT03582553](https://www.clinicaltrials.gov/ct2/show/study?term=NCT03582553). Recruitment for the study commenced in May 2018 and the study was completed in October 2018.

Subjects

Eighteen male and female subjects, 18 years of age or older were enrolled. Subjects were eligible if they presented with a BMI between 20 and 35 kg/m² and no known history of diseases requiring regular medications. Subjects were excluded for: (i) chronic use of medications, except over the counter medications and supplements that they agreed to stop 72 hours prior to the test day; (ii) fasting glucose > 126 mg/dL; (iii) current pregnancy or lactation; (iv) clinically significant gastrointestinal malabsorption syndromes such as chronic diarrhea, celiac disease or malabsorption from bariatric surgery within one month of the study; (v) reported history of substance abuse or alcoholism, or significant psychiatric disorder that would interfere with the ability to complete the study; (vi) smoking; (vii) and (viii) having citrus allergies. Subjects were provided with a list of foods containing flavanones and were instructed to refrain from consuming these foods for at least 36 hours prior to each test day. A diagram illustrating subject flow through the study is presented in the Supplementary Appendix (Figure 1).

Clinical Assessments

Each eligible subject completed three visits to the clinic. All testing was performed in the morning after an eight-hour overnight fast where only water was permitted. Upon arrival weight and vital signs (blood pressure, heart rate, and temperature) were measured. Blood was drawn for a chemistry panel (glucose, creatinine, potassium, uric acid, albumin, calcium, magnesium, creatine phosphokinase, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, blood urea nitrogen, total bilirubin, iron, cholesterol [total, high density lipoprotein, low density lipoprotein], and triglycerides) and complete blood count before ingestion of each naringenin dose, or placebo. The subject returned 24 hours after ingestion of naringenin or placebo for a repeat chemistry panel and complete blood count, to assess the safety of naringenin. Adverse events (AE) were recorded

following administration of each dose or placebo and 24 hours later. The definition and classification of AEs is presented in the Supplementary Appendix.

Pharmacokinetic Testing

An intravenous line was placed and blood was drawn prior to ingestion of placebo and NAR 150 or NAR 600, and at 2, 3, 3.5, 4, 4.5, 6, 8, and 12 hours post-dose. Subjects consumed a standard lunch five hours after ingestion of the naringenin dose or placebo. A standard dinner was also provided at the end of 12 hours. Subjects were discharged and returned to the Center the next morning, for a 24-hour post-dose measurement (Visit 1). Complete pharmacokinetic profile including the maximal concentration achieved ($C_{\max}$) time to peak ($T_{\max}$), area under the 24-hour serum concentration-time curve (AUC_{0-24h}), apparent oral clearance ($Clearance_{\text{oral}}$), and $T_{1/2}$ was evaluated.

At Visit 3, subjects consumed the placebo, and NAR 300 or NAR 900 with a standard snack, which permitted evaluation of serum naringenin concentration in a fed state. Blood was drawn at four hours post-dose. Subjects were discharged and returned to the Center the next morning and a 24-hour post-dose blood sample was collected.

Quantitative Analysis of Extract

Quantitative analysis of naringenin was performed at the Rutgers University Botanical Center, New Jersey. Naringenin and naringin were purchased from Cayman Chemical Company (Ann Arbor, MI). Whole sweet oranges (*Citrus Sinensis*) were subjected to an aqueous and ethanolic extraction process, dried, milled, and provided as a fine powder by Green Chem/Gencor Lifestage Solutions (Irvine, CA). The extract can be ordered from Gencor™ (<https://gencorpacific.com/contact>) Methodological details are provided in the Supplementary Appendix.

Quantitative Analysis of Serum Naringenin

Serum naringenin concentrations were measured at the University of Tennessee, Knoxville. Serum concentrations were measured after hydrolysis of samples with β -glucuronidase/sulphatase^{15,16,20,26}. For each sample, a 200 μ L serum aliquot was enzymatically unconjugated in a 2 mL Eppendorf tube as previously described²⁸. Data was analyzed using the MAVEN software package^{29,30}. Methodological details are provided in the Supplementary Appendix.

Statistical Analysis

The primary aim of this Phase 1 study was to evaluate the effect of single oral administration of naringenin at four escalating doses (150, 300, 600, and 900 mg) on safety and tolerability in healthy volunteers. The secondary objective was to evaluate the 24-hour pharmacokinetic profile of naringenin in serum at 150 and 600 mg doses, and the four and 24-hour serum concentrations at 300 and 900 mg doses. As comparative efficacy of the doses was not the primary issue, power to detect effects was not specifically evaluated to justify sample sizes. Based on the safety and pharmacokinetic study done in humans²⁶, the sample size (n=6, at each dose) was deemed sufficient to evaluate safety and provide a pharmacokinetic profile of naringenin in serum.

The cohorts 1 and 2 were conducted in series. There was an interval of two weeks between the two cohorts during which an interim safety analysis was conducted. A summary of adverse events and blood safety markers for Cohort 1 was compiled and reviewed by the investigators, without breaking the blind. Dose safety was investigated by compiling by treatment (placebo, NAR 150, NAR 300, NAR 600, and NAR 900) a list of adverse events such as frequency of headaches and vomiting. The frequency of these events was counted and compared with the placebo. Changes in blood safety markers from pre-dose to 24 h post-dose were evaluated for significant differences among the doses. If there was a significant difference between the doses, the mean baseline value for each dose was added to the mean change from baseline for that dose and compared with the reference range for the marker. Pairwise comparisons of NAR 150, NAR 600 and placebo were tested with a linear mixed effect model for each of the parameters across all time points. Significance was set at $p < 0.05$. Individual minimum and maximum values were evaluated by the medical investigator to determine clinical significance.

Pharmacokinetic profile was analyzed using a non-compartmental model²⁷. The C_{max} and T_{max} were taken directly from the individual serum data. The elimination rate constant (k) was obtained by means of linear regression analysis of the semi-logarithmic serum concentration-time curve using the time points that best fit the terminal elimination phase of the curve. The $T_{1/2}$ was calculated by dividing $\ln 2$ by k . The AUC_{0-24h} was estimated using the linear trapezoidal method. The $Clearance_{(oral)}$ was calculated as: $Dose/AUC_{0-24h}$. The C_{max} , T_{max} , $T_{1/2}$, AUC_{0-24h} , and $Clearance_{(oral)}$ for each subject were determined and the means for subjects given NAR 150 and NAR 600 were calculated. All analyses were performed using SAS Version 9.4 software (SAS Institute Inc., Cary NC), by the study biostatistician.

Results

The chromatogram for the quantitative analysis of naringenin in the extract is presented in the Supplementary Appendix (Figure 2). The extract consisting of the plant materials found in the fruit and peel of *Citrus Sinensis* contained 28% naringenin and 8.5% naringin. Prunin was observed at a different ion ($m/z = 578.1883$, [-ESI]) and quantified as 2.5%. Eighteen subjects enrolled in and completed the study. Data related to 18 subjects were included in the analysis. Baseline characteristics of subjects are presented in Table 2. There were significant differences between the doses in the alanine aminotransferase, creatinine phosphokinase, and potassium concentrations, and eosinophil, and white blood cell counts. However, the mean change from baseline added to the mean baseline value was within the respective reference range. Individual values below and above the reference ranges pre- or post-dose were not clinically significant. The minimum and maximum values that were outside of the reference range are provided in the Supplementary Appendix.

The AEs reported during the study and their intensities are presented in Table 3. There were 14 total AEs reported. Three AEs (placebo, NAR 300, and NAR 900) were reported at Visit 3 and were therefore ongoing on completion of the study. There was a statistically significant overall effect of dose on the intensity of the AEs ($p=0.014$). However, the worst

effect was observed following ingestion of the placebo, and there was no statistically significant effect between the placebo and any of the doses.

The mean total serum concentrations after ingestion of NAR 150 or NAR 600, or placebo over 24 hours, and at four and 24 hours after ingestion of NAR 300 and NAR 900 are presented in Figure 1AB. Pharmacokinetic parameters of naringenin in serum are presented in Table 4. The $C_{\max}$ of naringenin increased by 307.5% in the NAR 600 dose compared to NAR 150 ($p=0.01$). There was no difference in the $T_{\max}$ ($p=0.49$) between NAR 150 and NAR 600, although the $T_{\max}$ increased by 31.5%, following ingestion of NAR 600 compared to NAR 150. The four-hour serum concentration increased by four times (404%) after ingestion of NAR 900 compared to NAR 300 ($p=0.001$, Range NAR 300: 4.93 – 20.43 μM [4h] and 0.02 – 1.30 μM [24h], Range NAR 900: 13.53 – 83.43 μM [4h] and 0.03 – 0.89 μM [24h]).

Based on the best fit of the terminal elimination curve, the 3.5, 4, 4.5, 6, 12, and 24 hour time-points were used in the determination of k ($r^2=0.63$ [NAR 150] and $r^2=0.90$ [NAR 600]), for calculation of $T_{1/2}$. The $T_{1/2}$ was approximately 12% lower after ingestion of NAR 600 compared to NAR 150, but the difference was not statistically significant ($p=0.39$). Serum concentrations of naringenin were approximately proportional to the dose administered, whether in the fasted or fed state. The apparent oral clearance increased by 34% following ingestion of NAR 600 compared to NAR 150, but the difference was not significant ($p=0.31$).

Discussion

This is the first study to establish the safety and tolerability of four single ascending doses (150, 300, 600, 900 mg) of naringenin in the aglycone form in humans, and to determine a complete pharmacokinetic profile including $C_{\max}$, $T_{\max}$, $T_{1/2}$, $\text{AUC}_{0-24\text{h}}$, and $\text{Clearance}_{(\text{oral})}$ at 150 mg and 600 mg doses. The kinetic curves of naringenin concentrations measured in serum over 24 hours after ingestion of NAR 150 and NAR 600 indicate that naringenin is present in circulation and has a half-life of approximately three hours. Naringenin is absorbed into circulation approximately proportional to the dose administered in both the fasted (NAR 150 and NAR 600) and fed states (NAR 300 and NAR 900) and is cleared from circulation within 24 hours.

Citrus flavonoids such as naringenin have diverse and powerful biological properties³¹. Scientific research on the physiologic relevance of naringenin has been limited to in vitro and animal models. Studies seeking to understand the therapeutic potential of naringenin in humans, have been hindered by ingestion of citrus juices or fruits whereby, the circulating concentration of naringenin is low. In cell culture and animal models, the range of naringenin determined to elicit a desired response ranges from 1–200 μM ^{31,32}. In humans, the maximum plasma concentrations achieved from food sources of naringenin has only reached <1 μM ^{15,16,19,20}.

In the only other clinical trial of naringenin in the aglycone form²⁶, ingestion of a single 135 mg dose of the pure compound delivered in a solid dispersion capsule produced a $C_{\max}$

of 7.39 μM in 3.67 hours. In comparison, ingestion of 150 mg naringenin delivered in an extract from whole oranges produced a C_{max} that was two-fold higher in less time ($T_{\text{max}}=3.17$ h). Following ingestion of 600 mg naringenin, the C_{max} was more than three-fold higher than the 150 mg dose, and the peak concentration was reached in 2.41 hours. Following ingestion of 900 mg naringenin, the serum naringenin concentration was more than four-fold higher than the 300 mg dose. The serum concentrations of naringenin following ascending doses show that naringenin absorption is approximately proportional to the dose administered. The half-life of naringenin following the 150 mg (3 h) and 600 mg doses (2.65 h) was not significantly different between the doses, and is consistent with the 2.31 h reported previously ²⁶.

In addition to naringenin, the extract from *Citrus Sinensis* also contained 8.5% naringin and 2.5% prunin. It is unlikely that naringin contributed to the naringenin C_{max} since naringin must reach the colon and be hydrolyzed by the gut bacteria for absorption. Previous studies have shown that the C_{max} values for flavanone metabolites occurred approximately five hours after ingestion of citrus fruits ^{16,19,20} containing naringin. Although prunin can be hydrolyzed in the human small intestine ^{33,34}, little is known of its bioavailability.

The evidence in the literature supports a role for naringenin in the treatment of dyslipidemia, insulin resistance, hepatic steatosis, obesity, and atherosclerosis ³¹. Several methods of drug design for delivery of naringenin are in the process of development such as liposomes, naringenin-encapsulated nanoparticles, self-nanoemulsifying drug delivery systems (SNEDDS), and nanosuspension ³⁵. However, the safety and efficacy of these delivery routes have never been tested in humans. The present study using an extract from whole sweet oranges demonstrates that serum naringenin concentrations are higher when naringenin is delivered along with its native plant materials compared to the isolated form delivered in solid dispersion capsules ²⁶. Synergistic effects can be produced if the constituents of a plant extract interact with one another in order to improve the solubility and thereby enhance the bioavailability of a particular component of an extract, compared to the isolated constituent ³⁶. This possibility is not uncommon in phyto-pharmacology, especially with polyphenols ³⁷, and enhanced absorption of naringenin following ingestion of the extract is likely due to a synergy among its various plant constituents.

Our study is limited by the lack of information on urinary excretion of naringenin metabolites. Flavonoid bioavailability studies have used urinary excretion as a measure of absorption. However, urinary excretion does not account for the possibility of metabolites being sequestered in tissues ³⁸. Moreover, in addition to urinary excretion, a significant proportion of bioavailable flavonoid metabolites may be excreted via bile into the feces ³⁹. In the study by Kanaze *et al*, a 135 mg dose of naringenin produced a urinary excretion of 5.81% and the relative urine excretion of naringenin reported in the literature has a wide range from 4% to 30% of the dose administered ^{19,20}. Although it has been suggested that the naringenin metabolites appearing in circulation are treated by the body as xenobiotics and are removed from the system, analysis of the serum concentrations provides valuable information on the pharmacokinetic profile of naringenin ³⁸. Further, we measured serum naringenin concentrations following hydrolysis of the conjugated form; however, the method provides an estimation of serum naringenin concentrations ^{15,16,20,26,40}.

Little is known about tissue uptake and disposition of flavonoid metabolites in humans which is important for the effects of naringenin on cell and tissue function ⁴¹. In rodent studies, dosing with naringenin or naringin produced inconsistent results. Following a single gastric gavage of naringenin (50mg/kg) in rats, naringenin aglycone was detected at higher levels in tissues than in plasma after 18 h ⁴². However, following gastric gavage of naringin at 210 mg/kg twice daily (17 doses) in rats, free forms of naringin and naringenin were not detected in plasma or major organs.⁴³ Future studies should evaluate the safety and physiologic effects of multiple dosing of naringenin on energy expenditure and glucose metabolism in humans, which will provide information on tissue uptake.

In conclusion, the purpose of this study was to determine the safety and tolerability of naringenin and evaluate its pharmacokinetic profile. We show that single doses of 150, 300, 600, and 900 mg of naringenin are safe and well tolerated in humans. At these doses, naringenin metabolites are present in circulation, and are cleared within 24 hours. Since naringenin at 8 μ M concentrations is effective in primary human adipocytes and primary human adipose tissue ⁹, 300 mg ingested twice daily would be sufficient to elicit a physiologic response.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

(A) Serum kinetics of naringenin after ingestion of Extract of whole oranges containing 150 mg (NAR 150) and 600 mg (NAR 600) of naringenin. (B) Four- and 24-hour serum concentration of naringenin after ingestion of extract of whole oranges containing 300 mg (NAR 300) and 900 mg (NAR 900) of naringenin. Concentration of aglycones was determined by LC-MS after hydrolysis of β -glucuronidase-sulphatase. Values are means $\pm$ SEM.

Table 1.

Ascending Oral Dose Schedule

	Visit 1	Visit 2	Visit 3
<i>Cohort 1</i>			
Sequence 1 (n=3)	NAR 150	Placebo	NAR 300
Sequence 2 (n=3)	NAR 150	NAR 300	Placebo
Sequence 3 (n=3)	Placebo	NAR 150	NAR 300
<i>Cohort 2</i>			
Sequence 4 (n=3)	NAR 600	Placebo	NAR 900
Sequence 5 (n=3)	NAR 600	NAR 900	Placebo
Sequence 6 (n=3)	Placebo	NAR 600	NAR 900

Note: In Cohort 1, the first three enrolled subjects were randomly assigned to Sequence 1, 2, or 3. The same assignment was followed for the next two blocks of three subjects for a total of nine subjects. Subjects were similarly assigned in Cohort 2.

Table 2.

Subject characteristics at baseline including age, BMI, gender, and race

n = 18	
Mean $\pm$ Standard Deviation	
Age	38 $\pm$ 15.1
BMI (kg/m ²)	24.8 $\pm$ 4.1
n (%)	
Gender	
Female	12 (67)
Male	6 (33)
Race	
White	12 (67)
Black	4 (22)
Asian	2 (11)

Table 3.

Adverse events reported during the study. Each check mark represents an event

Event	Placebo	NAR 150	NAR 300	NAR 600	NAR 900	Mild	Moderate
Itching			✓	✓			
Rash	✓						
Acne							
Cyst on Foot					✓		
Vomiting	§						
Diarrhea	§						
Abdominal Pain		¶					
Headache		¶					
Drowsiness							
Joint pain	✓						
Sinus Congestion							
Visual Disturbance							

✓ Reported at Visit 3 and unresolved at the end of the study.

¶ Events reported by same subjects

§ Events reported by same subjects

¶ Events reported by same subjects.

Pharmacokinetic parameters of serum naringenin over 24 hours after an oral dose of 150 mg and 600 mg of naringenin in an extract from whole oranges (NAR) administered in capsule form. Values are mean $\pm$ SEM.

Table 4.

Dose	AUC _{0-24h} [†] (μ M $\times$ h)	Cmax (μ M)	Tmax (h)	T _{1/2} [‡] (h)	AOC [§] (L/h)
NAR 150	67.61 $\pm$ 24.26	15.76 $\pm$ 7.88	3.17 $\pm$ 0.74	3.0	10.21 $\pm$ 2.34
Range	35.56 – 120.34	6.43 – 36.85	2 – 4		4.58 – 15.49
NAR 600	199.05 $\pm$ 24.36	48.45 $\pm$ 7.88	2.41 $\pm$ 0.74	2.65	13.70 $\pm$ 2.34
Range	97.63 – 316.74	22.01 – 94.94	2 – 3.5		6.96 – 22.57
Dose	AUC _{0-24h} [†] (μ g/ml) $\times$ h	Cmax (μ g/ml)			
NAR 150	18.41 $\pm$ 6.61	4.29 $\pm$ 2.15			
Range	9.68 – 32.77	1.75 – 10.03			
NAR 600	54.19 $\pm$ 6.63	13.19 $\pm$ 2.15			
Range	26.58 – 86.24	5.99 – 25.85			
p-value	0.001	0.01	0.49	0.39	0.31

[†]Area under the 24-hour serum concentration-time curve

[‡]Based on log transformed data using 3.5 to 24 hour time-points for best fit of terminal phase elimination curve

[§]Apparent Oral Clearance (Dose/AUC_{0-24h} (μ g/ml) $\times$ h)