

UNIVERSIDADE DE SÃO PAULO
Faculdade de Ciências Farmacêuticas
Programa de Pós-Graduação em Ciência dos Alimentos
Área de Bromatologia

Bioavailability of citrus flavanones and its effect on cardiometabolic parameters in humans

Layanne Nascimento Fraga

Tese para obtenção do grau de Doutor

Orientadora: Prof^ª. Dr^ª. Neuza Mariko
Aymoto Hassimotto

São Paulo
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To my parents Lázaro (in memorian), and Zailda .

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RESUMO

FRAGA, L. N. **Biodisponibilidade de flavanonas de citrus e efeito nos parâmetros cardiometabólicos em humanos**. 2023. 148f. Tese (Doutorado) - Faculdade de Ciências Farmacêuticas, Universidade de São Paulo, São Paulo, 2023.

Hesperidina e narirutina são os principais flavonoides presentes no suco de laranja (SL). O consumo crônico de SL tem sido associado à redução da ocorrência de doenças cardiometabólicas, contudo, é observada uma grande variabilidade interindividual na resposta biológica associada ao seu consumo, em parte devido a variabilidade interindividual na biodisponibilidade desses compostos bioativos. Assim, esse trabalho teve como objetivo geral identificar os fatores que influenciam a biodisponibilidade de flavanonas e avaliar os efeitos do consumo crônico de SL sobre parâmetros cardiometabólicos. Para isso, foram incluídos no estudo 85 homens e mulheres com idades entre 18 e 40 anos, eutróficos (19-24,9 Kg/m²) ou com sobrepeso (25-29,9 Kg/m²). Durante o período de 60 dias, os voluntários consumiram diariamente 500 mL de SL. Para avaliar os efeitos da intervenção, foram realizadas medidas antropométricas, aferição da pressão arterial e coleta de sangue, urina e fezes em jejum no primeiro dia do ensaio e após 30 e 60 dias da intervenção. Também foi coletada a urina de 24 horas após a primeira ingestão de SL em dose única, e nessas amostras os metabólitos de flavanonas foram identificados e quantificados por LC-qTOF-MS/MS. Após 60 dias de ingestão de SL, foi observada uma grande heterogeneidade nas respostas de cada parâmetro bioquímico, antropométrico e de pressão arterial avaliado, apresentando indivíduos que responderam e aqueles que não responderam à intervenção. Entretanto, foi observado redução significativa no percentual de gordura e na pressão arterial. Diversos metabólitos de flavanonas de fase II, sulfatados e glucuronidados, e ácidos fenólicos derivados da metabolização destes pela microbiota intestinal foram identificados na urina. Contudo, observou-se grande variabilidade na excreção destes metabólitos, os quais não foram influenciados pelo sexo ou IMC. Assim, os voluntários foram classificados em alto, médio e baixo excretadores com base na quantidade excretada de metabólitos conjugados de fase II e de ácidos fenólicos. A variação na excreção dos metabólitos de flavanonas foi associada à presença de polimorfismos de nucleotídeo único (SNP) em genes da sulfotransferase (SULT1A1, SULT1C4), enzima do metabolismo de fase II, e do transportador ABCC2. Utilizando desta abordagem, a responsividade ao consumo de SL foi atribuída principalmente aos conjugados de flavanonas de fase II, embora a importância dos ácidos fenólicos não possa ser descartada. Por outro lado, SNPs nos genes da APOE, APOA1 e LPL foram relacionados à heterogeneidade no perfil lipídico e na pressão arterial após a ingestão crônica de SL. Esses resultados demonstram que a responsividade a ingestão do suco de laranja depende da capacidade do indivíduo em metabolizar as flavanonas de citrus, além da presença de polimorfismo em determinados genes do metabolismo. Esses achados propõem novas abordagens o qual permite bases futuras para uma dieta nutricional personalizada ao consumo de alimentos fonte em flavanonas e maior benefício de suas propriedades de promoção à saúde.

Palavras-chave: Flavanonas; biodisponibilidade; resposta biológica; polimorfismo; nutrigenética, nutrigenômica.

ABSTRACT

FRAGA, L. N. **Bioavailability of citrus flavanones and its effect on cardiometabolic parameters in humans.** 2023. 148f. Tese (Doutorado) - Faculdade de Ciências Farmacêuticas, Universidade de São Paulo, São Paulo, 2023.

Hesperidin and narirutin are the main flavonoids present in orange juice (OJ). Chronic consumption of OJ has been associated with a reduction in the occurrence of cardiometabolic diseases. However, considerable inter-individual variability is observed in the biological response associated with OJ consumption, in part due to the inter-individual variability in the bioavailability of these bioactive compounds. The objectives of this study were to identify the factors that influence the bioavailability of flavanones and evaluate the effects of chronic consumption of OJ on cardiometabolic parameters. The study volunteers comprised 85 eutrophic (19-24.9 kg/m²) or overweight (25-29.9 kg/m²) men and women between the ages of 18 and 40. For 60 days, the volunteers consumed 500 mL of OJ daily. To assess the effects of this intervention, anthropometric measurements, blood pressure measurements, and fasting blood, urine, and feces samples were collected on the first day of the test and after 30 and 60 days of intervention. After the first single-dose OJ intake, a 24-hour urine sample was also collected; in these samples, flavanone metabolites were identified and quantified by LC-qTOF-MS/MS. After 60 days of OJ ingestion, substantial heterogeneity was observed in the responses of the biochemical, anthropometric, and blood pressure data: some individuals responded to the intervention, while others did not. However, significant reductions in fat percentage and blood pressure were observed. Several phase II flavanone metabolites (sulfated and glucuronidated) and phenolic acids derived from their metabolism by intestinal microbiota were identified in the urine. There was notable metabolite excretion variability that was not influenced by gender or BMI. Thus, the volunteers were classified as high, medium, or low excretors based on the excreted amount of phase II conjugated metabolites and phenolic acids. Variations in flavanone metabolite excretion were associated with the presence of single nucleotide polymorphisms (SNPs) in genes for sulfotransferase (SULT1A1, SULT1C4), a phase II metabolic enzyme, and the ABCC2 transporter. Using this approach, responsiveness to OJ intake was primarily attributed to phase II flavanone conjugates, although the importance of phenolic acids cannot be ruled out. SNPs in the APOE, APOA1, and LPL genes were related to heterogeneity in lipid profiles and blood pressure after chronic OJ ingestion. These results demonstrate that responsiveness to orange juice intake depends on an individual's ability to metabolize citrus flavanones and the presence of polymorphisms in certain metabolic genes. These findings may inform new approaches in personalized nutrition that promote the consumption of foods rich in flavanones, given their health benefits.

Keywords: Flavanones; bioavailability; biological response; polymorphism; nutrigenetics, nutrigenomics.