JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

Viewpoint

Cite This: J. Agric. Food Chem. XXXX, XXX, XXX−XXX

pubs.acs.org/JAFC

Interindividual Variability in Absorption, Distribution, Metabolism, and Excretion of Food Phytochemicals Should Be Reported

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It has been rather difficult to demonstrate the biological effects of food phytochemicals and especially (poly)phenols in human intervention trials. Although accumulating evidence from epidemiological and experimental studies support the preventive role of these phytochemicals, particularly in cardiovascular disease (CVD), the demonstration of direct effects decreasing different disease biomarkers in human studies remains elusive. In fact, in an intervention trial, it is easy to find volunteers that positively respond to the intervention, while others do not. This heterogeneity in responsiveness has often led to inconclusive results in clinical trials that aim to demonstrate the health effects of specific phytochemical compounds.[1]

The determinants for this interindividual variability have been studied during the last 4 years within the European COST Action POSITIVe (https://www6.inra.fr/cost-positive). The results of this scientific network have shown that interindividual variations in absorption, distribution, metabolism, and excretion (ADME) of the phytochemicals can be a key determinant.[2] When trying to establish correlations between variations in ADME and the observed effects on CVD biomarkers, it has been difficult to find studies in which the individual values for the effect observed and the ADME are reported, making the establishment of this correlation impossible.

A large variability in ADME of food phytochemicals and particularly (poly)phenols between different individuals in an intervention study that aims to investigate the impact on cardiovascular end points has probably been considered as a negative result or due to an inaccurate experimental design. Often, error bars showing standard errors are reported, instead of larger error bars based on standard deviations (SDs), to show "nicer" figures. This large SD is an indication of the high variability in ADME among different volunteers and can reflect differences in gut microbiota metabolism, intestinal absorption, human metabolism, tissue uptake, or kidney excretion. If the circulating phytochemical metabolites resulting from both microbial and host metabolism of parent compounds are responsible for the biological effects observed, then a large between subject variability in the CVD biomarkers would be expected. This is probably the case, although there is no report available that has studied this correlation.

Studies showing large SDs (interindividual variability) in the absorption and excretion of phytochemical metabolites have been reported for flavanone rutinosides, proanthocyanidins, ellagitannins, lignans, and isoflavones, among others, showing that this can be a very common situation in intervention trials with (poly)phenols (Table 1).

Therefore, the variability among individuals needs to be reported because it reflects relevant differences in human genetics (polymorphisms) (digestive enzymes, intestinal transporters, phase I and phase II metabolism, and kidney transporters) and also in the gut microbiota composition and functionality that affect the catabolism of non-absorbed phytochemicals in the small intestine.[3]

The study of this variability using previously published data has always been a problem, because most of the reported data are shown as mean values of different volunteers and include some statistical figures to show the dispersion of the data. Therefore, it is not possible to evaluate the physiological response (biomarkers of effects) of each specific individual after the intake of a specific polyphenol-rich food or an isolated phytochemical and to correlate these results with the concentration of circulating metabolites.

In the demonstration of the cardiovascular health effects of food phytochemicals, the classical approach has aimed to evaluate foods with different doses of the bioactive compared to a placebo on a panel of biomarkers of the effect, assessed in the biological fluids [plasma oxidized cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), etc.] or through functional measurements (flow-mediated dilatation, blood pressure, and arterial stiffness). These studies often lead to statistically non-significant results or results with a very low significance because some volunteers show a high response to the treatment, while others only show a very limited or no

Received: February 19, 2019

Table 1. Cases for Large Interindividual Variability in (Poly)phenol Gut Microbiota Metabolism and ADME[3]

food product	food phytochemical	gut microbiota metabolites produced	metabolites excreted	interindividual variability
berries, pomegranate, nuts, and tea	ellagitannins and ellagic acid	urolithins	urolithin glucuronides and sulfates	metabotypes reported and differences in quantity of excreted metabolites
citrus fruits and beverages	hesperetin rutinosides	hesperetin and hydroxylphenylacetic and phenylpropionic acids	hesperetin glucuronides and sulfates and hydroxylphenylacetic and phenylpropionic acids	differences in the quantity of absorbed and excreted metabolites
soybean	isoflavones	daidzin, *O*-desmethylangolensin, and equol	glucuronide and sulfate conjugates	metabotypes reported and differences in quantity of excreted metabolites
hop (beer)	isoxanthohumol	prenylnaringenin	glucuronide and sulfate conjugates	differences in the quantity of absorbed and excreted metabolites
cocoa, apple, grape and wine, fruits, and tea	proanthocyanidins	valerolactones	glucuronide and sulfate conjugates	differences in the quantity of absorbed and excreted metabolites
flaxseed	lignans	enterolactone and enterodiol	glucuronide and sulfate conjugates	differences in the quantity of absorbed and excreted metabolites

response. If the metabolites of the food (poly)phenols are eventually responsible for the health effects and if there is a large between subject variability in their ADME, it is essential to study if the variability in the effect correlates with differences in ADME of the food phytochemicals. Therefore, the new approach should aim to look at a correlation between a biomarker of effect and biomarkers of exposure to the phytochemical metabolites.

After studying the interindividual variability of ADME, volunteers can be stratified according to their degree of exposure to the food bioactive metabolites. This stratification, conducted before starting or after an intervention trial, can also be a sensible approach, insofar as an upstream statistical power analysis has been performed to allow for this stratification. This method has already been successfully used to study the effects on CVD biomarkers after the stratification of individuals consuming soybean isoflavones into equol producer and equol non-producer phenotypes, as well as after the intake of pomegranate ellagitannins stratified by urolithin-producing metabotypes. In these studies, the equol producers, after soybean isoflavone intake, and the urolithin metabotype B volunteers, after the intake of pomegranate ellagitannins, responded better to the treatment, while a non-significant effect was observed in the equol non-producers and the urolithin metabotypes A and 0 volunteers.[4,5]

In future studies, the reporting of the observed values for each subject regarding both biomarkers of exposure to the phytochemical metabolites and biomarkers associated with cardiometabolic risk is strongly recommended, for the posterior conducting of correlation studies. This approach is essential for the better understanding of why some compounds work in some individuals while having a smaller effect or not at all in others. Ultimately, the results will help estimate the personal health benefits that an individual can gain from different phytochemical-rich foods while, at the same time, helping to make progress in the development of effective and innovative dietary solutions for the improvement of cardiometabolic health. For the human intervention trials that examine the impact of food phytochemicals on health biomarkers without any assessment of exposure or bioavailability, the lack of ADME data can be considered a limitation of the study, and this should be acknowledged in the publication.

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Funding

This work was funded by Projects 201870E014 (CSIC, Spain) and Fundación Séneca (19900/GERM/15).

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors acknowledge networking support by the COST Action FA 1403 POSITIVe (Interindividual Variation in Response to Consumption of Plant Food Bioactives and Determinants Involved), supported by the European Cooperation in Science and Technology (COST).

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DOI: 10.1021/acs.jafc.9b01175
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