

Breakthroughs in the Health Effects of Plant Food Bioactives: A Perspective on Microbiomics, Nutri(epi)genomics, and Metabolomics

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S Supporting Information

ABSTRACT: Plant bioactive compounds consumed as part of our diet are able to influence human health. They include secondary metabolites like (poly)phenols, carotenoids, glucosinolates, alkaloids, and terpenes. Although much knowledge has been gained, there is still need for studies unravelling the effects of plant bioactives on cardiometabolic health at the individual level, using cutting-edge high-resolution and data-rich holistic approaches. The aim of this Perspective is to review the prospects of microbiomics, nutrigenomics and nutriepigenomics, and metabolomics to assess the response to plant bioactive consumption while considering interindividual variability. Insights for future research in the field toward personalized nutrition are discussed.

KEYWORDS: *phytochemicals, interindividual variability, personalized nutrition, metabolome, gut microbiota*

■ INTRODUCTION

Plant food bioactive compounds have moved under the spotlight of nutritional research over the last decades owing to their putative ability to impact human health. Beyond macro- and micronutrients and dietary fiber, plant secondary metabolites (phytochemicals) such as (poly)phenolic compounds, carotenoids, glucosinolates, alkaloids, terpenes, peptides, etc. are “non-nutritive” compounds constituting key players in the health benefits attributed to plant-based diets.¹ However, despite the high amount of information available on the health benefits of plant bioactive compounds, results in humans are still inconsistent and insufficient to fully support most of their cardiometabolic preventative features.¹ One of the main reasons behind this lack of conclusive outcomes is related to the high interindividual variation observed in the metabolism of plant bioactives and the heterogeneity of individual biological responsiveness to their intake.^{2,3}

Improving our knowledge of the factors that influence the bioavailability and the bioefficacy of plant food bioactives is essential to understand why some compounds work effectively in some individuals but not or less in others. It has been stated that a wide number of factors (including age, gender, ethnicity, weight or BMI, health status, genetic polymorphisms, lifestyle,

and gut microbiota composition) may affect the interindividual variation in response to plant food bioactives consumption.^{2,3} Identifying these factors for the main categories of plant bioactives is crucial to ensure an optimal integration of these compounds in future personalized nutrition strategies. However, to date, only a few studies targeting specifically interindividual differences and the causes thereof are present in the literature.^{2,3} To tackle the complexity of this topic, innovative approaches studying the effects of plant bioactives on health maintenance, in collaboration with other relevant disciplines, are required.

High-throughput “omics” technologies, such as microbiomics, nutri(epi)genomics, and metabolomics, may provide a holistic view of how the human body reacts to plant bioactive consumption while assisting the investigation of individual differences and, thus, favoring personalized nutrition (Figure 1).^{2,4} The adoption of these technologies may help to describe how plant bioactives affect human metagenome, genome, and metabolome. They may be used to assess shifts in microbiota

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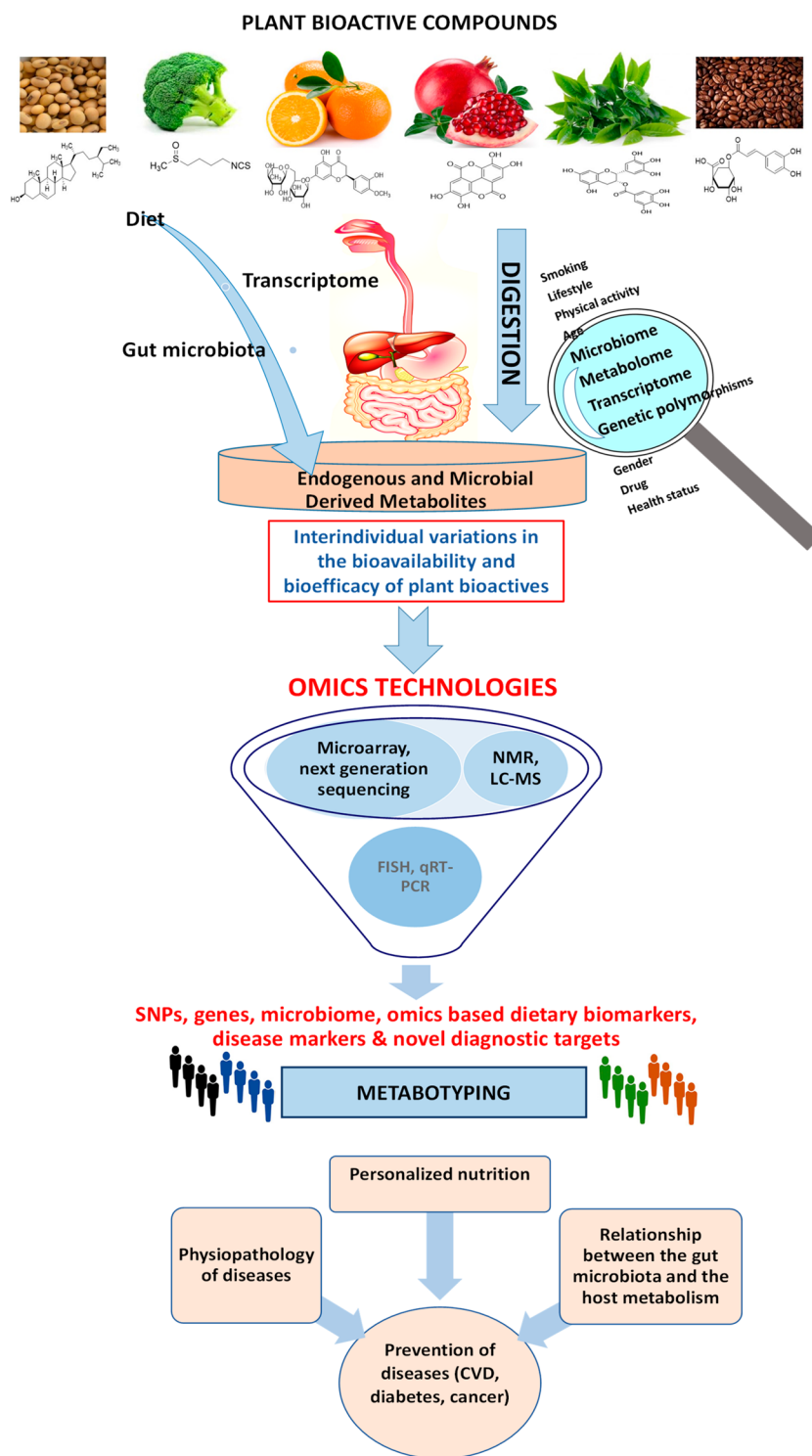


Figure 1. Overview of the role of omics technologies in the study of the effects of plant bioactives on health while considering interindividual variability.

composition, to better understand how gene polymorphisms affect the individual response, and to identify new biomarkers, as well as to evaluate the complex mechanisms behind the human response to plant bioactives.⁴

The aim of this Perspective is to highlight (1) the potential of advanced omics technologies to unravel the health effects of plant bioactives while considering interindividual variability and (2) the need to increase knowledge in the field by developing effective strategies to optimize the beneficial effects of plant food bioactives for all population groups.

■ MICROBIOMICS

All animals with an organized gut host complex communities of microorganisms that comprise the intestinal microbiota. These bacteria, fungi, viruses, and protozoa shape host immune function; contribute significantly to host metabolome; are partners in cometabolism of dietary components, especially complex plant bioactives like (poly)phenols and fibers; and mount a barrier to invading pathogenic microorganisms by occupying ecological niches within the open system that is the intestine.

Several studies have revealed that there is a strong relationship between the composition of human microbiota and health. Moreover, microbiome dysbiosis is a characteristic feature of several chronic diseases, such as diabetes, obesity, inflammatory bowel disease, and cardiovascular diseases, and may indeed be involved in disease onset or progression.⁵

The application of next-generation sequencing, in particular amplicon-based 16S rRNA meta-taxonomics and whole community metagenomics, has revolutionized our ability to describe human associated microbiomes in terms of taxonomic composition and metabolic potential. Together with older tools like quantitative PCR and fluorescent in situ hybridization using 16S rRNA targeted primers and probes (which can still generate valuable information where exact quantification of specific bacteria or groups of bacteria is important), these culture-independent technologies could be described as microbiomics. The total community genome of the intestinal microbiome comprises about 150 times more genes than that of the human genome, corresponding to more than 3 million genes.⁶ This complex and great genetic potential contributes to affect human health, enabling the expression of a vast number of genes in their metabolic and biosynthetic pathways and significantly expanding the metabolic potential of the human genome, allowing access to nutrients and energy otherwise inaccessible to the host because of their complex chemical structure. This is particularly true for plant bioactive (poly)phenols and dietary fibers, the majority of which require biotransformation by the intestinal microbiota before becoming bioaccessible to the host and biologically active systemically.

The genome of human microbiota is largely unexplored. However, there are great efforts to understand their biochemical functions in disease development and effects on human health. The EU FP7MetaHIT (Metagenomics of the Human Intestinal Tract) project established the relationship between the genes of the human intestinal microbiota and human health and disease. Subsequently, the Human Microbiome Project (HMP) resulted in the characterization of the human microbiota to further understand the impact of the microbiome on human health and disease. In the second phase of the HMP, namely iHMP, integrated longitudinal data sets will be created from both the microbiome and host belonging to three different cohort studies of microbiome-associated conditions using multiple omics technologies. In particular, microbiome genome-wide association studies (mGWAS) discovered the associations between the composition of microbiome and human genes through 16S rRNA or metagenomic sequencing. Exploration of human genome and microbiome simultaneously has shown that genetic variations in the host are reflected in the microbiota composition, thus allowing us to observe the relationship between diseases and genotypes. However, it is still not clear whether the change in the composition of the microbiota in dysbiosis is the consequence or cause of the disease, which is accepted as a limitation of mGWAS studies.

Dietary factors have great effect on individuals' microbiota as a dynamic system. Dietary components, particularly some (poly)phenolic compounds, and gut microbiota present a two-sided relationship. On one hand, plant bioactives can modulate the composition of the gut microbiota, changing their metabolic output (e.g., concentrations and ratios of short chain fatty acids and bile acids) and possibly their impact on host metabolic pathways and immune function. Such dietary modulation of microbiome structure and metabolic function could impact disease risk (Supporting Information, Table S1). On the other

hand, a vast number of metabolites are generated through microbial transformations of dietary phenolic compounds which then become available to the host upon absorption.⁷ Interestingly, the bioavailability and bioefficacy of these plant bioactives and their metabolites may vary because of interindividual differences in the gut microbiota composition.⁸ Moreover, the concentration of microbial-derived metabolites of some plant bioactives has been found to be higher than the parent compounds.⁷ Therefore, the specificity and individual variability existing in the production of some phenolic metabolites of microbial origin, such as phenyl- γ -valerolactones (derived from flavan-3-ols),⁹ equol (isoflavone daidzein),¹⁰ urolithins (ellagic acid and ellagitannins),⁸ and 8-prenylaringenin (hop prenylflavonoids),¹¹ may be key factors behind the different responsiveness to consumption of plant bioactives. Unfortunately, the health effects of these gut-derived metabolites have been reported in only a few human studies.

Although studies have correlated particular genera or species of gut bacteria with plant phenolic metabolites in blood, most studies have been performed on fasted blood samples, which does not capture the true nutrkinetics of phenolic metabolites absorbed from the gut following microbial biotransformation. One attempt to directly correlate microbiota composition with plant bioactive nutrkinetics has recently shown that related classes of metabolites derived from apple (poly)phenol metabolism in postprandial blood (up to 5 h post ingestion) and 24 h urines can be correlated with specific members of the gut microbiota.¹² A major surprise from this work was the observation that bacteria from very different phylogenetic backgrounds (e.g., genus *Bifidobacterium* in the Actinobacteria, and *Alistipes*, a genus within the phylum Bacteroidetes) correlate with the production of exactly the same classes of metabolites in blood and urine. This observation has two major implications. First, it provides direct evidence that metabolic redundancy between distantly related bacteria within the gut microbiome can signify occupancy of the same or similar ecological niches. Metabolic redundancy is likely to afford increased microbiome resilience in the face of disruptive environmental pressures (e.g., antibiotics, invading pathogens, poor diet) and constitutes an inherent resistance mechanism against microbiome dysbiosis. Second, it highlights that metabolic functionality within the gut microbiome may not be tightly connected to phylogenetic identity. It also highlights the power of multi-omics approaches to provide the necessary and complementary information islands required to define microbiome community structure and measure microbiome metabolic or functional output.

In summary, microbiomics enables the detection of the composition and biological activities of gut microbiota, thus explaining host–microbiota interactions. Microbiomics findings might indeed allow the discovery of the physiopathology of some diseases, supporting a new generation of disease markers resulting from microbial metabolism as crucial tools in diagnostics to determine disease risks. The role of microbiomics in these fields still needs to be developed, and several issues need to be taken into account for future personalized nutrition microbiomics-based approaches. Human microbiomics, together with metabolomics, are valuable targets that play a vital role in the success of further personalized nutrition studies. Therefore, novel microbial metabolomics biomarkers are candidates for personalized nutrition approaches. Metabotyping (grouping individuals with similar metabolic profiles) may be a key success factor in personalized nutrition

when taking into account plant bioactives. Ideally, it would give tailored dietary advice entailing decreased disease risks. Nevertheless, before these desired scenarios can be achieved, the mechanism of homeostatic maintenance of microbiome—human genome and the conditions that cause disturbances in microbial compositions need to be studied. Fecal samples are critical materials to further investigate the change of microbial composition upon bioactive consumption in different disease conditions. The differences in sampling and methods of quantification, as well as the lack of standardized methods, result in difficulties when comparing data generated from different laboratories. To better support the role of microbiomics in the assessment of plant bioactives features, these factors should be harmonized.

■ NUTRI(EPI)GENOMICS AND NUTRI(EPI)GENETICS

Since the early 2000s, together with the awareness of the existence of close interactions between our diet and our genes, the interest among researchers in exploring nutrition at the molecular and genetic level has strongly evolved. Nutri(epi)-genomics asks how dietary components influence gene expression or epigenetic changes that may turn certain genes on or off. On the other hand, nutrigenetics asks how our genetic makeup makes us a responder or nonresponder to dietary interventions. The focus on bidirectional gene—diet/nutrient interactions has allowed changes to the concept of traditional nutrition, resulting in improved population nourishing methodologies, better life quality and health, disease prevention, and more efficient individual dietary intervention strategies. Indeed, the sequencing of the human genome and the subsequent increased knowledge regarding human genetic variation, identifying genes or polymorphisms involved in the physiological responses to various dietary nutrients, is contributing to the emergence of personalized nutrition to preserve health and well-being and to prevent diseases related to diet.¹³

Even though ongoing research continues to elucidate the role of nutrition in gene expression and to prevent and manage several human diseases, its influence on the application of personalized nutrition is still discussed. As such, much of the nutrigenomics effects attributed to plant food bioactives are derived from cell and animal models, with only a few of them backed-up by human intervention studies. The limited evidence regarding gene—diet interactions in human chronic diseases, such as cardiovascular diseases (CVDs) or cancer, is mostly inconclusive because of (1) the small number of human nutri(epi)genomics and -genetics studies carried out and (2) the limitations of the experimental designs. Examples of the few human trials on genomic changes upon consumption of plant food bioactives are shown in the [Supporting Information](#), Table S2.

The lack of randomized controlled trials in humans to date brings about many gaps in the interactions between diet, genes, and health, making personalized nutrition a concept rather than a reality. In addition, there are still critical issues (such as social, economic, legal, and ethical aspects, as well as its application in clinical practice) regarding the use of personal genetic information to develop dietary guidelines and personal recommendations to reduce the risk and prevalence of nutrition-related diseases.¹³ Indeed, during recent years, it has become increasingly evident that nutrigenomics is an important aspect of precision medicine which examines the bidirectional interactions of the genome and nutritional exposures to be used as therapeutic interventions. However, both disciplines are not

completely applied yet into the daily routine because of a lack of robust and reproducible results, as well as ethical implementation issues.¹⁴

We do believe that, in the future, it will be possible to provide knowledge of individual genetic predisposition to chronic diseases, such as CVDs and obesity, by the integration of nutri(epi)genomics and -genetics together with ethics and medicine.¹⁵ In our view, more complex intervention studies designed with larger population groups as well as clinical trials and dietary component-specific trials in subjects or cohorts selected for specific genetic variants are of crucial interest. This will allow researchers to investigate genetic—dietary component interactions with the final aim of diet personalization and developing effective dietary strategies.

On the other hand, with the aim of responding to the challenge that consumers increasingly demand “functional foods”, it is necessary to boost the research focused on the heterogeneity in the responsiveness of individuals to these dietary compounds. Whereas most of these compounds are absorbed and metabolized through the same polymorphic carriers and enzymatic systems as drugs and other xenobiotics, until now, only a few genetic factors have been reported. The limited evidence focused on (epi)genetic factors involved in the interindividual variability in response to plant food bioactives has been recently reviewed.^{2,3} They are mostly genetic polymorphisms of genes involved in the bioavailability and phase I and phase II metabolism of plant food bioactives, such as various cytochromes P450 (CYP) isoforms, catechol-*O*-methyltransferase (COMT), UDP-glucuronosyltransferases isoforms, etc. In this regard, Bohn et al.¹⁶ reported the critical role of some single-nucleotide polymorphisms (SNPs) related to interindividual variability of carotenoid bioavailability in humans, including SNPs in genes encoding for uptake/efflux transporters, digestion and metabolism enzymes, and proteins involved in further tissue distribution. However, regarding dietary (poly)phenols, the identification of the protein carriers involved in their absorption, distribution, and elimination remains a prerequisite to progress in the understanding of to what extent changes in gene variants can actually contribute to between-subject differences in (poly)phenol bioavailability. Consequently, there is a high need for more studies focused on the identification of candidate genes and/or noncoding RNAs underlying the interindividual variation and their subsequent potential effect on human health beyond those involved in bioavailability in response to plant food bioactives intake. Indeed, few studies have indicated an association of apolipoprotein E (ApoE) genetic polymorphisms and the different cholesterol-raising effects of coffee¹⁷ or the reduction of blood lipids in hypercholesterolemic subjects,¹⁸ among others.

Finally, the worldwide (epi)genomic research of human exposure to plant food bioactives will tend to generate a huge amount of data directly and indirectly linked to restoring and preserving health and to assessing interindividual variability. Therefore, in the long run, it will be necessary to develop and implement a cross-disciplinary approach to achieve real health-beneficial personalized nutrition for individuals based on genomics and genetics, among other factors. In the coming years, both nutrigenomics and nutrigenetics will be helpful in providing evidence-based dietary intervention strategies (personalized diet) to preserve health and well-being and to prevent diet-related diseases. We conclude that, undoubtedly, the research on the coding and noncoding genes related to the

complex mechanisms of action of plant food bioactives should be actively investigated and validated.

■ METABOLOMICS

There is a growing interest in better understanding the mechanisms by which foods are able to impact human health, as well as on how dietary habits are reflected in biospecimens. Metabolomics studies global changes in the metabolites present in an organism and shows different applications in food science and nutrition.¹⁹ The application of metabolomics in the field of food science and nutrition is helping to support the previous research on the relationships between diet and health derived from many epidemiological and clinical studies.

First, to study the effects of plant food bioactives on health, it is important to characterize the food product itself. In this sense, metabolomics has been demonstrated to be an essential tool for the identification of hundreds of bioactive compounds in different foods and for the evaluation of their authenticity, quality, and safety, as well to study the consequences of food processing.²⁰

In addition, to improve the knowledge of the effects of food bioactives on human health, it is necessary to understand the digestion process, which can provide molecules with biological activities. Metabolomics allows a more comprehensive view of the compounds released during digestion and the metabolites present in body fluids.²¹ These metabolites, rather than their parent compounds, could be responsible for the beneficial effects on human health. The bioactivity of digestion products can be assessed by correlating their levels in blood or urine to changes in different parameters related to health status. Several studies have determined the associations between metabolites obtained after consumption of bioactive compounds present in foods, such as cocoa, nuts, orange juice, coffee, blackberries, and pomegranate, and health effects (colorectal cancer, obesity, diabetes, cardiovascular disease, etc.).²⁰ Other studies have been focused on evaluating the changes resulting from whole dietary patterns. For instance, specific plasma metabolites determined after consumption of a Mediterranean diet have been associated with the prevention of CVD.²²

Another point of view of the application of metabolomics in nutrition science is the evaluation of changes in the overall metabolome in response to food compounds (and specifically plant food bioactives) and dietary patterns. For instance, biomarkers related to endogenous modifications after the consumption of wine or olive oil have been reported.²³

Accurate measurement of food intake is essential to understand the links between diet and health. Dietary patterns and evaluation of dietary intake of food nutrients have generally been done using frequency questionnaires, 24 h recalls, or dietary records. However, such data are often subjected to possible errors. The use of dietary biomarkers has been proposed as a potential alternative to provide a more objective and accurate measure of food intake. The application of metabolomics for the determination of food intake biomarkers has been expanded rapidly in recent years (Supporting Information, Table S3). A recent review has collected several applications of metabolomics to identify novel biomarkers of dietary intake.²⁴ These studies generally applied untargeted metabolomics approaches and resulted in the identification of candidate biomarkers of specific foods or food groups such as citrus fruit, cruciferous vegetables, red meat, coffee, tea, sugar-sweetened beverages, and wine.²⁴ A very comprehensive list of all the potential biomarkers related to plant bioactives can be found in the review

of Manach et al.²⁵ Although some potential biomarkers have been reported, only a few of them have been validated. The gaps to be addressed for such biomarkers to reach their full potential related to their specificity, interindividual variation, validation, and quantification have been recently discussed.²⁶ A good example of a robust food intake biomarker is proline betaine to monitor citrus consumption. It was validated by different research groups and in a large cohort study using different analytical strategies.²⁷ Furthermore, it has also been demonstrated that this biomarker is capable of precisely quantifying the intake of citrus foods.²⁸ More studies like this are required to validate the specificity and utility of these potential biomarkers in an epidemiologic context. Moreover, some metabolites of plant bioactives with long clearing life in the body are good candidates to serve as biomarkers of consumption of plant food bioactives.

Apart from biomarkers of food intake, there has been an increased interest in recent years in classifying subjects into dietary patterns associated with different disease risks.²⁹ Several studies have evaluated metabolic profiles associated with dietary patterns, including Mediterranean, Nordic, Western, prudent, and vegetarian dietary patterns, among others.²⁹ The identification of biomarkers of dietary patterns may also be important for studying relationships between diet and disease as well as a niche for new research on plant food bioactives.

Although most of the studies investigating dietary biomarkers have been focused on single candidates, this reductive option presents some limitations (i.e., low specificity). Consequently, the tendency is to work with multimetabolite biomarker panels, a field practically unexplored so far. The real issue would be to find a simple group of metabolites that is able to properly evaluate dietary exposure. In this sense, a recent study demonstrated that combining different metabolites as biomarker models improves prediction of dietary exposure to cocoa in free-living volunteers.³⁰

The future challenge is to integrate all these metabolomics results with those from other omics technologies to better understand the complex relationship among plant food bioactives, nutrition, and human health while taking into account inter-individual differences.

■ FUTURE PERSPECTIVES

Omics technologies offer many possibilities to tackle the great research challenges derived from the complexity of the interactions on an individual basis between plant bioactives and health outcomes. Nevertheless, there is a lack of information on the use of these top-down, holistic approaches to unravel the effects of plant food bioactives, at both the population and individual levels. Consequently, further studies using and integrating microbiomics, nutri(epi)genomics, and metabolomics are required. Well-designed studies addressed to phenotype individuals upon consumption of plant food bioactives and considering the bioavailability of the compound(s) and the physiological response would benefit from the impressive amount of data generated by omics tools. The characteristics of the gut microbiome, the genotype for those genes showing interindividual variability, and the metabolome profile after plant bioactive consumption should be taken into account to guarantee an adequate in-depth characterization of the individual as well as its response to the plant food or the dietary pattern evaluated.²

To draw robust conclusions on the effects of plant bioactives on human health, as assisted by omics technologies allowing an

extensive phenotyping of individuals, it is of paramount importance to fill the gaps currently threatening omics disciplines and conditioning the study of plant bioactives while keeping in mind interindividual differences. Among other aspects, microbiomics should be able to identify the impact of plant bioactives and their colonic metabolites on the bidirectional interaction between human organism and gut microbiome. Nutri(epi)genomics should identify the genes or epigenetic mechanisms underlying interindividual variability and cope with the sensitive issues raised from handling genetic information. Metabolomics should address the current limitations of most of the biomarkers of exposure, related mainly to their specificity, individual variation, validation, and quantification. Moreover, some other limitations related to omics approaches should be tackled, such as (i) the high cost of omics studies, which may limit its use; (ii) the small data set available to date on result repeatability in the same subject over a short time (intraindividual variability); and (iii) the relatively large number of factors that could influence the results when the methods are applied to subjects changing remarkably their habits (for instance, changing diet, smoking cessation, etc.) or patients changing pharmacological treatments over time. Lastly, great efforts are needed to integrate these complementary big data approaches together with well-established biomarkers of health in order to comprehensively investigate the effects of plant bioactives taking into account person-to-person and population heterogeneity. The transition toward personalized approaches would also benefit from simplified procedures or platforms for big data analysis and interpretation, which to date is almost exclusively available for highly qualified users with multidisciplinary expertise. Overall, the development and implementation of cross-disciplinary strategies is necessary to fully elucidate plant bioactives–health relationships and to achieve real personalized nutritional recommendations for plant bioactives. This would open a new field with clear societal benefits related to healthier populations and boosted industrial opportunities.

■ ASSOCIATED CONTENT

📄 Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.jafc.8b03385](https://doi.org/10.1021/acs.jafc.8b03385).

Examples of studies investigating the prebiotic effect of plant food bioactives (Table S1); examples of randomized controlled trials investigating the impact of plant food bioactives on human gene expression (Table S2); examples of human interventions where food intake biomarkers related to plant bioactive consumption have been identified (Table S3) (PDF)

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Notes

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