# Measuring Dietary Botanical Diversity as a Proxy for Phytochemical Exposure

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**Abstract:** The study of natural plant molecules and their medicinal properties, pharmacognosy, provides a taxonomy for botanical families that represent diverse chemical groupings with potentially distinct functions in relation to human health. Yet, this reservoir of knowledge has not been systematically applied to elucidating the role of patterns of plant food consumption on gut microbial ecology and function. All chemical classes of dietary phytochemicals can affect the composition of the microbes that colonize the gut and their function. In turn, the gut microbiome affects the host via multiple mechanisms including gut barrier function, immune function, satiety and taste regulation and the activity of biological signaling pathways that influence health and disease. Herein, we report the development of a botanical diversity index (BDI) to evaluate plant food consumption as a novel metric for identifying and quantifying phytochemicals to which an individual is exposed. A rationale is advanced for using the BDI to investigate how plant food diversity impacts gut microbial ecology and functionality.

**Keywords:** botanical diversity; chronic disease risk; gut microbiome; metagenomics; metabolomics; dietary pattern

## 1. Introduction

Major chronic diseases including obesity, type 2 diabetes, cardiovascular disease, stroke, and cancer account for more than 60% of global mortality per annum [1,2]. Evidence continues to emerge that the deregulation of cell signaling pathways underlying the pathogenesis of these diseases, such as chronic inflammation, are interrelated [3]. This provides an avenue for reducing the complexity of preventing and controlling chronic diseases to a common framework. In parallel with understanding shared chronic disease mechanisms, efforts to promote diet and nutrition for chronic disease prevention and control have evolved from a focus on specific nutrients or foods to a recognition of the importance of dietary patterns, which represent the totality of foods and beverages habitually consumed and the interactive, synergistic, and antagonistic nature of dietary exposures on human metabolism and disease [4–6]. Food pattern modeling further characterizes amounts and types of foods within a dietary pattern, such as fruits, vegetables, and grains [7]. Recent advances in next-generation sequencing have revealed that the gut microbiome is a key mediator of the effects of food on chronic disease processes; although there is not yet a consensus on either what constitutes a healthy gut microbiome or on

which food consumption patterns are most effective in maintaining the functional activity of the gut microbiome [8–11]. Emerging evidence suggests that plant food diversity may play a role. For example, a study from the American Gut Project citizen science initiative showed that the number of unique plant species eaten was associated with microbial diversity. Short-chain fatty acid fermenters were associated with eating >30 versus <10 plant types per week [12]. We advance the idea that new insights about the interface of diet, the gut microbiome, and chronic disease mechanisms can be gained by considering botanical plant food diversity through the lens of pharmacognosy, which in this context pertains to the study of drug substances of natural origin. This approach has the potential to pave the way to applying a precision medicine framework to the concept of "culinary medicine" with the goal of intervening through diet–gut microbiome interactions to modulate shared chronic disease processes for disease prevention and control [11,13].

## 2. Characterizing Dietary Diversity

Dietary variety, representing the pattern of food and beverage diversity in the diet, has been promoted to help achieve a nutritionally adequate diet [7,14]. Many studies exist on the topic of dietary diversity, using a variety of indices to quantify it in a population setting. Dietary diversity algorithms have tended to count number of servings of dietary guideline-recommended food groups or subgroups consumed in a specified timeframe, with or without penalization according to meeting consumption targets [15–24]. Some diversity scores consider, in addition to number of food items, the distribution and health value of consumed foods, with higher scores assigned as variation in food intake becomes healthier [25,26]. More quantitatively rigorous capture of dietary diversity has been accomplished with the use of a modified Berry–Simpson index, a common measure of diversity used in ecology and economics [20,27,28]. Such scores account for both the number of foods or food groups consumed and the quantity consumed across these food groups. Functional diversity indices further reflect diversity in nutrient composition of the foods consumed [29], thus additionally capturing nutritional adequacy.

A limitation of existing methods for measuring dietary diversity is that diversity scores can be inclusive of both healthy (nutrient dense) and less healthy (not nutrient dense) food items and may fail to account for proportionality of dietary components. In light of several recent studies [21,26], an American Heart Association science advisory concluded that dietary diversity may be associated with increased energy consumption and obesity [30]. The advisory's primary recommendation was to focus on increasing diet quality through adequate consumption of plant food, protein sources, low-fat dairy products, vegetable oils, and nuts and limiting consumption of sweets, sugar-sweetened beverages, and red meats, while stating a need for further research into the more specific aspects of dietary variety [30]. These reported concerns provide an opportunity to thoughtfully reconsider how plant food intake patterns are identified.

## 3. Rethinking the Assessment of the Plant Food Components of Dietary Patterns

A common axiom in the nutrition and dietetics community and government nutrition education programs is to "eat a variety of foods", also communicated as, "eat the rainbow" [31,32]. This traditional recommendation is reflected in the Dietary Guidelines for Americans and other international dietary guidelines and is formulated using culinary definitions of foods (e.g., fruits, vegetables, and grains) [7]. A careful inspection of how these terms are defined and the manner in which they are used reveals a surprising amount of ambiguity about the rationale for grouping foods, especially the subgroups [33]. In the interest of better understanding the benefits of plant food intake, both individually and in combination, on the gut microbiome, the current food groups and subgroups may be insufficiently granular to capture the chemistry that dictates both what microbes are likely to populate the gut and their functional activity. In the following sections, we consider the advantages gained from evaluating diet with a focus on plant food diversity.

### 3.1. Pharmocognosy

The American Society of Pharmacognosy defines pharmacognosy as, "the study of the physical, chemical, biochemical, and biological properties of drugs, drug substances, or potential drugs or drug substances of natural origin as well as the search for new drugs from natural sources". While the term is not new, first being used in 1841, to our knowledge, leveraging the principles of pharmacognosy to systematically categorize commonly consumed plant foods based on the probability of chemical similarity is novel. The organizational structure that we have developed is illustrated in an updated version of the Evolutionary Tree of Plant-Based Foods (Figure 1) that we originally published [34]. The tree was designed using principles of chemotaxonomy, the classification of plants based on similarities and differences in biochemical composition [35]. Accordingly, the probability for chemical similarities among foods derived from the same botanical family is greater than foods derived from different botanical families [36]. Many potentially significant bioactive phytochemicals remain unidentified. However, botanical groupings may provide direction for emerging technologies like mass spectrometry to identify and quantify compounds linked to biological function, health status, and disease. One such example highlighting the potential of this approach is the finding that consumption of cruciferous vegetables belonging to the botanical family *Brassicaceae* has been linked to reduced risk of chronic diseases and mortality [37]. Glucoraphanin [38], a glucosinolate, serves as an inert precursor to the frequently studied chemoprotective compound sulforaphane. Identification of edible plants containing this metabolite provides a roadmap for identifying similar functional foods or "plants as medicine".
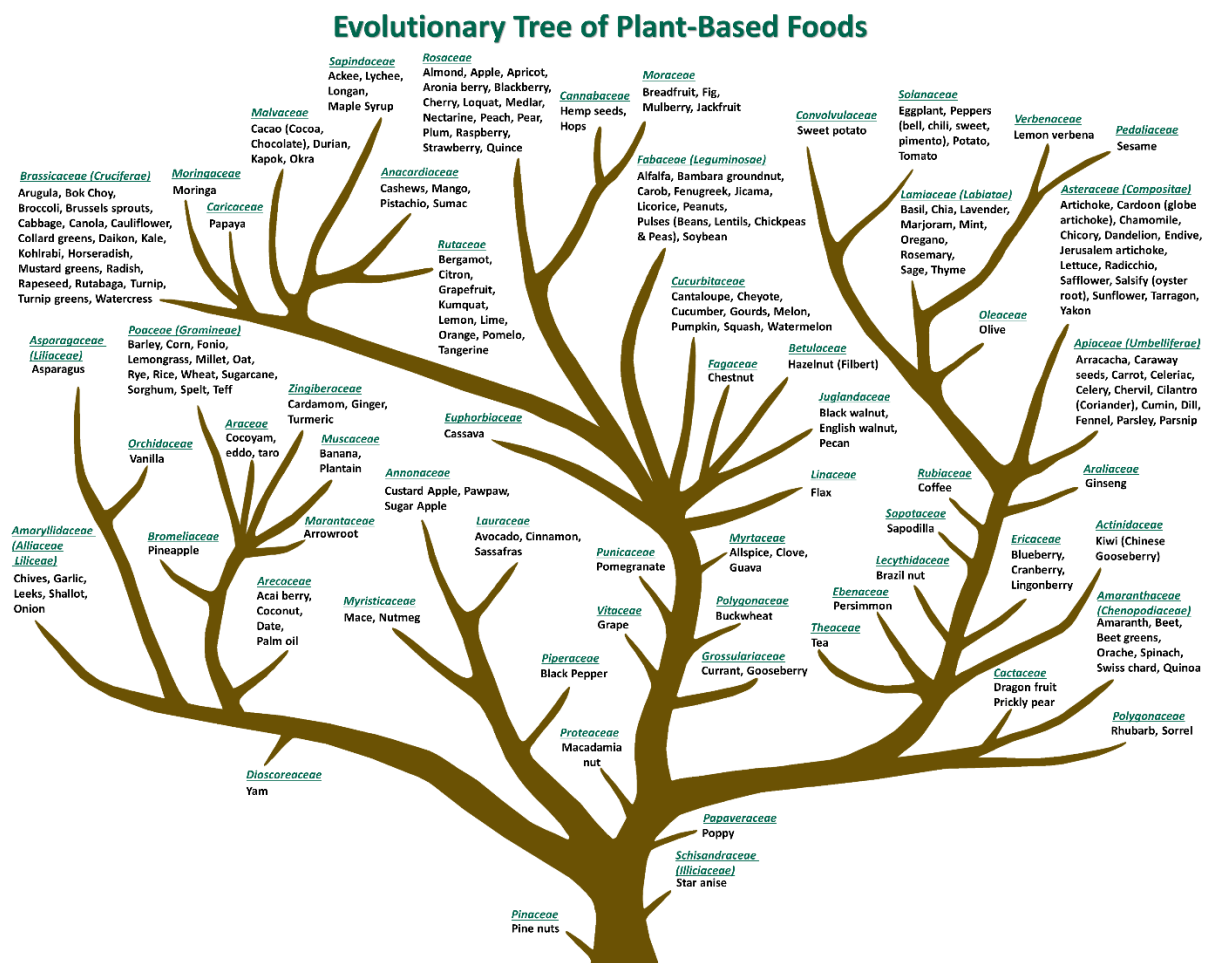


**Figure 1.** Evolutionary Tree of Plant-Based Foods. Botanical families occupying proximal branches are more chemically similar than those on distant branches. Reprinted with the permission of Elsevier (2021).

### 3.2. Phytochemicals

The rationale for developing a novel dietary pattern score for measuring plant food botanical diversity stems from the premise that genetically distinct plant foods, as depicted in the Evolutionary Tree of Plant-Based Foods, contain diverse phytochemicals that may be digested, used as substrate by microbes, absorbed, and metabolized to different extents. Phytochemicals represent the primary and secondary metabolites derived from biosynthetic processes underlying growth, development, and reproduction in every plant [35]. Primary metabolites include carbohydrates, amino acids, lipids, and nucleic acids. They exist in many complex conformations that affect both the ability to digest them to absorbable structures and that also affect the ability of microorganisms to assimilate them as fuel sources [39]. It is estimated that up to 5 g of dietary fat; 25 g of dietary protein, peptides, and amino acids; and 40 g of dietary carbohydrate enter the large intestine each day, affecting the type, amount, and function of the microbes that colonize that intestinal segment (reviewed in [40]). Microbial access to these macromolecules as fuel sources is determined by the primary, secondary, and tertiary structure of their "digested macronutrient". Plant secondary metabolites fall within a wide range of chemical classes and are estimated to include over 10,000 distinct chemicals (Table 1). Secondary metabolites generally exist in plants bound to other molecules, for example, carbohydrates, lipids, and proteins; and this affects their bioavailability as well as the microbial species that occupy the intestinal tract. Details of the interactions of microbes with both primary and secondary phytochemicals have recently been reviewed [13,40].

### 3.3. Botanical Diversity Index (BDI)

A prior human randomized dietary diversity trial compared diets providing 5 versus 18 botanical families per day and demonstrated the efficacy of botanical diversity for modulating disease-relevant biological pathways including oxidative stress [19]. We propose modeling the diversity of botanical foods consumed as a useful means of examining the complex interaction between diet, microbiome, and host metabolism. This required the development of a novel, quantitative metric to sufficiently capture dietary botanical diversity. We adapted the Berry–Simpson index [41] to create the BDI. The index was derived from a food frequency questionnaire (FFQ). For each line item representing a botanical food, the amount of food reported was converted to cup equivalents (for fruits, vegetables, and legumes) or ounce equivalents (for grains) per day, using the 2017–2018 United States Department of Agriculture (USDA) Food Patterns Equivalents Database (FPED) [42]. Intake of each botanical group was quantified as the square of the number of cup or ounce equivalents consumed per day divided by the total number of botanical families evaluated; the values for each botanical group were then summed, and the result was subtracted from one. Possible values for the index range from 0 to $[1-1/n]$ (n being the number of botanical groups evaluated). Theoretically, a BDI score of 0 would indicate plant food consumption from only one botanical family, while a score of 1 would indicate consumption of all botanical families evaluated.

A limitation of this approach to generating a diversity index is that the number of botanical families represented is limited by the number captured by the dietary assessment method used, as in the case with an FFQ. Twenty-four-hour dietary recalls yield greater granularity and, therefore, may capture more botanical families. On the other hand, they may capture fewer botanical families because the observation period is very short. Multiple 24 h recalls would be needed to model dietary botanical diversity in the diet. Depending on the research question of interest, multiple administrations of a 24 h recall can be used to model usual dietary intake for nutrients and food groups [43]; however, statistical models would need to be developed to estimate the BDI.

**Table 1.** Bioactive compounds in each class of plant secondary metabolites.

| Chemical Classes | Examples of Bioactive Compounds |
| --- | --- |
| Alkaloids | 7-Acetylintermedine, 7-Acetyllycopsamine, Anabasine, Anatabine, Atropine, Berberine, Brucine, Caffeine, Capsaicin, Catuabine, Codeine, Coniine, Cytisine, Ecgonine, Emetine, Ephedrine, Ergine, Hydrastine, Hygrine, Morphine, Narceine, Narcotine, Nicotine, Nornicotine, Papaverine, Pelletierine, Pilocarpine, Piperine, Quinine, Sanguinarine, Scopolamine, Seratonin, Sparteine, Strychnine, Symphytine, Thebaine, Theobromine, Trigonelline, Vinblastine, Vincristine |
| Amines | Piperazine, Piperidine, Pyrrolidine (Tetrahdyropyrrole) |
| Cyanogenic glycosides | Dhurrin, Laetrile (Amygdalin), Linamarin, Lotaustralin, Prunasin, Sambunigrin, Taxiphyllin, Vicianin |
| Diterpenes | Dihydrogrindelaldehyde, Dihydrogrindelic Acid, Erythrofordin, Hedychilactone, Hedychinone, labd-13E-en-15-oate, Norerythrofordin, Phytol, Retinoids, Retinol, Taxol |
| Flavonoids | Apigenin, Baicalein, Biochanin A, Catechin, Coumestrol, Cyanidin, Daidzein, Deguelin, Delphinidin, Epicatechin, Epicatechin, Epigallocatechin, Eriodictyol, Fisetin, Galangin, gallate, gallate, Gallocatechin, Genistein, Glycitein, Hesperidin, Isorhamnetin, Kaempferol, Luteolin, Malvidin, Myricetin, Naringenin, Naringin, Pachypodol, Pelargonidin, Peonidin, Petunidin, Quercetin, Rhamnazin, Rotenone, Rutin, Silymarin, Tangeritin, Wogonin |
| Glucosinolates | Glucoberteroin, Glucobrassicanapin, Glucobrassicin, Glucocheirolin, Glucoerucin, Glucoiberin, Gluconapin, Gluconapoleiferin, Gluconasturtiin, Progoitrin, Sinigrin |
| Monoterpenes | Borneol, Camphor, Carene, Carveol, Carvone, Citral, Citronellal, Citronellol, Eucalyptol, Eucalyptol, Geraniol, Limonene, Linalool, Myrcene, α-Pinene, β-Pinene, Terpineol |
| Non-protein amino acids | Alliin, Butiin, Canavanine, S-Allyl Cysteine, Djenkolic Acid, Ethionine, Etiin, Isoalliin, Methiin, Propiin |
| Phenylpropanes | Caffeic Acid, Piceatannol, Pterostilbene, Resveratrol, Rosavins, Sesamol, Theaflavin, Thearubigin |
| Polyacetylenes | Capillin, Dihydropanaxacol, Falcarindiol, Falcarinone, Panaxacol, Panaxydol, Panaxynol (Falcarinol), Panaxytriol |
| Polyketides | Acetogenins (Annonacin Uvaricin), Aflatoxin, Aloenin, Aloesin, Amphotericin, Anthraquinones, Azithromycin, Barbaloin, Bullatacin, Clarithromycin, Discodermolide, Erythromycin A, Pikromycin, Tetracyclines |
| Sesquiterpenes | Artemisinin, Bisabolol, Cadinene, Caryophyllene, Copaene, Farnesene, Farnesol, Guaiazulene, Lactucin, Longifolene, Parthenolide, Vetivazulene |
| Tetraterpenes | Annatto, α-Carotene, β-Carotene, and β-Cryptoxanthin, Crocetin, Crocin, Cryptoxanthine, Lutein, Lycopene, Phytoene, Phytofluene, Sporopollenin, Zeaxanthine |
| Triterpenes, saponins, steroids | Betulinic Acid, Ginsenosides, Glabrolide, Glycyrrhizin, Lanosterol, Lantadene, Lantanolic Acid, Lantic Acid, Licorice Acid, Liquiritic Acid, Lupeol, Oleanolic Acid, β-Sitosterol, Squalene, SU1, Ursolic Acid |

An example of the BDI score algorithm is presented in Equation (1).

$$\textbf{BDS Score } \left[1 - \sum s_i^2\right] = 1 - \Big[(\text{rosaceae}/\text{n})^2 + (\text{musaceae}/\text{n})^2 + (\text{fabaceae}/\text{n})^2 +$$
$$(\text{amaranthaceae}/\text{n})^2 + (\text{poaceae}/\text{n})^2 + (\text{brassicaceae}/\text{n})^2 + (\text{malvaceae}/\text{n})^2 +$$
$$(\text{cucurbitaceae}/\text{n})^2 + (\text{apiaceae}/\text{n})^2 + (\text{rubiaceae}/\text{n})^2 + (\text{amaryllidaceae}/\text{n})^2 +$$
$$(\text{rutaceae}/\text{n})^2 + (\text{vitaceae}/\text{n})^2 + (\text{solanaceae}/\text{n})^2 + (\text{convolvulaceae}/\text{n})^2 +$$
$$(\text{asteraceae}/\text{n})^2 + (\text{bromeliaceae}/\text{n})^2 + (\text{Theaceae}/\text{n})^2\Big]$$

(1)

n: total number of botanical families represented on the food frequency questionnaire. All values in servings/day.

We calculated the BDI for the menus provided in the randomized dietary trial by Thompson et al., (2006), where study groups were given 8–10 servings of plant foods per day but assigned a low (5 families) or high (18 families) botanical diversity diet over 14 days [44]. The low-diversity menu received a BDI score of 0.76 while the high-diversity menu scored 0.93. Applying the same scoring algorithm to data from a nested study within the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) that measured dietary intake using a National Cancer Institute food frequency questionnaire, the Diet Questionnaire,

Version No. 10/99, ref. [45] yielded a range of scores from 0.34 to 0.89 (mean 0.75 and median 0.77). Average intake of foods according to botanical family is presented in Table 2.

**Table 2.** Mean intake (servings * per day) of botanical families, estimated from the Diet Questionnaire used in the Prostate, Lung, Colorectal and Ovarian cancer cohort (*n* = 354).

| Botanical Family | Example Foods | Mean ± SD Servings */day |
|---|---|---|
| Poaceae (Gramineae) | Cereals/grains, corn, rice | 4.29 ± 2.26 |
| Rubiaceae | Coffee | 3.15 ± 4.13 |
| Theaceae | Tea | 1.29 ± 2.79 |
| Solanaceae | Potatoes, tomatoes, peppers | 2.32 ± 3.5 |
| Rosaceae | Other fruits (apples, pears, apricots, strawberries) | 1.74 ± 1.56 |
| Fabaceae (Leguminosae) | Dried beans and peas, peanuts | 1.52 ± 2.00 |
| Rutaceae | Citrus fruits | 1.36 ± 1.46 |
| Vitaceae | Grapes, raisins | 0.78 ± 1.56 |
| Cucurbitaceae | Cantaloupe, cucumber, squash, watermelon | 0.76 ± 0.60 |
| Musaceae | Banana | 0.58 ± 0.48 |
| Brassicaceae (Cruciferae) | Broccoli, Brussels sprouts, cabbage, kale | 0.56 ± 0.44 |
| Asteraceae (Compositae) | Lettuce | 0.56 ± 0.42 |
| Apiaceae (Umbelliferae) | Celery, carrots, cauliflower | 0.32 ± 0.26 |
| Amaranthaceae (Chenopodiaceae) | Spinach, Swiss chard, beet greens | 0.20 ± 0.30 |
| Amaryllidaceae (Alliaceae, Liliaceae) | Garlic, onion | 0.14 ± 0.12 |
| Convolvulaceae | Sweet potato | 0.06 ± 0.12 |
| Bromeliaceae | Pineapple | 0.04 ± 0.08 |

* 1 serving = 1 oz equivalent of grains, 1 cup of coffee or tea, or $\frac{1}{2}$ cup equivalent of fruit or vegetable.

Although the study population was relatively homogenous (i.e., predominantly post-menopausal white women), these results demonstrate the broad range of dietary botanical diversity consumed. We stratified BDI score in the PLCO study by demographic and lifestyle characteristics, finding no differences in the distribution of scores across strata for body mass index, energy intake, or age group; but differences were observed by the number of hours spent per day in vigorous physical activity (Table 3).

**Table 3.** Botanical Diversity Index (BDI) stratified by demographic and lifestyle factors in the Prostate, Lung, Colorectal and Ovarian cancer cohort (*n* = 354).

| | *N* | Mean ± SD | ANOVA *p*-Value |
|---|---|---|---|
| Daily energy intake (kcal) | | | |
| <1500 | 119 | 0.76 ± 0.10 | 0.80 |
| 1500–<2000 | 119 | 0.75 ± 0.08 | |
| 2000–<2500 | 66 | 0.76 ± 0.09 | |
| ≥2500 | 50 | 0.75 ± 0.09 | |
| Hours spent in vigorous physical activity per week | | | |
| None | 60 | 0.72 ± 0.09 | 0.002 |
| <1 | 64 | 0.75 ± 0.08 | |
| 1 | 45 | 0.76 ± 0.09 | |
| 2 | 55 | 0.76 ± 0.09 | |
| 3 | 52 | 0.78 ± 0.06 | |
| 4+ | 75 | 0.76 ± 0.09 | |
| Body mass index (kg/m$^2$) | | | |
| <25 | 88 | 0.76 ± 0.09 | 0.44 |
| 25–<30 | 121 | 0.76 ± 0.09 | |
| 30+ | 145 | 0.75 ± 0.08 | |
| Age (years) | | | |
| <55 | 34 | 0.77 ± 0.09 | 0.90 |
| 55–<60 | 83 | 0.76 ± 0.09 | |
| 60–<65 | 114 | 0.75 ± 0.09 | |
| 65–<70 | 92 | 0.76 ± 0.08 | |
| 70+ | 31 | 0.75 ± 0.09 | |

### 4. Food Intake Pattern, the Gut Microbiome, and Human Health and Disease

There has been an explosive expansion of the literature on food, the gut microbiome, and human health and disease, with major reviews being published [13,40,46]. It is apparent that increased granularity in the assessment of foods to which the gut is exposed is required to understand microbial ecology and function in relation to human health and disease. The human gut microbiota consists of the 10–100 trillion symbiotic microbial cells harbored by each person, primarily bacteria [47]. These microbiota are phylogenetically diverse, and this gives rise to metabolic heterogeneity. A human microbiome constitutes 3 million non-redundant genes; whereas, the human genome is comprised of approximately 20,000 genes of metabolism [48]. The gut microbiota impact essential functions of the host including gut barrier function, immune function, satiety, and taste regulation and the activity of biological signaling pathways that influence health and disease [46,49,50]. The location of microbiota throughout the intestinal tract is determined by exposure to substrates, including those derived from the diet, and host interactions that promote microbial transcriptional activity (i.e., the meta-transcriptome) with disease-relevant targets [51]. An example is the gut bacterial fermentation of fiber to butyrate, which can lead to direct oncogene suppression in colonocytes and other cancer-preventive effects on inflammation and immune modulation [52–54].

The interface of diet with microbial activity is complex. In addition to gut microbial diversity, there is considerable inter-individual variation in nutrient requirements and utilization. Nutritional adequacy and diet-related disease risk are determined by diet exposure, genetic variation in nutrient metabolism, their interaction with the gut microbiome, and the effects on the metabolome and proteome. However, little is known about how dietary botanical diversity influences the interplay between human gene expression, microbial activity, and human metabolism. Diet quality (e.g., as measured by the Healthy Eating Index and Mediterranean Diet Score), on the other hand, has been associated with gut microbial diversity [55–57] and hundreds of both endogenous metabolites and products of exogenous food metabolism [58]. The interaction of the gut microbiome with host metabolism via microbial metabolites [59,60] can lead to disease-relevant metabolic alterations such as changes in circulating glucose [61] and cell signaling that can be either beneficial or harmful [62]. Added to this complexity, culinary techniques that modify the chemical composition of food (e.g., preserving (salting, additives), processing, preparing (removing vegetable/fruit skin), and cooking) may alter microbial-food interaction and subsequent phytochemical exposure. To disentangle this complexity with a view to identifying patterns of eating that optimize health, methods to better evaluate phytochemical exposures in the intestinal tract are needed. To this end, the BDI was developed as a tool to measure dietary botanical diversity as a proxy for phytochemical exposure to the human gut microbiome. Superimposing this botanical scoring system on an individual's omics and meta-omics profiles using deep learning algorithms is a promising approach to support an omics-driven era of precision culinary medicine for health promotion and disease prevention. Once these interactions are mapped, clinical value may be obtained by measuring alpha and beta diversity of gut microbial species or stool metabolites and recommending combinations and diversity of plant foods for re-shaping the gut microbial landscape.

### 5. Final Comments

The BDI is a novel metric for examining the interplay among plant foods, the thousands of dietary phytochemicals to which an individual is exposed, and the human gut microbiome. Considering the suggestive associations between the gut microbiome and human health, this approach has exciting potential to improve understanding of the molecular underpinnings with which plant foods exert their health effects and provides a robust chemical framework for developing personalized dietary guidance.

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## References

1. Hajat, C.; Stein, E. The global burden of multiple chronic conditions: A narrative review. *Prev. Med. Rep.* **2018**, *12*, 284–293. [CrossRef] [PubMed]
2. Swinburn, B.A.; Kraak, V.I.; Allender, S.; Atkins, V.J.; Baker, P.I.; Bogard, J.R.; Brinsden, H.; Calvillo, A.; De Schutter, O.; Devarajan, R.; et al. The global syndemic of obesity, undernutrition, and climate change: The lancet commission report. *Lancet* **2019**, *393*, 791–846. [CrossRef]
3. Hirsch, H.A.; Iliopoulos, D.; Joshi, A.; Zhang, Y.; Jaeger, S.A.; Bulyk, M.; Tsichlis, P.N.; Shirley Liu, X.; Struhl, K. A transcriptional signature and common gene networks link cancer with lipid metabolism and diverse human diseases. *Cancer Cell* **2010**, *17*, 348–361. [CrossRef] [PubMed]
4. Cena, H.; Calder, P.C. Defining a healthy diet: Evidence for the role of contemporary dietary patterns in health and disease. *Nutrients* **2020**, *12*, 334. [CrossRef] [PubMed]
5. Herforth, A.; Arimond, M.; Alvarez-Sanchez, C.; Coates, J.; Christianson, K.; Muehlhoff, E. A global review of food-based dietary guidelines. *Adv. Nutr.* **2019**, *10*, 590–605. [CrossRef] [PubMed]
6. Department of Health and Human Services National Institutes of Health. 2020–2030 Strategic Plan for NIH Nutrition Research. 2020. Available online: https://www.niddk.nih.gov/about-niddk/strategic-plans-reports/strategic-plan-nih-nutrition-research (accessed on 1 March 2021).
7. U.S. Department of Health and Human Services; U.S. Department of Agriculture. *2020–2025 Dietary Guidelines for Americans*, 9th ed.; US Department of Agriculture: Washington, DC, USA, 2020.
8. Frame, L.A.; Costa, E.; Jackson, S.A. Current explorations of nutrition and the gut microbiome: A comprehensive evaluation of the review literature. *Nutr. Rev.* **2020**. [CrossRef] [PubMed]
9. McBurney, M.I.; Davis, C.; Fraser, C.M.; Schneeman, B.O.; Huttenhower, C.; Verbeke, K.; Walter, J.; Latulippe, M.E. Establishing what constitutes a healthy human gut microbiome: State of the science, regulatory considerations, and future directions. *J. Nutr.* **2019**, *149*, 1882–1895. [CrossRef]
10. Bilotta, A.J.; Cong, Y. Gut microbiota metabolite regulation of host defenses at mucosal surfaces: Implication in precision medicine. *Precis. Clin. Med.* **2019**, *2*, 110–119. [CrossRef]
11. Rodgers, G.P.; Collins, F.S. Precision nutrition–the answer to "What to eat to stay healthy". *JAMA* **2020**. [CrossRef]
12. McDonald, D.; Hyde, E.; Debelius, J.W.; Morton, J.T.; Gonzalez, A.; Ackermann, G.; Aksenov, A.A.; Behsaz, B.; Brennan, C.; Chen, Y.; et al. American gut: An open platform for citizen science microbiome research. *Msystems* **2018**, *3*. [CrossRef]
13. Mills, S.; Lane, J.A.; Smith, G.J.; Grimaldi, K.A.; Ross, R.P.; Stanton, C. Precision nutrition and the microbiome part II: Potential opportunities and pathways to commercialisation. *Nutrients* **2019**, *11*, 1468. [CrossRef]
14. Ruel, M.T. Operationalizing dietary diversity: A review of measurement issues and research priorities. *J. Nutr.* **2003**, *133*, 3911S–3926S. [CrossRef]
15. Cano-Ibanez, N.; Gea, A.; Martinez-Gonzalez, M.A.; Salas-Salvado, J.; Corella, D.; Zomeno, M.D.; Romaguera, D.; Vioque, J.; Aros, F.; Warnberg, J.; et al. Dietary diversity and nutritional adequacy among an older spanish population with metabolic syndrome in the PREDIMED-plus study: A cross-sectional analysis. *Nutrients* **2019**, *11*, 958. [CrossRef] [PubMed]
16. Farhangi, M.A.; Jahangiry, L. Dietary diversity score is associated with cardiovascular risk factors and serum adiponectin concentrations in patients with metabolic syndrome. *BMC Cardiovasc. Disord.* **2018**, *18*, 68. [CrossRef] [PubMed]
17. Kant, A.K.; Schatzkin, A.; Harris, T.B.; Ziegler, R.G.; Block, G. Dietary diversity and subsequent mortality in the first national health and nutrition examination survey epidemiologic follow-up study. *Am. J. Clin. Nutr.* **1993**, *57*, 434–440. [CrossRef] [PubMed]

18. Isa, F.; Xie, L.P.; Hu, Z.; Zhong, Z.; Hemelt, M.; Reulen, R.C.; Wong, Y.C.; Tam, P.C.; Yang, K.; Chai, C.; et al. Dietary consumption and diet diversity and risk of developing bladder cancer: Results from the South and East China case-control study. *Cancer Causes Control* **2013**, *24*, 885–895. [CrossRef] [PubMed]

19. Conrad, Z.; Raatz, S.; Jahns, L. Greater vegetable variety and amount are associated with lower prevalence of coronary heart disease: National health and nutrition examination survey, 1999–2014. *Nutr. J.* **2018**, *17*, 67. [CrossRef]

20. Drescher, L.S.; Thiele, S.; Mensink, G.B. A new index to measure healthy food diversity better reflects a healthy diet than traditional measures. *J. Nutr.* **2007**, *137*, 647–651. [CrossRef]

21. Jayawardena, R.; Byrne, N.M.; Soares, M.J.; Katulanda, P.; Yadav, B.; Hills, A.P. High dietary diversity is associated with obesity in Sri Lankan adults: An evaluation of three dietary scores. *BMC Public Health* **2013**, *13*, 314. [CrossRef]

22. Cooper, A.J.; Sharp, S.J.; Lentjes, M.A.; Luben, R.N.; Khaw, K.T.; Wareham, N.J.; Forouhi, N.G. A prospective study of the association between quantity and variety of fruit and vegetable intake and incident type 2 diabetes. *Diabetes Care* **2012**, *35*, 1293–1300. [CrossRef]

23. Jeurnink, S.M.; Buchner, F.L.; Bueno-de-Mesquita, H.B.; Siersema, P.D.; Boshuizen, H.C.; Numans, M.E.; Dahm, C.C.; Overvad, K.; Tjonneland, A.; Roswall, N.; et al. Variety in vegetable and fruit consumption and the risk of gastric and esophageal cancer in the European Prospective Investigation into Cancer and Nutrition. *Int. J. Cancer* **2012**, *131*, E963–E973. [CrossRef] [PubMed]

24. Kapoor, D.; Iqbal, R.; Singh, K.; Jaacks, L.M.; Shivashankar, R.; Sudha, V.; Anjana, R.M.; Kadir, M.; Mohan, V.; Ali, M.K.; et al. Association of dietary patterns and dietary diversity with cardiometabolic disease risk factors among adults in South Asia: The CARRS study. *Asia Pac. J. Clin. Nutr.* **2018**, *27*, 1332–1343. [CrossRef] [PubMed]

25. Truthmann, J.; Richter, A.; Thiele, S.; Drescher, L.; Roosen, J.; Mensink, G.B. Associations of dietary indices with biomarkers of dietary exposure and cardiovascular status among adolescents in Germany. *Nutr. Metab.* **2012**, *9*, 92. [CrossRef] [PubMed]

26. Otto, M.C.; Padhye, N.S.; Bertoni, A.G.; Jacobs, D.R., Jr.; Mozaffarian, D. Everything in moderation–dietary diversity and quality, central obesity and risk of diabetes. *PLoS ONE* **2015**, *10*, e0141341. [CrossRef]

27. Katanoda, K.; Kim, H.S.; Matsumura, Y. New quantitative index for dietary diversity (QUANTIDD) and its annual changes in the Japanese. *Nutrition* **2006**, *22*, 283–287. [CrossRef] [PubMed]

28. Salome, M.; de Gavelle, E.; Dufour, A.; Dubuisson, C.; Volatier, J.L.; Fouillet, H.; Huneau, J.F.; Mariotti, F. Plant-protein diversity is critical to ensuring the nutritional adequacy of diets when replacing animal with plant protein: Observed and modeled diets of french adults (INCA3). *J. Nutr.* **2019**. [CrossRef] [PubMed]

29. Lachat, C.; Raneri, J.E.; Smith, K.W.; Kolsteren, P.; Van Damme, P.; Verzelen, K.; Penafiel, D.; Vanhove, W.; Kennedy, G.; Hunter, D.; et al. Dietary species richness as a measure of food biodiversity and nutritional quality of diets. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, 127–132. [CrossRef] [PubMed]

30. de Oliveira Otto, M.C.; Anderson, C.A.M.; Dearborn, J.L.; Ferranti, E.P.; Mozaffarian, D.; Rao, G.; Wylie-Rosett, J.; Lichtenstein, A.H. Dietary diversity: Implications for obesity prevention in adult populations: A science advisory from the american heart association. *Circulation* **2018**, *138*, e160–e168. [CrossRef] [PubMed]

31. United States Department of Agriculture. Fruits and Vegetables Messages, Tips, Advice and Tools. Available online: https://www.fns.usda.gov/core-nutrition/fruits-and-vegetables (accessed on 16 February 2021).

32. Minich, D.M. A review of the science of colorful, plant-based food and practical strategies for "eating the rainbow". *J. Nutr. Metab.* **2019**, *2019*, 2125070. [CrossRef]

33. Marcoe, K.; Juan, W.; Yamini, S.; Carlson, A.; Britten, P. Development of food group composites and nutrient profiles for the mypyramid food guidance system. *J. Nutr. Educ. Behav.* **2006**, *38*, S93–S107. [CrossRef]

34. Thompson, H.J. Chapter 2-Vegetable and fruit intake and the development of cancer: A brief review and analysis. In *Bioactive Foods in Promoting Health*; Watson, R.R., Preedy, V.R., Eds.; Academic Press: San Diego, CA, USA, 2010; pp. 19–36. [CrossRef]

35. Wink, M. Plant secondary metabolism: Diversity, function and its evolution. *Nat. Prod. Commun.* **2008**, *3*, 1205–1216. [CrossRef]

36. Wink, M. Evolution of secondary metabolites from an ecological and molecular phylogenetic perspective. *Phytochemistry* **2003**, *64*, 3–19. [CrossRef]

37. Aune, D.; Giovannucci, E.; Boffetta, P.; Fadnes, L.T.; Keum, N.; Norat, T.; Greenwood, D.C.; Riboli, E.; Vatten, L.J.; Tonstad, S. Fruit and vegetable intake and the risk of cardiovascular disease, total cancer and all-cause mortality-a systematic review and dose-response meta-analysis of prospective studies. *Int. J. Epidemiol.* **2017**, *46*, 1029–1056. [CrossRef] [PubMed]

38. The Metabolomics Innovation Centre. HMDB: Showing Metabocard for Glucoraphanin (HMDB0038404). Available online: https://hmdb.ca/metabolites/HMDB0038404 (accessed on 4 January 2021).

39. Klurfeld, D.M.; Davis, C.D.; Karp, R.W.; Allen-Vercoe, E.; Chang, E.B.; Chassaing, B.; Fahey, G.C., Jr.; Hamaker, B.R.; Holscher, H.D.; Lampe, J.W.; et al. Considerations for best practices in studies of fiber or other dietary components and the intestinal microbiome. *Am. J. Physiol. Endocrinol. Metab.* **2018**, *315*, E1087–E1097. [CrossRef]

40. Mills, S.; Stanton, C.; Lane, J.A.; Smith, G.J.; Ross, R.P. Precision nutrition and the microbiome, Part I: Current state of the science. *Nutrients* **2019**, *11*, 923. [CrossRef] [PubMed]

41. Berry, C.H. Corporate growth and diversification. *J. Law Econ.* **1971**, *14*. [CrossRef]

42. Bowman, S.A.; Clemens, J.C.; Friday, J.E.; Moshfegh, A.J.; Food Surveys Research Group; Beltsville Human Nutrition Research Center; Agricultural Research Service; U.S. Department of Agriculture. Food Patterns Equivalents Database 2017–2018: Methodology and User Guide. 2020. Available online: http://www.ars.usda.gov/nea/bhnrc/fsrg (accessed on 30 March 2021).

43. Thompson, F.E.; Kirkpatrick, S.I.; Subar, A.F.; Reedy, J.; Schap, T.E.; Wilson, M.M.; Krebs-Smith, S.M. The national cancer institute's dietary assessment primer: A resource for diet research. *J. Acad. Nutr. Diet* **2015**, *115*, 1986–1995. [CrossRef]

44. Thompson, H.J.; Heimendinger, J.; Diker, A.; O'Neill, C.; Haegele, A.; Meinecke, B.; Wolfe, P.; Sedlacek, S.; Zhu, Z.; Jiang, W. Dietary botanical diversity affects the reduction of oxidative biomarkers in women due to high vegetable and fruit intake. *J. Nutr.* **2006**, *136*, 2207–2212. [CrossRef]

45. National Cancer Institute. Dietary Questionnaire (DQX) Datasets. National Cancer Institute Cancer Data Access System Website. Available online: https://cdas.cancer.gov/datasets/plco/97/ (accessed on 29 March 2021).

46. Zinocker, M.K.; Lindseth, I.A. The western diet-microbiome-host interaction and its role in metabolic disease. *Nutrients* **2018**, *10*, 365. [CrossRef]

47. Sender, R.; Fuchs, S.; Milo, R. Are we really vastly outnumbered? Revisiting the ratio of bacterial to host cells in humans. *Cell* **2016**, *164*, 337–340. [CrossRef]

48. Bäckhed, F.; Ley, R.E.; Sonnenburg, J.L.; Peterson, D.A.; Gordon, J.I. Host-bacterial mutualism in the human intestine. *Science* **2005**, *307*, 1915–1920. [CrossRef] [PubMed]

49. De Angelis, M.; Ferrocino, I.; Calabrese, F.M.; De Filippis, F.; Cavallo, N.; Siragusa, S.; Rampelli, S.; Di Cagno, R.; Rantsiou, K.; Vannini, L.; et al. Diet influences the functions of the human intestinal microbiome. *Sci. Rep.* **2020**, *10*, 4247. [CrossRef] [PubMed]

50. Riaz Rajoka, M.S.; Shi, J.; Mehwish, H.M.; Zhu, J.; Li, Q.; Shao, D.; Huang, Q.; Yang, H. Interaction between diet composition and gut microbiota and its impact on gastrointestinal tract health. *Food Sci. Human Wellness* **2017**, *6*, 121–130. [CrossRef]

51. Leeming, E.R.; Louca, P.; Gibson, R.; Menni, C.; Spector, T.D.; Le Roy, C.I. The complexities of the diet-microbiome relationship: Advances and perspectives. *Genome Med.* **2021**, *13*, 10. [CrossRef] [PubMed]

52. Wilson, A.S.; Koller, K.R.; Ramaboli, M.C.; Nesengani, L.T.; Ocvirk, S.; Chen, C.; Flanagan, C.A.; Sapp, F.R.; Merritt, Z.T.; Bhatti, F.; et al. Diet and the human gut microbiome: An international review. *Dig. Dis. Sci.* **2020**, *65*, 723–740. [CrossRef]

53. Vipperla, K.; O'Keefe, S.J. Diet, microbiota, and dysbiosis: A 'recipe' for colorectal cancer. *Food Funct.* **2016**, *7*, 1731–1740. [CrossRef]

54. O'Keefe, S.J.; Li, J.V.; Lahti, L.; Ou, J.; Carbonero, F.; Mohammed, K.; Posma, J.M.; Kinross, J.; Wahl, E.; Ruder, E.; et al. Fat, fibre and cancer risk in African Americans and rural Africans. *Nat. Commun.* **2015**, *6*, 6342. [CrossRef]

55. Maskarinec, G.; Hullar, M.A.J.; Monroe, K.R.; Shepherd, J.A.; Hunt, J.; Randolph, T.W.; Wilkens, L.R.; Boushey, C.J.; Le Marchand, L.; Lim, U.; et al. Fecal microbial diversity and structure are associated with diet quality in the multiethnic cohort adiposity phenotype study. *J. Nutr.* **2019**, *149*, 1575–1584. [CrossRef]

56. Johnson, A.J.; Vangay, P.; Al-Ghalith, G.A.; Hillmann, B.M.; Ward, T.L.; Shields-Cutler, R.R.; Kim, A.D.; Shmagel, A.K.; Syed, A.N.; Personalized Microbiome Class Students; et al. Daily sampling reveals personalized diet-microbiome associations in humans. *Cell Host Microbe* **2019**, *25*, 789–802.e785. [CrossRef]

57. Laitinen, K.; Mokkala, K. Overall dietary quality relates to gut microbiota diversity and abundance. *Int. J. Mol. Sci.* **2019**, *20*, 1835. [CrossRef]

58. Maruvada, P.; Lampe, J.W.; Wishart, D.S.; Barupal, D.; Chester, D.N.; Dodd, D.; Djoumbou-Feunang, Y.; Dorrestein, P.C.; Dragsted, L.O.; Draper, J.; et al. Perspective: Dietary biomarkers of intake and exposure-exploration with omics approaches. *Adv. Nutr.* **2020**, *11*, 200–215. [CrossRef] [PubMed]

59. Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. *Nature* **2012**, *486*, 207–214. [CrossRef] [PubMed]

60. Blacher, E.; Levy, M.; Tatirovsky, E.; Elinav, E. Microbiome-modulated metabolites at the interface of host immunity. *J. Immunol.* **2017**, *198*, 572–580. [CrossRef] [PubMed]

61. Houghton, D.; Hardy, T.; Stewart, C.; Errington, L.; Day, C.P.; Trenell, M.I.; Avery, L. Systematic review assessing the effectiveness of dietary intervention on gut microbiota in adults with type 2 diabetes. *Diabetologia* **2018**, *61*, 1700–1711. [CrossRef]

62. Cresci, G.A.M.; Lampe, J.W.; Gibson, G. Targeted approaches for in situ gut microbiome manipulation. *J. Parenter. Enteral Nutr.* **2020**. [CrossRef]