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# Food as Medicine: Enhancing Crop Breeding and Food Processing to Shift the Gut Microbiome for Prevention and Treatment of Chronic Diseases

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A B S T R A C T

Prebiotics are useful tools for shifting the gut microbiome and metabolome to confer immune, metabolic, and preventive benefits for human disease. However, there are emerging concerns about methods for discovering optimal candidate compounds and their sustainable production for long-term success in targeting mechanisms of disease. In this perspective, we review the current state of prebiotics moving from nutrition to function in health, highlighting the opportunities for using food as medicine in treating a model disease, inflammatory bowel disease, discussing the ways crop breeding can be used to identify and improve the functional (beyond nutritional) value of a prebiotic and the critical role that food processing plays in sustaining the integrity and scalability of the prebiotic compound while influencing consumer adoption of these agents. This information supports a trajectory for the future of food as medicine to be moving from population-scale dietary guidelines to personalized or precision nutrition guidelines, from "eat more fiber" to "eat this specific type of fiber that has been enhanced in and processed from this specific genotype of food crop". This could include developing designer fibers by crop breeding to develop panels of genotypes with different fiber structures that deliver reliable shifts in the microbiome and metabolome for most patients with the targeted disease. Finally, there needs to be a commitment to sustainability of the plant-derived product so that future generations will have access to the same benefits of the food as medicine initially developed for disease prevention and treatment.

*Keywords*: prebiotics, microbiome, plant genetics, plant breeding, food processing, inflammatory bowel disease

## Introduction

Food as medicine as a concept can be difficult to envision and implement given the essential roles food plays in as basic a function as staving off starvation to preventing diseases of nutritional deficiencies. Food per se has not yet been specially compounded or prepared for the treatment or cure of a specific illness like a medicine would be. In fact, the modern food supply and the so-called Western diet and highly processed foods are being cast as the opposite of a medicine and being seen as a root cause or enhancer of risk of cancer, obesity, and metabolic-associated diseases. Because of the reassessment of food and its relationship to health, there are opportunities to look beyond meeting basic nutritional needs and enhancing the benefits that food can provide to sustain health and prevent or mitigate disease. A key component of this idea is the way the gut microbiome metabolizes otherwise indigestible plant-based compounds into usable molecules that have far-reaching healthful effects on human physiology. This perspective, although focusing on the potential for prebiotics to work

*Abbreviations:* AX, arabinoxylan; NCD, noncommunicable disease; IBD, inflammatory bowel disease; SCFA, short-chain fatty acid.

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through the gut microbiome to influence our health and modify our approach to disease treatment, also considers critical elements of research and development that specifically highlight the complexity of this unique bench-to-bedside or farm-to-medicine system. The use of plant genetics and breeding, the effects of food processing, the variety of targetable mechanisms of disease and the challenges of implementation of treatments all will need to be incorporated into this research so that like the steps for new pharmaceuticals that come to market, if rigorously followed, should lead to successful development of food as medicine.

## Food Moving Beyond Nutrition: The Gut Microbiome

In recent decades, the gut microbiota has been increasingly recognized as a fundamental component of human immunity and metabolism [1]. Its influence extends beyond the gastrointestinal tract, and abnormal patterns of microbial community structure or function—commonly referred to as dysbiosis—have been implicated in a wide range of noncommunicable diseases (NCDs), including inflammatory bowel disease (IBD) [2], obesity [3], and cardiovascular disease [4]. As the symbiotic relationship between gut microbes and their human host is evolutionary [5], industrialization and urbanization have produced dramatic changes that are associated with reduced diversity of the gut microbiota [6] and increased risk of developing NCDs [7–10]. Accordingly, there is a critical need to understand the relationship among environmental factors, the gut microbiome, and human health to develop safe, accessible, and sustainable strategies to prevent and treat disease.

Diet is the key environmental factor linking the gut microbiota and industrialization. A major function of the gut microbiome is the degradation and biotransformation of macromolecules in the large intestine—particularly indigestible, food-derived compounds—to support microbial metabolism. Through this process, many bioactive metabolites that influence host physiology are produced. Although the gut microbiota of humans has adapted to our diet on evolutionary timescales [5], it can be meaningfully modified through long- and short-term dietary shifts that alter the availability of fermentation substrates in the large intestine [11,12]. Although diet-induced changes in the gut microbiota have been implicated in the pathogenesis of NCDs, evidence from recent randomized clinical trials support that even relatively short-term changes in diet can modify the human gut microbiota in ways that meaningfully affect host immunity [13] and metabolism [14,15].

The consequences of dietary changes for microbial metabolism can range from detrimental (e.g., production of trimethylamine N-oxide from carnitine) [16] to beneficial. Plant-derived dietary substrates with recognized or proposed beneficial effects (prebiotics) [17] include fiber (nondigestible carbohydrates), polyphenols, and unsaturated fatty acids. Broadly, fermentation of prebiotics such as fibers, resistant starches, fructans, and polyphenols [18] in the large intestine promotes the growth and metabolic activity of putative beneficial microbes [19]; suppresses the expansion of opportunistic or pathogenic taxa; and reduces the biotransformation of substrates associated with deleterious effects for the host, such as mucin loss [20] and production of certain proteins [21].

Among prebiotic substrates, dietary fiber as a primary and most abundant substrate for microbial energy metabolism is an important dietary component for shaping both gut microbial ecology and human health. Indeed, recognition of the critical the role of fiber in normal gastrointestinal function predates the advent of microbiome science [22]. Decreased fiber consumption is a hallmark of the diet of industrialized regions—paired with increased intake of highly processed foods, red meat, and saturated fats [23]. Furthermore, metagenomic studies comparing the microbiomes of nonindustrialized or rural populations to those of industrialized nations have further highlighted a higher microbial fiber-fermentative capacity in nonindustrialized groups [24–26], which decreases after immigration to industrialized regions or the onset of local urbanization reflecting changes in dietary patterns [6]. Fiber consumption remains low in industrialized nations experiencing the highest rates of NCDs, despite longstanding expert recommendations to increase fiber intake [27].

Increased total dietary fiber consumption for disease prevention remains a public health priority but the efficacy of fiber for disease treatment or management is less understood. For example, data from RCTs in patients with IBD show beneficial effects of both very high-fiber [28] and low-fiber diets [29,30] for reducing inflammation. As fiber is a structurally diverse class of polymers and only a narrow consortium of bacteria are capable of initiating fermentation of each distinct structure, responses to a given fiber are highly individualized [31]. Although some recent studies have demonstrated predictable effects of specific fiber structures [19], mixtures of fibers [32], and high-fiber diets [15], disease-associated dysbiosis represents an altered context for fermentation and negative consequences of fiber supplementation have been reported in experimental models of disease [33–37]. Consequently, more research is needed to delineate specific fiber structure–function relationships in disease contexts.

Although whole food approaches remain the current preferred means of increasing fiber intake for disease prevention and management, current efforts to increase fruit, vegetable, and whole grain consumption in industrialized populations continues to fall short [38,39]. In the United States, dietary fiber intake averages only 8.1 g per 1000 kcal—roughly half of the recommended 14 g per 1000 kcal—and has increased by just about 1 g per 1000 kcal since 1977 [40]. Although fiber intake in high-income, European nations is generally higher, fiber consumption trends have been similarly stagnant [41]. This is despite several public health efforts during this period aimed at increasing high-fiber food consumption to improve population-level adherence to national dietary guidelines.

Current guidelines for fiber intake also fail to account for the functional properties of the diverse complex carbohydrate structures present in food that influence physiological responses in humans and gut-microbiome-targeted effects [31]. Although promoting a diverse intake of dietary fiber structures could, in principle, benefit the greatest number of individuals [42], achieving this remains difficult in practice. Simply meeting quantitative fiber intake recommendations may not confer equivalent benefits in the absence of structural fiber diversity. Further, the gut microbiome is highly individualized (mostly by

microbial composition though less so by the microbial metagenome) and efforts to predict the effects of whole foods on the microbiome or biomarkers are only just emerging [13,27,43,44]. Alternatively, there is increasing evidence that defined fiber structures, provided individually, can produce predictable microbiome-targeted effects in humans, although the specific effects and associated contexts remain to be defined [19,45–47]. Consequently, as efforts to increase dietary diversity—and thus exposure to diverse fiber structures—remain limited, the ability to deliver personalized dietary fiber interventions represents a promising goal in precision nutrition.

In this perspective, and in line with other researchers [47,48], we propose that applying food science to produce functional fiber ingredients and fortified foods that support the microbiome represents a viable avenue for promoting consumer adoption [49], improving health and treating disease [50]. Furthermore, we suggest that fibers with the capacity to promote health already exist within the genetic diversity of common food crops [51–53], presenting an opportunity to leverage the existing food system to drive discovery and deliver these foods to populations affordably and at scale. In this study, we highlight IBD as a use case to illustrate how advances in microbiome science, nutrition, and plant genetics can converge on dietary fiber to inform food-as-medicine approaches for both disease treatment and prevention.

## IBD: A Model Disease for Food as Medicine

IBDs, including Crohn disease and ulcerative colitis (UC), are model conditions for considering food as medicine because of the centrality of the gut microbiome to the gut the inflammatory response. The current understanding of IBD pathoetiology involves the nexus of multiple factors: *1*) a person with a genetic IBD susceptibility risk background; *2*) a likely triggering event (such as an environmental exposure or an infection) that overwhelms gut epithelial barrier integrity and restitution processes, thereby allowing excessive exposure to a dysbiotic gut microbiome; and *3*) initiation of a dysregulated immune response and establishment of aberrant immune memory. Repeated and prolonged inflammatory mucosal immune response leads to gut organ damage, sustains gut dysbiosis, and confers chronic disease. Current conventional IBD treatments (mesalamine, corticosteroids, anticytokine antibodies and Janus kinase inhibitors, and anti-integrin antibodies and trafficking receptor regulators) target the immune response component of this inflammatory disease paradigm. Conventional drugs that primarily enhance epithelial barrier function are lacking. As none of these drugs (except for vedolizumab) had been developed specifically to treat IBD, the large gap in treatment response, only 1 in 5 patients having long-term remission to one of these agents, should come as no surprise [54]. However, there is a growing appreciation that manipulating the gut microbiome to sustain epithelial barrier function and regulate the mucosal immune response offers novel treatment approaches in IBD [55–57].

Gut microbes are critical to IBD development. Many experimental murine models of colitis [adoptive transfer, interleukin (IL)-10$^{-/-}$, IL-2$^{-/-}$, and TCRαβ$^{-/-}$] cannot be fully expressed in germ-free animals. Moreover, dysbiosis of the gut microbiome in patients with IBD is widely recognized and recent data show that gut dysbiosis may even precede clinical disease [58]. The IBD-associated dysbiosis is similar across patients, generally including an enrichment of proinflammatory organisms belonging to Proteobacteria phylum and a depletion of organisms such as *Faecealibacterium, Roseburia,* and *Coprococcus* (*Clostridium* cluster of the phylum Firmicutes) and *Bifidobacterium* (phylum Actinobacteria) species. Loss of these microbes reduces beneficial short-chain fatty acid (SCFA) production capacity and the well-known SCFA anti-inflammatory characteristics [55,59,60].

Whether the dysbiosis is an actual cause or effect of IBD is unknown. Certain colitogenic gut microbial communities develop during experimental colitis in specific mutant mice and can transfer the colitis [61,62], supporting the concept of inherently proinflammatory gut microbiomes. Specific microbes have been shown to induce either regulatory or inflammatory T cells in murine models of colitis, but such linking of specific microbes to specific immune effects has not translated to human disease [63,64]. Importantly, the gut dysbiosis in IBD persists during periods of clinical remission, providing a potential trigger for recurrent disease and continued loss of beneficial microbe-derived metabolites [65–69]. Fecal microbial transplant in patients with IBD as a stand-alone treatment has not been robustly successful [57,70,71]. It is not yet known if the loss of the presumed-beneficial microbes or the increased abundances of proinflammatory Proteobacteria, or both, contribute more to disease progression. Yet, it is widely accepted in the field that dietary treatment strategies should be investigated to determine if they can prevent the loss of these beneficial microbes and the expansion of disease-associated taxa and induce a gut metabolome that provides a permissive environment for optimal epithelial barrier function and regulates the immune response [72–74].

Gut microbes metabolize unabsorbed dietary carbohydrates and produce beneficial small molecules. In the normal healthy setting (and a balanced diet 60%–70% of total calories from carbohydrates, 10%–12% from proteins, and 20%–25% of total calories from fat), there is more saccharolytic than proteolytic metabolism in the gut lumen. Dietary components that are indigestible by humans such as fibers, resistant starches, and fructans are the most influential components in modulating gut microbial composition and function and saccharolytic fermentation. Illnesses such as chronic kidney and liver disease or IBD can tip the balance toward proteolytic metabolism [75–77]. Multiple studies in humans have documented the ability of fiber to shift the gut microbiome and metabolome to carbohydrate metabolism [78,79]. Arabinoxylan (AX) is among one of the most studied fibers for its effect on gut microbial growth and metabolism and has been evaluated in multiple human trials establishing its positive effects on *Bifidobacterium* species and butyrogenic bacteria outgrowth and SCFA production in stool [80,81].

Whole food-based dietary interventions in IBD to control active inflammation have not been very successful to date, supporting a search for individual dietary components that confer specific effects [82]. These dietary interventions have typically been tested during active inflammatory disease and relied on measures limited to clinical improvement measured by a symptom score or more objective biologic effects like serum and stool inflammatory markers alone without detailed

microbiomeand metabolome changes and shown modest if any results [83,84]. Use of exclusive enteral nutrition (liquid elementaldiet tube feeding) mostly limited to children with IBD hasbeen adapted for adults with active or nonresponsive Crohn disease, also shows variable results, notwithstanding the cost, discomfort, and impracticality of long-term use [85]. On the contrary,a low-fat, high-fiber whole diet tested in patients with remissionUC reversed some features of dysbiosis and decreased inflammatory marker although with limited but statistically significant effects on SCFA production highlighting a role of dietaryfiber [28].

Unlike other diseases such as diabetes and obesity, food as medicinein IBD may exert benefit via multiple mechanisms of actionsince the intestinal site of inflammation is so exposed to thegut lumen. As IBD develops from a nexus of patient genetic susceptibility, effects of toxic environmental exposures (infections, drugs, smoking, and pollution) and a dysbiotic gut microbiome (that can precede clinical disease [86]) that activatesboth innate and adaptive immune responses to microbes as well as degrades gut epithelial barrier function, these food-as-medicine therapeutic mechanisms could include the following:*1*) reducing specific microbes that evoke a direct inflammatory T-cell response (or modulate dendritic cell effects on T cells) [87]; *2*) enhancing specific microbes that induce a regulatory immune response [88]; *3*) inducing increases in microbe-mediated metabolites (e.g., SCFA), which have anti-inflammatory effects [89]; and *4*) supporting epithelial barrierrestitution, resilience, and integrity [90]. Prebiotics used to shift the gut microbiome and metabolome (via microbial saccharolytic fermentation in the colon) can restore the dysbiosistoward a more normal microbial composition and reduce theabundance of gut microbial pathobionts typically with the proliferation of those bacteria using the prebiotic itself or its metabolitesfor their own outgrowth and nutritional needs. The futureof food as medicine for IBD will require a comprehensive knowledge of which microbes, singly or in a corsortia, along withtheir CAZymes and metagenomes, and together with which prebiotics can exert beneficial effects (e.g., anti-inflammatory and probarrier) and how these actions can be sustained over time. Further, successful development of food as medicine for IBD will need to identify which prebiutics or synbiotics can be universallyapplied to benefit large populations of patients with IBDor, conversely, we will need a way to predict how a patient's gut microbiome and metabolome will respond to specific food-derived constituents so precision nutrition could accomplishmedical outcomes.

## Breeding for Improved Functional Profiles in Our Food Crops

Contemporarycrop breeding programs use powerful combinations of direct phenotypic selection and genome-assisted accelerated breeding strategies to improve productivity and sustainabilityin our primary food crops [91]. Traits targeted for improvementby crop breeders extend beyond pure production goals to include increasing the efficient use of nitrogen and water,enhancing tolerance to abiotic stresses and ever-evolving array of pests and pathogens, and improving traits that affect end-use quality (e.g., baking quality in wheat). Despite this powerful capacity to adapt plant genotypes/phenotypes to environmental and production challenges, improving the functional biologic profile is typically not a direct target for most major breeding programs. A growing body of compelling epidemiologic evidence associating consumption of foods high in certain nutrients, phytochemicals, and bioactives with reduced incidence of chronic diseases highlights the need and opportunity of improving these traits in our food crops [92–96]. Indeed, developing food crops with improved healthful-functional profiles, particularly for nutritional components that are associated with reduced risk of chronic diseases, could have significant impacts on not only the incidence but also the economic burden of chronic diseases [97,98]. Consequently, the recent emphasis of United States DHHS, FDA, and USDA on reducing the incidence of diet-associated chronic diseases should also explicity recognize and prioritize the capacity to breed food crops with traits that can mitigate human diseases along with the current emphasis of understanding the links between ultraprocessed foods, food additives, and the incidence/mechanisms of chronic disease.

One straightforward approach to directly increase the abundance of desirable nutritional and functional properties of a food crop is through genetic engineering to upregulate pathways or critical steps in biosynthesis of bioactive and microbiome-active components. The Norfolk purple tomato is an example of how this can be achieved. In this example, genetic engineering was used to introduce exogenous transcription factors from *Antirrhinum majus* (snapdragon) into tomato, and together, these factors upregulate production of endogenous anthocyanins, producing purple tomatoes [99]. However, the cost of securing regulatory approval for genetically engineered crops remains a substantial economic barrier in the United States [100], and regulatory barriers and social acceptance limit the potential of genetic engineering approaches to improve nutritional profiles in many other parts of the world [101]. Thus, despite the significant potential of genetic engineering and gene editing strategies, the regulatory and social challenges currently limit applications of this approach.

In many cases, it may be possible to achieve large changes in nutritional strategies without genetic engineering by characterizing and exploiting the substantial standing genetic and functional diversity already present within crop species. Much of the genetic diversity of a plant species is typically preserved in heirloom cultivars (including wild ancestors, landraces, and inbreeds from which cultivated hybrids were derived). Breeders identify novel traits of interest in these populations and create new hybrids by crossing these traits through conventional breeding into genetic backgrounds of currently cultivated crops. In the case of nutritional traits, there are many examples where natural variation has been identified. For example, genetic variation in regulatory genes are known to affect levels of polyphenols in tomatoes [102] and condensed tannins in sorghum [103]. Variation affecting seed protein content has been described in wheat [104], and naturally-occurring mutations in maize have been identified that change seed protein composition, improving essential amino acid content [105]. Naturally occurring variation in maize [106] and soybean [107] is also known to control oil content, which could enable development of oils with altered lipid profiles (although the latter has been achieved in several oil seed crops using genetically modified

organism–based approaches). Structural variation in complex fibers [arabinoxylans (AXs)] has also been described in different genotypes of maize [108,109] and variation in amylose and β-glucan content in barley varieties has been shown to influence glycemic control [110–112]. Thus, there is significant evidence to support the idea that standing genetic and phenotypic variation in diverse genotypes of food crops can be used as a source of novel nutritional and functional traits that can be used to create novel, commercially viable hybrids. Indeed, incorporating these traits into commercially viable genetic backgrounds could help ensure that the food-as-medicine approach would become part of major crop improvement programs for the future.

One of the challenges of in breeding for enhanced nutritional and functional traits lies in the goal of identifying plant genotypes with the desirable profiles since high-throughput systems are needed for measuring these characteristics across hundreds to thousands of genotypes of a plant species. Although existing analytical methods for micronutrients and vitamins would be sufficient for these components, the sample preparation and analytical methods for quantifying complex combinations of polyphenols and other categories of bioactive secondary metabolites are much more challenging to implement in a high-throughput manner [113]. Even more challenging are the sample preparation and analytical methods necessary to quantify and analyze structural characteristics of dietary fibers, which have highly complex structures that must be broken down chemically and/or enzymatically into analyzable units and subjected to different types of analytical methods [114]. Thus, alternative strategies are needed to prioritize genotypes with desirable nutritional and functional traits and reduce the applications of complex analytical chemistry to limited sets of high-priority varieties.

Given the growing understanding of the interactions of major plant nutrients (simple carbohydrates, starches, fibers, lipids, and protein) and plant bioactives in our diets with the human gut microbiome and disease susceptibility [27,115–119], there is growing interest in using the gut microbiome itself or individual species from the gut microbiome as high-throughput bioassays to detect variation in the functional components of food crops (e.g., fermentable fiber). Such a strategy can prioritize genotypes and reduce the number of genotypes that must be characterized chemically (Figure 1). Early applications of this strategy focused on structural variation in candidate molecules such as AX, where the effects of structural variation between different species of cereal grains were measured in in vitro microbiome fermentations [114,120]. Growth rates and expression patterns of bacterial genes encoding enzymes for AX degradation have also been used in monocultures of gut species such as *Bifidobacterium* species and *Bacteroides* to examine plant AX phenotypes [159,121]. Recent studies have also used in vitro microbiome fermentations to compare the effects of structural variation in AXs that occur between different genotypes of wheat [122], sorghum [46], and maize [109]. Although

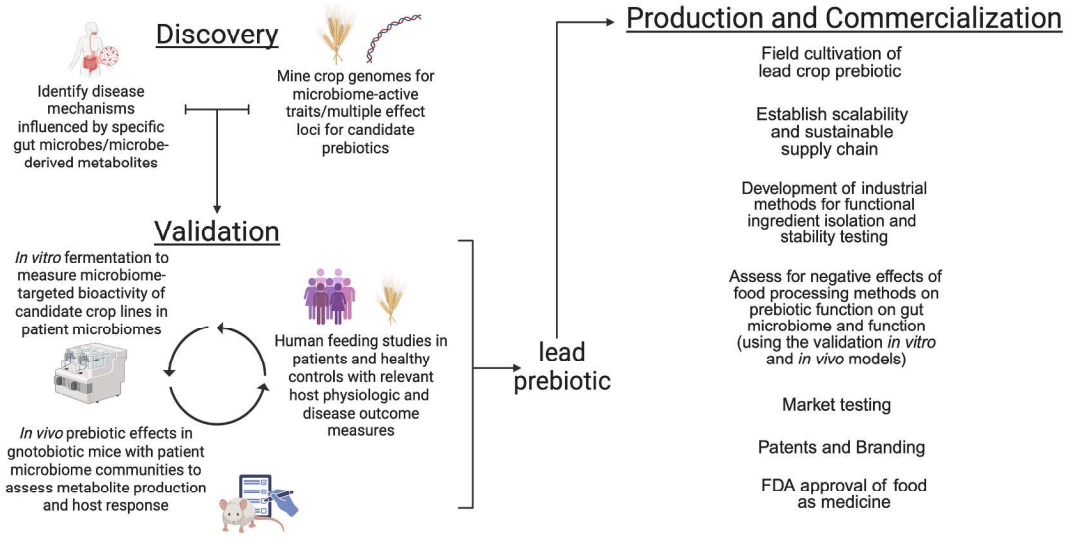


**FIGURE1.** The ladders followed for the identification of prebiotics as possible candidates to develop as food as medicine. Initially, roles for gut microbes and metabolic pathways implicated in a disease process (often a relative absence of species and their beneficial metabolic activity) are identified,and separately crop genomes are examined for traits that predict possible use of the crop prebiotic by specific microbes associated with the disease (discovery). Then, these microbes and compounds are tested together (validation) using *in vitro* fermentation platforms (to show that the microbes do interact with the prebiotic in metabolically beneficial ways, with increased short-chain fatty acid productions), *in vivo* models(e.g., gnotobiotic mice colonized with known communities of human gut microbiota for similar beneficial metabolic activity and even some improvement in certain diseases modeled by mice), and finally in human clinical feeding trials to show that the prebiotic shifts the gut microbiome predictably, induces a beneficial metabolic profile, and, in a pivotal trial, shows that markers of disease are reversed (e.g., lower gut inflammation,lower fasting blood sugar, and lower total cholesterol). Any lead prebiotic with a validated effect on a disease would then undergo multiple steps to increase production so that large numbers of patients could be treated for long periods with typically higher doses than were used in the *in vitro* and *in vivo* validation steps (although effective doses are usually defined by the human trials). As part of this continued food as medicinedevelopment (production and commercialization), increases in crop production, efficiencies in prebiotic isolation and processing into consumer-friendly (but dose-appropriate) supplement formulation and then measures to protect intellectual property to sustain ongoing production are all required to successfully bring to market a new food as medicine.

the underlying genetic causes driving the AX structural variation in these crop species is not known, these studies do illustrate that structural variation in AX, even among different cultivars of a single crop, can be significant and this variation can drive distinct responses in microbiome fermentations.

Functional genetics have also been combined with *in vitro* microbiome fermentations to test the effects of specific mutations in candidate genes that would likely affect the gut microbiome. In this strategy, grains or other food material produced by near-isogenic lines of a single crop that differ only in a naturally-occurring mutation of single genes that alters a candidate nutrient function are compared. Recent work shows how alterations in seed protein composition caused by the maize *opaque-2* mutation affects *in vitro* fermentation patterns by the human gut microbiome [123]. The *opaque-2* mutation reduces nutritionally poor α-zein protein, which typically dominates the seed protein, with proteins that are much higher in the essential amino acids, lysine and tryptophan [105]. Microbiome fermentation of popcorn lines with *opaque-2* mutations showed elevated levels of desirable, lysine-degrading taxa in multiple microbiomes and in half of the microbiomes tested, elevated levels of the beneficial SCFA fermentation product butyrate were also detected [123]. In another study, the effects of the waxy mutation on starch composition was studied in otherwise isogenic lines of sorghum. The waxy mutations are loss-of-function mutations in the granule-bound starch synthase that essentially block synthesis of amylose, making the starch component of the endosperm primarily composed of highly digestible amylopectin. *In vitro* digestion-fermentation reactions with microbiomes from multiple human subjects showed dramatic effects of the waxy mutation, which significantly reduced the abundance of desirable amylolytic bacteria in the fermentations compared with that in wildtype parent [51]. The effects were also significant in a humanized mouse model (germ-free mice conventionalized with the same human microbiomes used in vitro), and in this model, mice fed grain from waxy sorghum not only had distinct microbiome outcomes but also had significantly higher weight gain [51]. Although the use of whole grains from near-isogenic lines is a powerful way to test the effects of variation in individual nutritional components in their natural context, this candidate gene–based functional genomic strategy is rate limited by the set of nutrients already known to impact the human gut microbiome and the set of genes known to play a role in determining the abundance and properties of those nutrients.

An alternative strategy to identify high-functional value varieties of crop foods is to use microbiome bioassays to identify candidate genes and nutrients using mapping or diversity populations of plants in conjunction with *in vitro* microbiome fermentation assays. This strategy requires microbiome fermentation-generated data on many hundreds or thousands of distinct plant genotypes but has the potential to identify both new microbially active nutrients and genes not previously known to play a role in controlling the abundance and properties of those nutrients. Automated *in vitro* microbiome screening (AiMS) was developed for high-throughput in vitro digestion-microbiome fermentation screening of hundreds-thousands of plant genotypes, enabling the use of the gut microbiome as a bioassay across large plant populations [52]. The AiMS technology miniaturizes and automates several steps in the *in vitro* digestion-microbiome fermentation process and uses the fermentation patterns and corresponding changes in microbe abundances and their metabolites as a complex set of phenotypes that can detect variation in a wide variety of plant components. These microbiome fermentation phenotypes (e.g., changes in abundances of individual taxa, groups of taxa, ecological metrics, and metabolite profiles), measured from *in vitro* fermentations across a large number of plant genotypes, are then tested for association with genetic variation in the population of plants being studied. In its first application, AiMS was used to phenotype >300 different recombinant inbred lines from a bi-parental cross in sorghum, and quantitative trait locus mapping identified 6 different regions in the sorghum genome where genetic variation had significant impacts on microbes in the fermentations [52]. The effects of genetic variation at these loci on the microbiome were so significant that the term multiple effect loci (MEL) was coined as a new genetic term to describe regions in a plant genome where variation can affect multiple microbial species in AiMS fermentations. The allelic effects at MEL can be quite strong, and when plants carrying different alleles at the MEL are tested across multiple human microbiomes, allelic effects are often preserved across different individuals, and even some of the same taxa in different microbiomes will show similar responses to the allelic variation. In this same study, candidate genes were identified at 2 of the MEL, both encoding regulatory genes involved in synthesis of condensed tannins. Further experiments using molecular complementation, where purified condensed tannins are introduced into fermentations of tannin-negative seed, resulted in similar microbiome outcomes that were observed in tannin-positive seed. Collectively, the studies by Yang et al. [52] illustrated how research can progress quickly from AiMS microbiome phenotypes to genetic variation in candidate plant genes and pathways and variation in a single nutrient, which will point to new lead prebiotic agents to test as food as medicine.

In a second AiMS study, microbiome fermentations were used to phenotype >300 seed lines from a genetically diverse population of sorghum genotypes (a diversity panel representing total genetic diversity in the *Sorghum bicolor* species) and detected 15 MEL [53]. Although the second study used microbiomes from entirely different human subjects and very different sorghum populations, 4 of the 6 original MEL from the study by Yang et al. [52] were detected in both studies [53], further illustrating the repeatability of the microbiome phenotyping and the strong effects of genetic variation in the plant. Indeed, MEL on chromosomes 2 and 4 affecting tannin synthesis drove similar microbiome phenotypes, affecting *Faecalibacterium* species in nearly all microbiomes that were tested in both studies. Korth et al. [53] also mapped >200 agronomic and biochemical traits that had been quantified in this same sorghum population and found that the 15 MEL affecting the microbiome co-localized with variation affecting agronomic traits. The significance of such co-localization suggests that genetic variation affecting the MEL and agronomic traits can be tightly linked genetically. Consequently, selective breeding for agronomic phenotypes driven by allelic variation localizing near MELs would also have a high probability of selecting for linked alleles at the MEL, further illustrating how improvement of agronomic traits could have trade-off effects on nutritional and functional characteristics that affect the gut microbiome.

Although the tools for developing high-value nutritionally improvedcrops are on the horizon, there are still several challenges with scaling production of such crops for commercialization across our domestic population, let alone a global population(Figure 1). One of the challenges relates to trade-off effects, as selection for improved nutritional traits could also impact important agronomic traits. For example, cell wall componentssuch as hemicellulose and hydroxy-cinnanimates in maize affect resistance to pests such as corn borers and mold such as *Fusarium* species [124]. Consequently, plants bred for structural variation in hemicelluloses such as AX, which have desirableeffects on the microbiome, could also exhibit reduced pestor mold resistance. Cell wall traits also affect lodging and stalk strength, particularly hydroxy-cinnamates and cellulose content[125]. Tannins and other polyphenols are also important in mold resistance and resistance to biotic and abiotic stresses in sorghum [126,127]. Thus, crops with improved functionalprofiles may be more challenging to produce at scale if they are agronomically frailer. Even if the high-functional value crops can be produced at scale, a second challenge lies inthe volatility in commercial supply chains for high-value ingredients,leading to products with inconsistent properties. Such volatility is multifactorial as the economics of processing and productionmethods, consumer demands, and changes in federal regulations can drive adoption of alternative production/manufacturing methods. As an example, recent clinical studies illustrated the desirable effects of a commercial corn bran AX ingredient on the gut microbiota and host metabolic benefits [128,129]. However, the manufacturing process for the AX producthave changed since the clinical research was done, and thecurrent product is structurally different to what was used in theclinical studies.

Finally,preserving the identity of a crop source becomes a challenge at scale with high-value crops as grain from nutritionallyimproved genotypes must be harvested and segregated from commodity grain. For most commodity crops such as cereal grains and oilseeds, segregating grain harvested from high-nutritional value genotypes from commodity genotypes increases costt substantially, and, in some cases, the infrastructureto do so does not exist at scale in many target growing regions.

Althoughthese challenges are certainly not insurmountable, thevalue of the nutritional/functional improvements will have tojustify investment in breeding and infrastructure for scale. It hasbeen argued that if such improvements can be made in food cropsthat are major staples in our food supply (e.g., improving fiber content in wheat), the outcomes in reduced economic burden of chronic diseases at a population scale could offset investments necessary to produce high-nutritional value crops atscale [130]. Protecting the intellectual property surrounding food-as-medicine products is also an area that needs exploration.In general, the strategies would be similar to other types of foods, including a combination of patents, trademarks, trade-secrets,and branding. Individual genotypes or hybrids of foodcrops can be patented through the plant variety protection [131], and process/utility patents could protect new methods fordownstream processing for preserving the nutritional profile. Utilitypatents could also protect specific formulation of products(e.g., a product formulation containing 12% of AX with an average degree of polymerization of 12 and arabinose:xylose ratio of 0.7), although the challenge here may be that environmental variation (e.g., soil type or climate where a given genotype is grown) can also influence its nutritional/functional profile, which could require a broader range of claims related to formulation. Method of use patents could also protect specific applications of novel product, such as specific changes in the microbiome and/or use for glycemic control. As with many food products, some of the intellectual property may also be protected as a trade secret, which prevents disclosure in the patenting process, and through branding and trademarks.

Regulatory approvals are another way that intellectual property of food-as-medicine products could be protected; however, the path for regulatory approval of a food-as-medicine product is a ittle murky. If regulated under the Food category by the United States FDA, the most straightforward type of claim language would be a specific nutritional component claim such as high in fiber. Structure/function claims are also permitted, although most related to food-as-medicine products would likely be linked to nutritional claims [132]. Specific health claims would potentially be permitted, but the evidence-based review system used by the FDA would require significant levels of substantiation through a body of evidence in the scientific literature and significant scientific agreement among qualified experts on the food/ingredient-disease relationship (e.g., from a government body such as the National Academy of Sciences or a professional organization such as the American Heart Association) [133]. This bar would be quite high for a specific type of food-as-medicine product and not likely to yield return on investment for a single commercial manufacturer.

Regulatory approval for a food-as-medicine product through the drug path is also problematic for several reasons. First and foremost, the level of evidence is also quite high, requiring phase I–phase III clinical trials and significant investment prior to commercialization. The drug path could also be challenging for a novel food product due to the stringent requirements for specific formulation and the potential environmental effects on nutritional profiles mentioned earlier. The dietary supplement category also poses several challenges for food-as-medicine products [134]. As a conventional food or sole item of a meal, food-as-medicine products, even with compelling clinical evidence, would not necessarily qualify under the DSHEA act [135], and it would be challenging to differentiate a food-as-medicine product from the >71,000 other products labeled in this category [136]. Even if significant clinical data are generated to substantiate the health benefits of a food-as-medicine product, claims that can be made in the supplement category are limited to structure/function or general health claims [137], which would not capture the true value of the product nor return the investment in clinical research necessary for substantiation. There is also a lack of consensus internationally on definitions and standards for quality and substantiation in this category [136], which further complicates any global marketing strategies. The Medical Food path is intended for “a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation [138].” This would seem to be a potentially relevant path for

some food-as-medicine products but would bear the burden of being marketed solely for use under medical supervision. Certainly, the field would benefit from a combination of investments in agronomic and biomedical research, economic analyses, and research related to policy.

## The Impact of Food Processing on Prebiotic Structure and Function

Considerable efforts have been directed toward identifying and characterizing chemical compounds in foods that can influence human health through their metabolism by the gut microbiota. The transition from *in vitro* or animal studies to human intervention studies introduces unique challenges, including formulation challenges, product stability, and cost-effectiveness. High-value candidate food ingredients or isolated compounds are typically identified after *in vitro* and animal studies on gut microbiota. When testing these components in humans, they are often delivered as pills or powders. However, for dietary fibers and prebiotics, daily doses are typically many grams, making delivery of these compounds in pill form a significant burden for participants, requiring the intake of 10 or more large pills per day. Most fiber tablets or capsules contain only ~0.4 to 0.5 g of fiber each, which makes it impractical to deliver clinically relevant doses—typically 10 g or more per day—through pills alone [139,140]. This high pill burden makes tablet forms unsuitable for human studies on prebiotics or dietary fibers.

Delivering fibers in powder form can overcome the pill burden by delivering several grams in a simple sachet. This can be used for low-viscosity, soluble fibers or other soluble ingredients. However, many dietary fibers, prebiotics, or other microbiota-active compounds are not soluble and have strong flavors, odors, or colors, making delivery this way difficult. Additionally, delivering food ingredients as a powder can pose food safety concerns if the ingredient may contain microbial contamination and is normally intended to be cooked before consumption. There are examples of human trials being conducted where insoluble fibers [141] or complex food ingredients [142] were distributed in powder form directly to participants for incorporation into their diet. In these cases, literature and training were provided to highly motivated participants to ensure they knew how to properly consume the test substances.

In contrast to using pills and powders to evaluate the bioactivity of dietary compounds, the food-as-medicine approach requires that candidate microbiota-active ingredients or compounds be formulated into a food that people can eat. However, processing techniques—such as fermentation, boiling, baking, frying, and extrusion—can significantly alter the chemical composition and physical matrix of foods. These modifications influence the digestibility and absorption of food components, ultimately changing the types and concentrations of unabsorbed compounds that arrive at the large intestine to interact with the gut microbiota. As summarized in Table 1 [143–149], the processing history of food compounds must be considered when examining their effects on the human gut microbiota. For

**TABLE 1**
Effect of food processing on gut microbiota

| Processing | Chemical/structural change | Effect on gut microbiota | References |
|---|---|---|---|
| Cooking (boiling/frying/grilling) | Gelatinization and altered microbial substrate availability | When vegetables are fried versus raw, boiled, or roasted, the gut microbiota composition changes: for example, frying increases genera within the Lachnospiraceae (e.g., *Lachnoclostridium* and *Blautia* species) and decreases others like *Alistipes*, *Coprobacter*, *Barnesiella*, and *Eggerthella* species. Grilling tends to reduce other taxa compared with other cooking methods such as boiling or roasting, although some Firmicutes (e.g., *Oscillospira* species) may increase. | [143–145] |
| Extrusion cooking | Breakdown of antinutrients and enhanced fiber solubility | More accessible polysaccharides; alter fermentation potential | [146] |
| Polyphenol processing | Altered bioactivity and bioavailability | Techniques like thermal treatment, drying, fermentation, and other processing methods can significantly alter the quantity, chemical structure, and bioavailability of polyphenols. These changes ultimately affect how polyphenols are metabolized by the gut microbiota, influencing their health-promoting potentials. | [147] |
| Ultraprocessed foods (UPFs) | Additives, low fiber, and emulsifiers | Although less about 1 method and more about overall industrial processing, UPFs—characterized by multiple additives, emulsifiers, and low fiber—disrupt the gut microbiome by reducing microbial diversity and beneficial bacteria (e.g., *Akkermansia muciniphila* and *Faecalibacterium prausnitzii*), while promoting proinflammatory species. They also increase gut permeability and may reduce production of protective metabolites like short-chain fatty acids. | [148,149] |

instance, severe extrusion of whole wheat markedly increased microbiota-accessible carbohydrates but unexpectedly reduced markers of improved gut health. In high carbohydrate-utilization microbiomes, extrusion disrupted cell wall structures to the extent that rapidly growing, non–butyrate-producing microbes (e.g., *Acinetobacter* and *Enterococcus* species) outcompeted slower-growing butyrate producers from the *Ruminococcaceae* and *Lachnospiraceae*. This shift lowered microbial diversity, decreased butyrate production, and favored acetate formation, which was associated with greater energy harvest and potential weight gain. Additionally, food processing can induce physicochemical changes that may either enhance or diminish prebiotic functionality. For example, during baking, xylanases can convert the naturally occurring, endogenous, long-chain AX into AX oligosaccharides [150,151]. AX oligosaccharide act as prebiotics, selectively promoting the growth of *Bifidobacterium* species in humans and animals. Chemical modifications introduced by processing can also change the structure of food components, thereby altering prebiotic selectivity for specific probiotic strains. The Maillard reaction occurs when reducing sugars react with amino groups during high-temperature processing. Early Maillard reaction stages form glycosylated intermediates that can change nutrient digestibility, fermentability, and prebiotic activity [152]. These intermediates eventually polymerize, yielding melanoidins that can resist digestion and influence the composition and function of the gut microbiota [153]. The Maillard reaction can also produce advanced glycation end products and crosslinked proteins that resist microbial breakdown or exert antimicrobial effects [154]. So the physical processing of prebiotics, although necessary for product development, can introduce physicochemical changes in the prebiotic, which need to be continuously validated to affirm that the original desired functionality of the prebiotic on the microbiome is preserved.

Production of test compounds or food ingredients on a scale needed for human trials, while maintaining functional efficacy, presents several challenges. Stability during processing and storage is a key concern, as degradation before consumption can substantially affect how the test food interacts with the gut microbiota. To address these challenges, various strategies have been explored to enhance the stability of compounds throughout processing and storage. Techniques such as microencapsulation, spray drying, and co-processing with stabilizing agents can protect labile compounds from thermal degradation, oxidation, and moisture-related breakdown [155,156]. Packaging also plays a critical role; barrier materials that limit oxygen and moisture ingress can significantly extend shelf life. These protective approaches, many of which are inspired by technologies developed for probiotic stabilization, are essential for ensuring that prebiotics maintain their targeted health benefits when delivered to consumers.

*In vitro* and even animal models require relatively small amounts of test compounds relative to human feeding trials. Laboratory-isolated or purchased compounds or ingredients that can be tested using *in vitro* or animal models can be unreasonably expensive when planning human trials due to costs or personnel, or equipment time for prebiotic isolation. For instance, in many *in vitro* fermentation studies, researchers test structurally defined prebiotics—such as individual oligosaccharides or phenolic compounds—which are commercially available in small quantities but are prohibitively expensive when scaled up. Additionally, some compounds used in laboratory studies undergo complex, multistep extraction and purification procedures that are not practical for researchers to scale up for human testing. A relevant example is the use of feruloylated oligosaccharides and polysaccharides, which were purified from corn bran material using autohydrolysis, concentration, reverse osmosis, and freeze drying [157,158]. Although these compounds provided valuable insights *in vitro* and in an animal model, replicating the same process at a scale suitable for human consumption required significant cost, time, and technical resources that prohibited human testing. These barriers highlight why certain promising ingredients identified through *in vitro* or animal models may never reach the stage of human testing. Overall, although *in vitro* and animal models are indispensable for early-stage screening and mechanistic exploration, the cost and scalability constraints of many test compounds limit their direct translation to human trials. Addressing these economic and production challenges is essential to bridge the gap between laboratory findings and practical dietary applications.

In conclusion, in this perspective, we highlight the many steps that need to be taken when developing food as medicine to produce widely effective and sustainable compounds such as specific prebiotics. How this pathway looks will depend on the diseases targeted and the mechanisms of action desired, including whether this mechanism will involve the microbiome, be a primary pharmacologic agent, provide chemoprevention for cancer or before onset of metabolic diseases. Although basic discovery platforms will always be needed to hypothesize and test the effectiveness of candidate compounds for specific diseases, it will be important to the ultimate development of the food as medicine that a beneficial effect can be shown in a majority of patients or that precision nutrition will allow highly successful application to predicted responder populations. It seems clear that the future of food as medicine will be moving from population-scale dietary guidelines to personalized or precision nutrition guidelines: from “eat more fiber” to “eat this specific type of fiber that has been enhanced in this specific genotype of food crop”. This includes developing designer fibers by crop breeding to develop panels of genotypes with different fiber structures (e.g., AXs with longer or shorter chains, more of less arabinose decoration, and more or less crosslinking) that deliver reliable shifts in the microbiome and metabolome. Finally, there needs to be continual optimization of prebiotic functionality and sustainable production so that future generations will have access to the same benefits of the food as medicine originally developed for disease prevention and treatment.

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## Author contributions

PJM: Coceptualization, Writing-Original Draft, Writing-Reviewing & Editing, Visualiztion, Project Administration, Funding Acquisition.

AKB: Conceptualization, Writing-Original Draft, Writing-Reviewing & Editing, Project Administration.

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## Conflict of interest

The authors report no conflicts of interest.

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