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Health benefits of fermented foods: microbiota and beyond

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Fermented foods and beverages were among the first processed food products consumed by humans. The production of foods such as yogurt and cultured milk, wine and beer, sauerkraut and kimchi, and fermented sausage were initially valued because of their improved shelf life, safety, and organoleptic properties. It is increasingly understood that fermented foods can also have enhanced nutritional and functional properties due to transformation of substrates and formation of bioactive or bioavailable end-products. Many fermented foods also contain living microorganisms of which some are genetically similar to strains used as probiotics. Although only a limited number of clinical studies on fermented foods have been performed, there is evidence that these foods provide health benefits well-beyond the starting food materials.

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Introduction

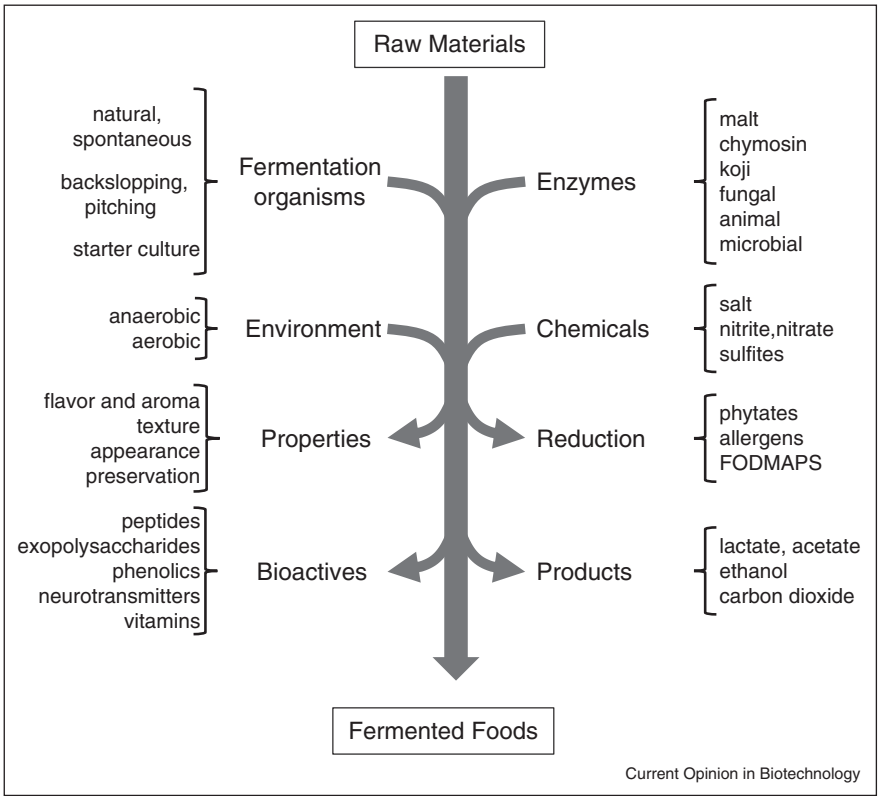
Fermented foods and beverages are staples of the human diet and have been produced and consumed since the development of human civilizations [1]. Fermented foods are generally defined as those foods or beverages made through controlled microbial growth and enzymatic conversions of major and minor food components (Figure 1). Food fermentation processes can be categorized by the primary metabolites and microorganisms involved: alcohol and carbon dioxide (yeast), acetic acid (*Acetobacter*), lactic acid (lactic acid bacteria (LAB) belonging to genera such as *Leuconostoc*, *Lactobacillus*, and *Streptococcus*), propionic acid (*Propionibacterium freudenreichii*), and ammonia and fatty acids (*Bacillus*, molds). Fermentations can also be described based on the food substrates, which include meats and fish, dairy, vegetables, soy beans and other legumes, cereals, starchy roots, and grapes and other fruits. Raw materials that contain high concentrations of monosaccharides and disaccharides, or in some cases starch, are fermented by yeasts or lactic acid bacteria. Molds and *Bacillus* are generally employed for starch saccharification or proteolysis or as secondary ripening microbiota after a primary fermentation.

As a result of the multitude of food-microbe combinations, there are thousands of different types of fermented foods and beverages. At least some form of these products is consumed by nearly every culture world-wide. Despite their long history, popularity, and culinary importance, the acceleration and industrialization of food production over the past century has reduced the diversity of fermented foods, particularly in the West. Recently, however, fermented foods have regained popularity as part of Western diets that emphasize artisanal processes. One reason for this surge in interest is their health-promoting potential. Recently, several groups have suggested that fermented foods should be included as part of national dietary recommendations [2,3]. This review will address what is currently known about how some of those foods support human health and the potential mechanisms underlying those effects.

Traditional fermented foods are diverse but stable microbial ecosystems

Traditional food fermentations are elegantly simple in that they generally require very few ingredients and minimal

Figure 1



Overview of the transformative nature of fermented foods. Raw materials are fermented in specific conditions to create interesting and desirable foods. Fermentation then creates novel and potentially health promoting compounds in foods, while removing those with negative health potential.

preparation and processing. Although some fermentations contain only a few dominant taxa (Table 1), strain differences and population dynamics during processing can be remarkably complex. In some foods, even minor alterations to species diversity or numbers can result in significantly different food products and variations in quality and organoleptic properties. Therefore, a microbial composition with temporal and spatial stability and resilience results in consistent fermentations and process conditions that are necessary to produce high quality food. Recent studies have explored the microbial diversity of numerous fermented food types and their associations with

Table 1

Primary source of fermentative organisms for common fermented foods and beverages. Microbial associations shown in the table are stable over time and show remarkable similarity in different regions or countries

Food	Source of organisms	Organisms
Yogurt	Starter culture	*St. thermophilus*, *L. delbrueckii* ssp. *bulgaricus*
Cheese, sour cream	Starter culture, backslopping	*Lc. lactis*, *Lu. mesenteroides*
Sausage	Backslopping, starter culture, spontaneous	*L. sake*, *L. plantarum*, *S. carnosus*, *S. xylosus*, *P. acidlactici*
Wine	Spontaneous, starter culture	*Sa. cerevisiae*, *O. oeni*
Beer	Backslopping, starter culture	*Sa. cerevisiae* (*L. brevis*)
Bread	Starter culture	*Sa. cerevisiae*
Sourdough bread	Backslopping	*L. sanfranciscensis*, *C. humilis*
Sauerkraut or kimchi	Spontaneous	*Lu. mesenteroides*, *L. plantarum*, *L. brevis*
Olives	Spontaneous	*L. plantarum*
Soy sauce, miso	Starter culture, spontaneous	*A. soyae*, *Z. rouxii*, *T. halophilus*
Tempeh	Starter culture, backslopping	*R. oligosporus*
Natto	Starter culture, backslopping	*B. subtilis* var. *natto*

St., *Streptococcus*; *L.*, *Lactobacillus*; *Lc*, *Lactococcus*; *Lu.*, *Leuconostoc*; *S.*, *Staphylococcus*; *P.*, *Pediococcus*; *Sa.*, *Saccharomyces*; *O.*, *Oenococcus*; *C.*, *Candida*; *A.*, *Aspergillus*; *Z.*, *Zygosaccharomyces*; *T.*, *Tetragenococcus*; *R.*, *Rhizopus*; *B.*, *Bacillus*.

metabolite and sensory attributes, such as acidity and texture. Importantly, this research not only informs fermentation management efforts, but also fundamental ecological concepts for improving the nutritional properties and organoleptic quality of fermented foods [4,5••,6].

Benefits of fermented foods

Fermentation can be viewed as a biological method of food preservation. Foods produced in this way have a reduced risk of contamination when enriched in antimicrobial end-products, such as organic acids, ethanol, and bacteriocins. Advantages of fermented foods also include the new and desirable tastes and textures that are completely unlike those present in the starting materials. Other benefits are more specific to the particular food type. Table olives, for example, are inedible without the microbial (or chemical) — induced removal of bitter-tasting phenolic compounds. Another example is the growth of bakers' yeast (*Saccharomyces cerevisiae*), alone or with lactic acid bacteria, that achieves dough leavening during bread manufacture.

Beyond these characteristics, it is increasingly understood that some fermented foods also promote human health in ways not directly attributable to the starting food materials. That is, the outcomes of fermentation, and the contributions of microbes, in particular, can provide additional properties beyond basic nutrition. Recent human clinical studies on fermented foods support this possibility (Table 2). Large cohort investigations have revealed strong associations between consumption of fermented dairy foods and weight maintenance [7]. Likewise, other long-term prospective studies show reductions in risk of cardiovascular disease (CVD), type 2 diabetes (T2D), and overall mortality from frequent yogurt consumption [8•,9–11]. These benefits might extend to immediate physiological responses, a possibility recently indicated by the finding that fermented milk consumption improved glucose metabolism and reduced muscle soreness induced by acute resistance exercise [12]. Similarly, evidence is accumulating for anti-diabetic and anti-obesity benefits of kimchi [13]. In inflammatory bowel diseases and other immune-related pathologies such as arthritis and sclerosis, health benefits of fermented foods have also been proposed, although clinical data have not yet been reported [14]. Lastly, although the microbiota-gut-brain axis is a nascent field of research, there is an indication that fermented food consumption can alter mood and brain activity [15–17]. The following sections discuss how fermented foods could lead to these outcomes by modifying the food constituents, synthesizing metabolites and proteins, and providing living microorganisms to the gastrointestinal (GI) tract.

Transformation of food constituents

During fermentation, the enzymatic activity of the raw material and the metabolic activity of microorganisms can change the nutritive and bioactive properties of food matrices in a manner that has beneficial consequences for human health. For example, most cheeses are typically well-tolerated by lactose-intolerant individuals because some of the lactose originally in the milk is fermented and the remaining lactose is separated into the whey fraction during cheese production. Yogurt, in particular, is generally well tolerated by lactose-maldigesters due to the *in vivo* release of β-galactosidase by yogurt cultures [18]. The bacterial β-galactosidases survive the acidic conditions of the stomach, apparently being physically protected within the bacterial cells and facilitated by the buffering capacity of yogurt. This mechanistic understanding was instrumental in these yogurt-associated species (*Lactobacillus delbrueckii* subsp. *bulgaricus* and *Streptococcus thermophilus*) becoming the only live microbes for which an EFSA health claim has been approved [19]. Specifically, the EFSA claim states that 'Live yogurt cultures in yogurt improve digestion of yogurt lactose in individuals with lactose maldigestion'.

Another dairy constituent, conjugated linoleic acid, a fatty acid with putative atheroprotective properties, can be enriched by LAB that possess linoleate isomerase. Some LAB also have proteolytic capacities active in milk and other foods that can result in increased concentrations of bioactive peptides and polyamines [20]. It should be noted that biogenic amines, which are generally undesirable, can also be produced in such fermentations [21]. Several peptides and peptide fractions having bioactive properties have been isolated from yogurt, sour milk, kefir, dahi, and other fermented food products. These and other peptides are being investigated for their anti-hypertensive, anti-thrombotic, satiety, opioid, immunomodulatory, osteogenic, and antioxidant effects [22]. Of particular interest are the peptides present in fermented dairy products that have activity as anti-hypertensive angiotensin-converting-enzyme (ACE) inhibitors [23].

In plant and vegetable fermentations, the growth of LAB enhances conversion of phenolic compounds such as flavonoids to biologically active metabolites via expression of glycosyl hydrolase, esterase, decarboxylase, and phenolic acid reductase [24]. The subsequent reaction of these metabolites with anthocyanidins results in formation of pyranoanthocyanidins or 3-desoxypyranoanthocyanidins [25]. Some of these alkyl catechols potently activate Nrf2 (NFE2L2), the master regulator of oxidant stress responses in mammals and thereby induce the expression of anti-oxidant and detoxifying enzymes protecting against oxidative and chemical damage [26••].

Additionally, fermentation can result in the removal of toxic or undesirable food constituents such as phytic acid. This plant-associated, anti-nutritional compound chelates divalent metal ions. Fermentation of cereal substrates reduces the pH which optimizes endogenous

Table 2

Recent human studies involving fermented foods

Target	Food type (organism(s) if referenced)	Study characteristics	Outcome	Reference (citation number)
T2D	Yogurt	Adult, 20-year factor-adjusted prospective, $N = 194\,458$	Consumption of one serving of yogurt per day was inversely correlated with T2D (HR = 0.83, $P < 0.001$)	Chen *et al.* [8•]
T2D, CHD, mortality	FMD	Adult, 10-year factor-adjusted prospective, $N = 4526$	Fermented dairy consumption was inversely associated with overall mortality (HR = 0.7, $P < 0.01$)	Soedamah-Muthu *et al.* [10]
IGM, T2D	FMD	Adult, extensive phenotyping, $N = 2391$	Fermented dairy consumption was inversely associated with IGM (HR = 0.74, 95% CI 0.54, 0.99)	Eussen *et al.* [9]
T2D	Yogurt	Elderly, 4.1-year factor-adjusted prospective, $N = 3454$	Total yogurt consumption was associated with a lower T2D risk (HR = 0.60 $P = 0.002$)	Díaz-López *et al.* [60]
IGM, T2D	Kimchi	Adult, PC, crossover RCT, $N = 21$, 8 weeks on diet, 4 week washout, 8 weeks on switched diet	Fermented kimchi decreased insulin resistance, and increased insulin sensitivity ($P = 0.004$ and 0.028, respectively). The percentages of participants who showed improved glucose tolerance were 9.5 and 33.3% in the fresh and fermented kimchi groups, respectively	An *et al.* [13]
Obesity	Chungkookjang (*Bacillus licheniformis*)	Adult, PC, DB, crossover RCT, $N = 120$, 12 week diet followed by 12 week diet switch	Percentage body fat, lean body mass, waist circumference and waist-to-hip ratio of women in the Chungkookjang group were significantly improved compared with the placebo group	Byun *et al.* [61]
CVD	Fermented soy product (*Enterococcus faecium* CRL 183, *Lactobacillus helveticus* 416)	Adult, PC, DB, RCT, $N = 49$, once daily consumption for 42 days	Consumption of fermented soy product led to improved total cholesterol, non-HDL-C and LDL concentrations (reduction of 13.8%, 14.7% and 24.2%, respectively, $P < 0.05$)	Cavallini *et al.* [62]
Hyperlipidemia	Kochujang (*Aspergillus oryzae*)	Adult, PC, DB, RCT, $N = 30$, three times daily consumption for 12 weeks	Kochujang-supplemented group, subjects' total cholesterol level significantly decreased (from 215.5 ± 16.1 mg/dL to 194.5 ± 25.4 mg/dL, $P = 0.001$)	Lim *et al.* [63]
Hypertension	Casein-derived lactotripeptides	Adult, meta-analysis of 20 RCTs	Pooled treatment effect for SBP was -2.95 mmHg (95% CI: -4.17, -1.73; $P < 0.001$), and for DBP was -1.51 mmHg (95% CI: -2.21, -0.80; $P < 0.001$)	Fekete *et al.* [23]
Osteoporosis	Kefir	Adult, PC, DB, RCT, $N = 40$, once daily consumption for 6 months	Kefir-fermented milk therapy was associated with short-term changes in turnover and greater 6-month increases in hip BMD among osteoporotic patients	Tu *et al.* [64]
Muscle soreness	FM (*Lactobacillus helveticus*)	Adult, PC, DB, RCT, $N = 18$, 3 doses of FM before and after exercise	Muscle soreness was significantly suppressed by the consumption of FM compared with placebo (placebo, 14.2 ± 1.2 score vs. fermented milk, 12.6 ± 1.1 score, $P < 0.05$)	Iwasa *et al.* [12]
Depression in T2D patients	Coffee	Adult, cross-sectional query based study, $N = 89$	Patients who drank 3 or more cups of coffee per day were more common in the non-depressed group (27/74 = 36.5%) than in depressed group (1/14 = 7.1%) ($P = 0.032$)	Omagari *et al.* [17]
Brain intrinsic activity or emotional attention	Fermented milk (*Bifidobacterium animalis* subsp. *lactis*, *Streptococcus thermophiles*, *Lactobacillus bulgaricus*, *Lactococcus lactis* subsp. *lactis*)	Adult, PC, RCT, $N = 36$, daily consumption for 4 weeks	Consumption of the FM by healthy women affected activity of brain regions that control central processing of emotion and sensation	Tillisch *et al.* [15]

Table 2 (*Continued*)

Target	Food type (organism(s) if referenced)	Study characteristics	Outcome	Reference (citation number)
Infection control, bowel movement normalcy	FM (*Lactobacillus casei* Shirota)	Elderly, PC, DB, RCT, $N = 72$, once daily consumption for 6 months	Consumption of FM resulted in significantly lower incidence of fever (1.1 days vs. 2.5 days, $P < 0.05$) and improved bowel movements (constipation 0.6 times vs. 1 time, $P < 0.05$) (diarrhea 0.3 days vs. 0.7 days, $P < 0.05$)	Nagata *et al.* [65]
IBS	Rye bread	Adult, PC, DB, crossover RCT, $N = 87$, 7–8 pieces per day, 4 week diet, 4 week washout, 4 week switch	Signs of IBS (flatulence, abdominal pain, cramps and stomach rumbling) were milder on the low-FODMAP rye bread (*P* values: 0.04; 0.049; 0.01 and 0.001)	Laatikainen *et al.* [27]

T2D, type 2 diabetes; CHD, coronary heart disease; IGM, impaired glucose metabolism; CVD, cardiovascular disease; IBS, irritable bowel syndrome; PC, placebo controlled; DB, double blinded; RCT, randomized clinical trial; HR, hazard ratio; FDP, fermented dairy products; FM, fermented milk; SBP, systolic blood pressure; Hg, mercury; DBP, diastolic blood pressure; BMD, bone mineral density; FODMAP, fermentable oligosaccharides, disaccharides, monosaccharides, polyols.

phytase activity thus removing most phytic acid. Additionally, sourdough fermentation and extended fermentation times on other breads can also reduce fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPS). Reductions in FODMAP content of wheat and rye bread can increase the tolerance of these compounds by IBS patients [27,28].

Synthesis of bioactive and nutritive compounds

Fermentation can also result in new compounds with health-modulating potential. Lactic acid is one such metabolite that is synthesized in amounts often reaching over 1% in LAB fermentations. Lactic acid (or lactate) was recently shown to reduce pro-inflammatory cytokine secretion of TLR-activated, bone-marrow-derived macrophages and dendritic cells in a dose-dependent manner [29]. Lactate also alters redox status by reducing the reactive oxygen species burden in intestinal enterocytes [30]. Therefore, should a fraction of the lactic acid or possibly other organic acids in fermented foods reach the small intestine those cell products might provide a core benefit of those foods.

Other microbial-derived products made during fermentation are typically strain dependent. The B vitamins including folate, riboflavin, and B12 are synthesized from various non-vitamin precursors by certain bacteria in plant and dairy foods [31,32]. Amino acids and derivatives with neurotransmitter (e.g. γ-aminobutyric acid) and immunomodulatory functions are also synthesized during fermentation [33]. Additionally, certain secreted proteins and exopolysaccharides produced during food fermentations might serve as anti-oxidants [34,35], prevent adhesion of pathogens to the intestinal mucosa [36], or confer immune-stimulatory [37] or hypocholesterolemic activities [38,39]. Some polysaccharides also act as prebiotics and are fermented by the intestinal microbiota to short chain fatty acids [40].

Delivery of commensal microbes to the GI tract

Many fermented food and beverage products are processed such that viable microorganisms are absent at the time of consumption. Nonetheless, some of the most familiar fermented foods, including sauerkraut, kimchi, kefir, dry fermented sausage, yogurt, cheese, kombucha, and miso ordinarily contain viable cells in notable quantities ranging between 10^6 and 10^9 cells/g or cells/ml. A relatively large fraction of those microbes survives passage through the human digestive tract [41,42]. The ingestion of fermented foods potentially increases the numbers of microbes in the diet by up to 10 000-fold [43], and consuming 'living' fermented foods on a daily basis could be equivalent to introducing new, albeit transient microbes into the indigenous, intestinal microbiota [44]. Such diets contrast with the highly processed and sanitized foods consumed in Western societies that limit microbial exposures. The hygiene (or diversity) hypothesis proposes that such microbial exposures are essential for the normal development of immune system and neural function [45,46]. Therefore, consumption of fermented foods may provide an indirect means of counteracting the hygienic, sanitized Western diet and lifestyle.

The delivery of high numbers of microorganisms to the GI tract is supported by the matrix of some fermented foods which promote the long-term survival of organisms during distribution and storage. Fermented foods show particular potential as a practical vehicle in which to provide established probiotic strains to people in low-income countries [47,48]. The health-modulating potential of some of those strains also might be enhanced by the delivery matrix as indicated by the significantly reduced levels of colitis in mice fed *L. casei* BL23 incubated in milk as opposed to the same strain incubated in non-nutritive buffer [49]. Interestingly, the cell-associated proteome of *L. casei* was modified in response to milk and expressed certain proteins that contributed to

reduced inflammatory responses in the mouse intestine [50•].

Probiotic features of fermented food microorganisms

Many of the species found in fermented foods are either identical to or share physiological traits with species relevant to promoting GI tract health (Table 3). The importance of this was recently demonstrated by a study in which cheeses were produced using starter culture strains (*L. delbrueckii* subsp. lactis CNRZ327 and *P. freudenreichii* ITG) that had been selected based on their *in vitro*, anti-inflammatory potential [51•]. When fed to mice, cheese containing those strains, but not the control cheese, protected against colitis and epithelial cell damage.

The concept that live microbes associated with food fermentations can provide beneficial functions in the GI tract is consistent with the emerging view that core health benefits of probiotic cultures can be assigned to a species, rather than to specific strains of a species [52•]. At least this is the case for some species of LAB for which certain strains have long been applied as probiotics. Therefore, when a fermented food (e.g. sauerkraut, kimchi) contains large numbers of live cells belonging to a species for which health benefits have been demonstrated (e.g. *L. plantarum*), a reasonable argument could be made that these foods should be considered to have similar health benefits as those conferred by probiotic lactobacilli of the same species. It is worth noting that some countries (e.g. Italy and Canada) incorporate a list of species considered as probiotics in their regulatory guidelines. In contrast, in most of Europe, foods are not permitted to use or mention 'probiotics' or 'contain probiotics' on labels.

Ingestion of viable, fermentation-associated microbes could therefore exert influence on intestinal epithelial, immune, and enteroendocrine cells in a manner similar to existing probiotic strains. Until now, such effects have been largely attributed to individual strains. Recent reports using strains of food-associated bacteria, *L. plantarum* and *L. rhamnosus* [53], *L. reuteri* [54••] and *P. freudenreichii* [55], demonstrate the potential of those bacteria to directly alter host responses in the GI tract. Synthesis of histamine *in vivo* by *L. reuteri* [54••] indicates that such outcomes could be due to metabolites already known to be made by many strains of a particular species.

Fermentation-associated microorganisms might alter the intestinal composition or function of the autochthonous microbiota in the GI tract. However the magnitude of these changes and importance to probiotic efficacy is currently a point of contention [56,57]. Three ways in which such changes could occur include trophic interactions (e.g. production of SCFA), direct inhibition or stimulation of competitors, and indirect effects as a result of impacting the host [41]. These effects are generally quite broad and therefore not likely limited to only certain strains. However, consistent with currently applied probiotics, fermentation-associated microbes are likely to be affected by host diet and other gut-associated factors [58] and are not likely to have long-lasting effects on the resident colonic microbiota [59].

Table 3

Traditional or novel food fermentations with probiotic organisms

Species with recognized probiotic activity[a]	Fermented foods that reproducibly contain high cell counts of strains of the species
Lactobacillus acidophilus	NSLAB long ripened cheese
Lactobacillus johnsonii	Kefir
Lactobacillus fermentum	Bushera, ting and other African cereal porridges and beverages
Lactobacillus plantarum	Salami[b], sauerkraut/kimchi, olives, others
Lactobacillus paracasei	Salami, kvass, NSLAB in long-ripened cheese
Lactobacillus rhamnosus	'Villi', fermented oatmeal
Lactobacillus casei	NSLAB long-ripened cheese

NSLAB, non-starter lactic acid bacteria.
[a] According to Health Canada.
[b] Fermented foods are printed in bold if presence of the probiotic organism depends on its addition as competitive starter culture.

Conclusions

Heightened interest in the human microbiome as a major determinant of human health and behavior underscores the need to understand the functions of microorganisms and their cell products that enter the GI tract through food and beverages. Fermented foods are increasingly understood for their properties that reach well-beyond preservation and sensory attributes. Therefore, there is a critical need for additional fundamental research comparing different fermentation-associated strains for core properties expressed either for food transformations, product synthesis, or survival and host-microbe interactions in the GI tract. Also needed are randomized, controlled, clinical trials to measure the quantitative and repeatable effects of different fermented foods on human health. These studies are implicitly challenging to design because 'blinding' is not possible when whole foods are compared. Such efforts are still needed, however, because the benefits of fermented foods are likely greater than the sum of their individual microbial, nutritive, or bioactive components. This research will clarify the relevance, and potentially the necessity, of certain fermented foods in the human diet and justification for inclusion into national dietary guidelines.

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