Supplement Article

Yogurt and other fermented foods as sources of health-promoting bacteria

Car Reen Kok and Robert Hutkins

Increased consumption of yogurt, kefir, and other fermented foods has been driven, in part, by the health benefits these products may confer. Epidemiological studies have shown that the consumption of fermented foods is associated with reduced risks of type 2 diabetes, metabolic syndrome, and heart disease, along with improved weight management. The microorganisms present in these foods are suggested to contribute to these health benefits. Among these are the yogurt starter culture organisms Streptococcus thermophilus *and* Lactobacillus delbrueckii *subsp* bulgaricus *as well as* Bifidobacterium *and* Lactobacillus *strains that are added for their probiotic properties. In contrast, for other fermented foods, such as sauerkraut, kimchi, and miso, fermentation is initiated by autochthonous microbes present in the raw material. In both cases, for these fermentation-associated microbes to influence the gut microbiome and contribute to host health, they must overcome, at least transiently, colonization resistance and other host defense factors. Culture and culture-independent methods have now clearly established that many of these microbes present in fermented dairy and nondairy foods do reach the gastrointestinal tract. Several studies have shown that consumption of yogurt and other fermented foods may improve intestinal and extraintestinal health and might be useful in improving lactose malabsorption, treating infectious diarrhea, reducing the duration and incidence of respiratory infections, and enhancing immune and anti-inflammatory responses.*

INTRODUCTION

For thousands of years, fermented foods have been a major part of the human diet,[1] largely because fermented milk, meat, and plant foods could be better preserved than the fresh raw materials from which they were made.[2] In the absence of drying, salting, or other forms of traditional preservation, perishable foods would spoil or become unsafe to consume. Most fermented foods, in contrast, naturally contain organic acids, ethanol, or other antimicrobial compounds that inhibit the growth of spoilage organisms and foodborne pathogens.

In addition to their enhanced preservation qualities, fermented foods have other attributes that account for their popularity, including unique flavors, textures, and appearances as well as added functionality and economic value. In many parts of the world, fermented foods are among the most important sources of nutrients.[3–5] Cultured dairy products, bread, and fermented sausage, for example, are rich sources of protein, minerals, and vitamins. Fermentation may also reduce the concentration of lactose and other fermentable sugars and increase phenolic compounds that provide antioxidant activity.[6,7] Importantly, there is emerging epidemiological and clinical evidence to

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suggest that the microorganisms responsible for fermentation, along with those added to fermented foods in the form of probiotics, may contribute directly to gastrointestinal and systemic health.[8]

The microorganisms that are predominantly involved in the manufacture of fermented dairy, meat, and vegetable products are lactic acid bacteria from the genera *Lactobacillus*, *Streptococcus*, *Pediococcus*, and *Leuconostoc*. Other bacteria, including acetic acid bacteria, are also important in the fermentation of cocoa beans, vinegar, and kombucha.[9,10] *Saccharomyces cerevisiae* and other yeasts are widely used in beer, wine, and bread manufacture, and *Penicillium* spp, *Aspergillus* spp, and other fungi are used in cheese, fermented meats, and soy-fermented foods. For many foods, bacteria and yeast are combined to produce the desired product.[11,12]

Although microorganisms are required for the production of the foods mentioned above, not all fermented foods contain live microbes at the time of consumption. For example, lactic acid bacteria and yeast are used in sourdough bread fermentation, but after baking, none of these organisms are present in the finished bread. Similarly, the organisms responsible for wine and beer fermentation are inactivated or physically removed and are absent from the finished product. Nonetheless, vitamins and bioactive molecules produced by the microbes may still be present. In addition, microbes also consume or transform food constituents during fermentation, resulting in compositional changes in the food. However, even in the absence of a heat or separation step, the number of microbes present at the time of consumption depends on the composition, the storage conditions, and the age of the food.[13,14]

Understanding the molecular basis for the manner in which fermented foods and fermentation-associated microorganisms affect human health has been challenging. However, next-generation sequencing and other molecular methods are now routinely used to identify and assess abundances of microbes present in fermented foods as well as within gastrointestinal microbiomes.[15,16] Thus, it is now possible to track specific strains present in fermented foods from consumption to the gastrointestinal tract.[17–19] Transcriptomics, metabolomics, and whole-metagenome sequencing are also being used to identify or predict functional traits of fermentation-associated microorganisms.[20–22]

The goal of this review was to assess the nutritional role of live microbes present in fermented foods, with an emphasis on yogurt and other cultured dairy products. The physiological and ecological challenges faced by fermentation-associated and food-related microbes during digestion and transit through the gastrointestinal tract will be described first. Evidence showing that many of these organisms do indeed survive transit will follow. The ability of food-associated microbes to influence the composition of the intestinal microbiota and ameliorate gut imbalances or dysbiosis will be described next. Finally, the health benefits of fermented foods, as reported in epidemiological and clinical studies, will be reviewed. In particular, improved lactose digestion by yogurt bacteria—currently the only approved health claim for a fermented food—will be described.

FERMENTATION-ASSOCIATED MICROBES AND THEIR JOURNEY TO THE GUT

For food-associated microorganisms to directly influence the intestinal microbiota and improve the nutritional status of the host, they must first traverse several early hurdles[23] (Figure 1). In the mouth, saliva contains enzymes and other antimicrobial constituents, and the oral microbiota itself provides colonization resistance.[24,25] In the stomach, gastric pH is usually less than 3.0 (depending on the fasting state), and pepsin, trypsin, and other digestive enzymes effectively degrade cell proteins.[23] Bile salts secreted into the small intestine disrupt cell membranes and contribute to cell permeabilization and death.[26]

Despite these challenges, evidence based on both culture and culture-independent methods shows that many of the organisms present in a wide range of fermented foods do indeed survive transit through the gastrointestinal tract. (Table 1)[18,27–38]. For example, using culture-based methods, *Streptococcus thermophilus* and *Lactobacillus delbrueckii* subsp *bulgaricus* were detected in duodenum samples from intubated subjects within 15 minutes after fresh yogurt had been consumed.[32] In ileal perfusion experiments in human participants, the same researchers also showed that more than 20% of a strain of *Bifidobacterium* sp consumed in milk reached the ileum.[28] Likewise, recovery rates of *Lactobacillus casei* DN-114 001 and *Lactobacillus plantarum* NCIMB 8826 consumed in fermented milk were above 50% and at 7%, respectively, in ileal samples.[29,30] In contrast, survival rates of other lactic acid bacteria (including strains of *Lactococcus lactis* and *Lactobacillus fermentum*) recovered from the ileum were 1% or less.[30]

Samples obtained by other means, including catheters, probes, or biopsy, have been used to assess microbiota communities in the digestive tract and have demonstrated survival of food-associated microbes during digestion (Table 1;[31]).[39] Ultimately, however, analyses of intestinal microbiomes are most often based on fecal samples.[27,34,37] Results from such analyses, therefore, reflect the net outcome of a given microbe's journey through the entire alimentary canal. Thus,

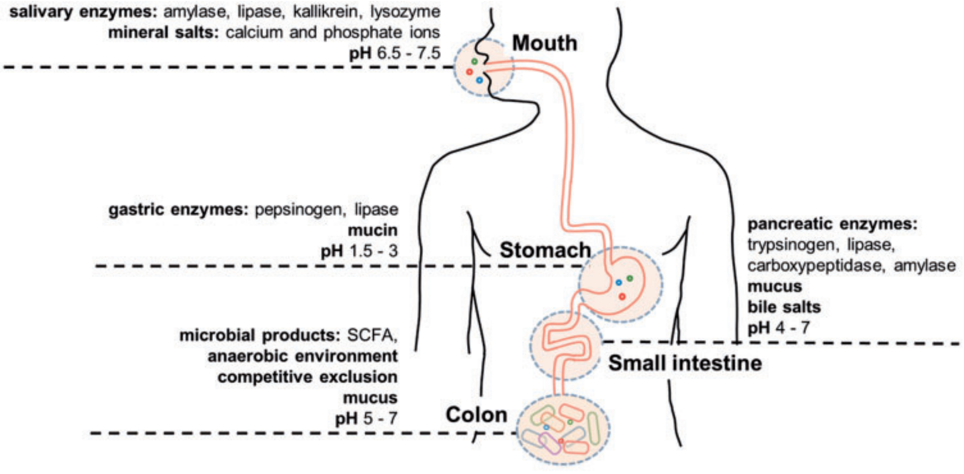

Figure 1 **Challenges faced by food-associated microbes during their transit through the alimentary canal**. The presence of proteases, lipases, and other digestive enzymes are initially responsible for the degradation of cell proteins and lipids. The change in pH along the digestive tract also acts as an additional barrier for these microbes. The pH is lowest in the stomach, owing partly to the secretion of hydrochloric acid by the gastric mucosa, and this can be especially detrimental to non–acid-tolerant microbes. Even if these microbes can successfully survive gastric challenges, bile acids are produced by the host in the small intestine, and the residential microbes present in the gastrointestinal tract release short-chain fatty acids. With all these hurdles in place, it is perhaps surprising that so many of these food-associated microbes are still able to survive transit into the colon. *Abbreviation*: SCFA, small-chain fatty acids.

when viable cells from fecal samples are enumerated, that measurement is a sum of both cell death and cell growth in the oral cavity, stomach, small intestine, and colon.[23] Experimentally, therefore, it is difficult to determine the actual number or percentage of consumed microorganisms that survived transit into the colon.

FOOD MICROBES AND COLONIZATION RESISTANCE

Food-associated microbes that have the physiological ability to reach the colon must then contend with the phenomenon of niche exclusion and colonization resistance. Colonization resistance is defined as "resistance to colonization by ingested bacteria or inhibition of overgrowth of resident bacteria normally present at low levels within the intestinal tract."[40] Collectively, it refers to those antagonistic, ecological, immunological, and structural factors that restrict access of potential new members to an established community (Figure 2;[41]).[42]

Colonization resistance against invading pathogens is considered one of the primary protective functions of the gastrointestinal microbiota and is mediated in several different ways.[43] Commensal microbes protect the gut lining by providing a physical barrier, and they produce bacteriocins and other antimicrobial agents that inhibit newly arrived competitors.[44] The production of short-chain fatty acids, in particular, lowers the pH and create an unfavorable environment for foreign microbes that are sensitive to low pH.[40,45] In general, commensal microbes outcompete transient or allochthonous organisms for nutrients and access to environmental niches.[41,46]

Even resident organisms such as *Clostridium difficile* are kept in check by commensal members of the gut microbiota.[47] However, the mechanisms responsible for colonization resistance do not necessarily discriminate between friend and foe. Other potentially beneficial microorganisms, including fermentation-associated lactobacilli, are subject to the same barriers. Thus, most putative probiotic organisms, especially those allochthonous to the gastrointestinal tract, are unsuccessful colonizers and may even be considered ecological invaders.[48–50] In this context, for live microorganisms to be successful invaders, they would need to be introduced in a viable state in high numbers; overcome digestive hurdles and reach the gastrointestinal tract; compete for nutritional resources, grow, and persist; and interact with the resident microbiota to ultimately effect change in the composition or function of the microbiota.[50,51] Such are the ecological challenges for probiotics and other food-associated microbes following ingestion.

Despite these limitations, the presence of fermentation microbes in fecal samples is not unusual. For example, lactobacilli are among the most common microbes in fermented foods, and they are also commonly found in human fecal samples, albeit at relatively low abundances.[52–56] Several reports suggest that microorganisms present in diets containing fermented foods may also affect the gut microbiota, at least transiently.[18,27] In the study by David et al,[27] participants

Table 1 **Detection and recovery of fermentation-associated microbes after ingestion**

Reference	Fermented food	Strains introduced	Food or amount ingested	Sample tested	Results	Method of identification
David et al (2014)[27]	Cheese & cured meat	–	Animal-based diet consisting of cheese and cured meats for dinner	Stool	Increase in *Lactococcus lactis*, *Pediococcus acidilactici*, and *Staphylococcus* spp	Molecular: 16S rRNA
					Increase in *Penicillium*-related fungi. Decrease in *Debaryomyces* spp and *Candida* spp	Molecular: ITS
Pochart et al (1992)[28]	Fermented milk	Bifidus milk containing *Bifidobacterium* sp strain BB	2.5×10^7 CFU/g	Ileal fluid	23.5% ± 10.4% survival[a]	Culture: plate count on TPY + 0.5% propionic acid
Oozeer et al (2006)[29]	Fermented milk	*Lactobacillus casei* DN-114 001	10^8 CFU/mL	Ileal fluid Stool	3.6% ± 1.8% survival[a] 7.6 $\log_{10}$ CFU/g	Culture: plate count on MRS agar + rifampin (100 ug/mL)
Vesa et al (2000)[30]	Fermented milk	*Lactobacillus fermentum* KLD	1.0×10^7 CFU/g	Ileal fluid	0.5% ± 0.5% survival[a]	Culture: plate count on MRS agar + rifampin (50 ug/mL) + streptomycin (200 ug/mL)
		Lactobacillus plantarum NCIMB 8826	7.6×10^8 CFU/g	Ileal fluid Stool	7.0% ± 2.0% survival[a] 25% ± 29% survival[a]	
		Lactococcus lactis MG 1363	3.0×10^7 CFU/g	Ileal fluid	1.0% ± 0.8% survival[a]	
Veiga et al (2014)[18]	Fermented milk	*Bifidobacterium animalis* subsp *lactis* CNCM I-2494	1.25×10^{10} CFU/serving	Stool	Increase in all 4 species in the fermented milk, Clostridiales and *Bifidobacterium dentium*. Decrease in *Bilophila wadsworthia*, *Parabacteroides distasonis*, and *Clostridium* sp HGF_2	Molecular: whole genome sequencing
		Streptococcus thermophilus CNCM I-1630	1.25×10^9 CFU/serving			
		Lactobacillus delbrueckii subsp *bulgaricus* CNCM I-1632 and CNCM I-1519	1.25×10^9 CFU/serving			
		Lactococcus lactis CNCM I-1631	1.25×10^9 CFU/serving			
Shibahara-Sone et al (2016)[31]	Fermented milk	*Bifidobacterium bifidum* YIT 10347	$\geq 10^9$ CFU/100 mL	Gastric body biopsy	Detected in all individuals[b]	Molecular: RT-qPCR
Pochart et al (1989)[32]	Fresh yogurt	*Lactobacillus bulgaricus* strain S85	1.26×10^8 CFU/g	Duodenal	1.99×10^2 CFU/g[c]	Culture: plate count on MRS agar
		Streptococcus thermophilus strain S85	5.01×10^8 CFU/g		1.58×10^3 CFU/g[c]	Culture: plate count on M17 agar
del Campo et al (2005)[33]	Fresh yogurt	*Streptococcus thermophilus*	2×10^8 CFU/g	Stool	Detected in 8.4% of total individuals	Molecular: DNA hybridization
		Lactobacillus delbrueckii	1.3×10^7 CFU/g		Detected in 3.15% of total individuals	
		Streptococcus thermophilus	2×10^8 CFU/g		Not detected	Culture: isolation on MRS and M17 agars
		Lactobacillus delbrueckii	1.3×10^7 CFU/g		Not detected	

(continued)

Table 1 **Continued**

Reference	Fermented food	Strains introduced	Food or amount ingested	Sample tested	Results	Method of identification
Mater et al (2005)[34]	Yogurt	*Streptococcus thermophilus*	7.8×10^8 CFU/mL	Stool	6.3×10^4 CFU/g	Culture: plate count on M17 agar + streptomycin (1 µg/mL) + rifampin (100 µg/mL)
		Lactobacillus delbrueckii subsp *bulgaricus*	7.5×10^8 CFU/mL		7.2×10^4 CFU/g	Culture: plate count on MRS agar + streptomycin (1 µg/mL) + rifampin (100 µg/mL)
Elli et al (2006)[35]	Yogurt	*Streptococcus thermophilus*	5×10^{10} CFU/serving	Stool	Detected in 5% of total individuals	Culture: plate count on RSM + 0.05% ruthenium red dye
		Lactobacillus delbrueckii subsp *bulgaricus*	6×10^9 CFU/serving		Detected in 65% of total individuals	
Kil et al (2004)[36]	Kimchi	*Lactobacillus* sp	60 g to 300 g of kimchi	Stool	3.5 – 6 log CFU/mL[d]	Culture: plate count on modified LBS medium
		Leuconostoc sp			4 – 6.5 log CFU/mL[d]	Culture: plate count on PES
Lee et al (1996)[37]	Kimchi	*Lactobacillus* sp *Leuconostoc* sp	200 g of kimchi	Stool	6.87 ± 1.05 log CFU/g 5.78 ± 1.35 log CFU/g	Culture: plate count on MRS agar + bromophenol blue
Han et al (2015)[38]	Fermented kimchi	–	180 g of kimchi	Stool	Increase in *Bacteroides* and *Prevotella*. Decrease in *Blautia*	Molecular: pyrosequencing

Abbreviations: CFU, colony-forming units; ITS, internal transcribed spacer; LBS, *Lactobacillus* selective; MRS, de Man, Rogosa and Sharpe; PES, phenylethyl alcohol sucrose; RSM, reconstituted skim milk; RT-qPCR, quantitative reverse transcriptase polymerase chain reaction; TPY, trypticase phytone yeast extract.

[a] To estimate the number of bacteria recovered from the ileum, the sum of counts was obtained for samples taken at 1-h periods over a duration of 8 h on respective media. Percentages of survival were calculated by dividing the total number of bacteria throughout the collection period by the number of bacteria ingested.

[b] Detection of *Bifidobacterium bifidum* 1 h after ingestion in both *Helicobacter pylori*-positive and -negative individuals.

[c] Viable bacterial count extrapolated at 90 min after ingestion.

[d] Viable bacterial count estimated from a graph corresponding to the intake of standardized kimchi.

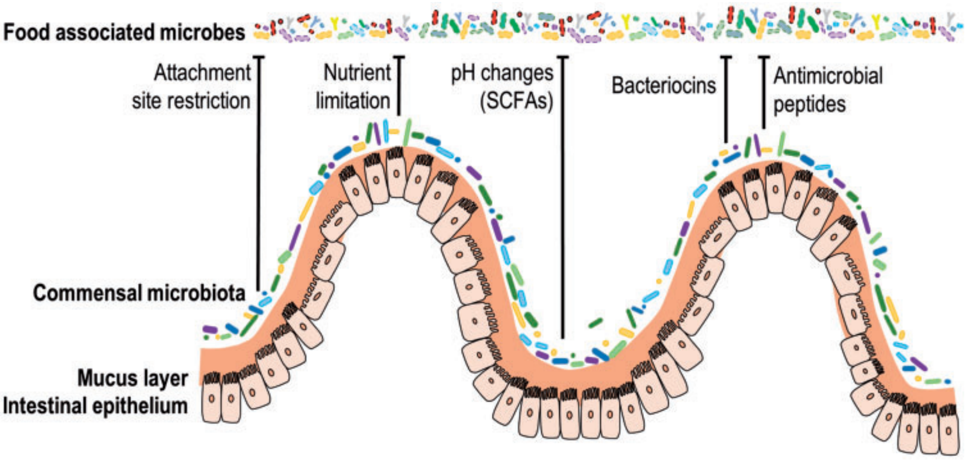

Figure 2 **Factors linked to the transient nature of food-associated microbes**. Colonization resistance has evolved, in part, to protect the host against invading pathogens. However, this phenomenon does not discriminate between pathogenic and nonpathogenic microbes and subjects food-associated microbes to the same resistance that pathogens (in red) encounter either directly or indirectly from the commensal microbiota. The presence of residential microbes that are strongly associated with the mucosal layer may also prevent attachment of other incoming microbes. The latter, therefore, must compete with commensals for adhesion receptors. The residential microbes may also release bacteriocins and other antimicrobial agents that inhibit newly ingested microbes. Microbes must also compete for nutrients, making it difficult for food-associated microbes to fill niches already occupied by commensal microbes. Collectively, the ability of food-associated microbes to evade competitors, tolerate antimicrobial agents, and compete for food and biogeographical niches determines whether these microbes will be able to cause changes in the microbiota. Adapted from Sassone-Corsi and Raffatellu.[41] *Abbreviation*: SCFA, small-chain fatty acids.

consumed either plant- or animal-based diets for 5 days, and fecal microbiomes were analyzed before and after treatment by sequencing the 16S rRNA and internal transcribed spacer regions.[27] Cheeses and cured meats were included among the animal-based products that were consumed. Results revealed that diet affected the microbiota, with changes in various taxa and functional traits corresponding to animal- or plant-based diets. Moreover, the researchers detected the presence of microbes (both bacterial and fungal) in the fecal microbiota that were associated with specific fermented foods and their respective starter cultures. The investigators confirmed, on the basis of recovery of either live cells or RNA transcripts, that the fermentation-derived organisms had survived digestion and had reached the colon. Specifically, transcriptomic analysis revealed an increased abundance of *Lactococcus lactis*, *Staphylococcus carnosus*, *Pediococcus acidilactici*, and a *Penicillium* species in the fecal microbiota derived from an animal-based diet.

In the study by Veiga et al,[18] individuals with irritable bowel syndrome consumed a yogurt-like fermented milk product containing *Bifidobacterium animalis* twice daily for 4 weeks, and DNA from all of the included strains was detected in fecal samples. Importantly, not only were the abundances of those strains significantly higher than those detected in baseline samples, but the results of metagenomics sequencing also revealed other changes in the microbiota. In particular, *Bifidobacterium dentium* was increased, whereas 2 pathobionts, *Bilophila wadsworthia* and *Parabacteroides distasonis*, were decreased following the dietary treatment. Other unidentified species were also increased, including those capable of producing butyrate and other short-chain fatty acids. The study participants also reported improvement in their irritable bowel syndrome symptoms, suggesting the possibility that the changes in the microbiota might be responsible.

In other studies, the ability of fermentation-associated organisms to survive digestion is more variable, depending on the food consumed and the methods of analysis. In particular, the organisms in yogurt are only occasionally isolated in fecal samples.[57] Thus, while Mater et al[34] and Elli et al[35] reported that *S thermophilus* or *L delbrueckii* subsp *bulgaricus* could be detected by culture-based methods in fecal samples following yogurt consumption, del Campo et al[33] could not recover the yogurt-containing isolates on nutrient agar. However, using a DNA hybridization method, they could detect these organisms in samples from 10 of 96 participants who consumed fresh yogurt. This suggested that the targeted organisms were detectable but not viable in the stool samples. However, it is important to note that the studies from Mater et al[34] and Eli et al[35] used a more selective media to obtain isolates (Table 1). Ideally, isolation followed by the use of molecular methods, whether based on polymerase chain reaction or sequencing, should be employed to identify these isolates at a higher resolution. The presence of fermentation-associated microbes in fecal samples (detected by molecular methods) from individuals who normally consume kimchi, sausage, sauerkraut, and other fermented foods has also been reported.[38,52]

Shifts in the gut microbiota following antibiotic treatment or other disturbing events may lead to dysbiosis, providing opportunities for growth of pathogenic microbes and onset of disease and inflammation.[58] One way to redress or correct dysbiosis is via ingestion of probiotics, fermented foods, and other dietary sources of beneficial microbes.[59] As noted above, however, ingested microbes encounter considerable environmental challenges on their way to the gut. On the basis of a systematic review of 63 clinical trials, Mcfarland[60] concluded that the ability of probiotic and other food-associated microbes to influence the microbiota and correct dysbiosis was dependent on the individual. Thus, for many people, changes in the gut microbiota were not observed. Nonetheless, probiotic strains that restored a disturbed gut microbiota were more often associated with improved clinical outcomes compared with those strains that had no effect on the microbiota.

EPIDEMIOLOGICAL EVIDENCE OF THE HEALTH BENEFITS OF YOGURT AND OTHER FERMENTED FOODS

Several large epidemiological studies have assessed the effect of consumption of yogurt and other fermented foods on the incidence of various diseases or health outcomes, and many have shown a reduced risk of disease or improvements in health. In one large cohort study of older Mediterranean adults, yogurt-rich diets were associated with a reduced risk of metabolic syndrome.[61] Results from another large prospective study of more than 80 000 Swedish adults suggested that high consumption of cultured milk lowered the risk of developing bladder cancer.[62] The Swedish Malmo Diet and Cancer cohort study also reported reduced risks of cardiovascular disease among individuals who consumed high amounts of fermented milk and among women who consumed cheese.[63] In another large cohort study, less long-term weight gain was associated with yogurt consumption.[64] Similarly, the prospective European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study of European adults revealed that cheese consumption, as well as combined consumption of cheese, yogurt, and fermented milk, was inversely associated with diabetes.[65] Additionally, in the EPIC-Italy cohort of over 45 000 adults, yogurt consumption was associated with a reduced risk of colorectal cancer.[66] However, among the same cohort, consumption of fermented dairy and other foods was not associated with reduced mortality from all causes, cancer, or cardiovascular disease.[67] The possibility exists that yogurt consumers, in general, have a higher overall diet quality than nonconsumers, and this would account for observed differences in metabolic health. However, results from the Quebec Family Study suggested that yogurt consumption was associated with improved health benefits and body composition, independent of diet quality.[68] Finally, it is important to note that, because these studies are based on dietary histories or consumption patterns, it is not possible to determine the type of yogurt consumed. As noted in the next section, many of the commercially marketed yogurts contain strains of probiotic bacteria in addition to the cultures used in yogurt manufacture.

The beneficial effects of fermented foods other than dairy products have also been assessed by epidemiological studies. In Korea, kimchi and other fermented vegetables are among the most widely consumed foods. Results from cross-sectional analyses of adults showed that high consumption (about three 40-g servings per day) of fermented vegetables and other Korean fermented foods was associated with reduced prevalence of asthma and atopic dermatitis.[69,70] The reduced rate of type 2 diabetes among Asian populations compared with Western populations was suggested to be due, in part, to the consumption of fermented soybean foods, which are rich in phytoestrogens and bioactive peptides.[71] Likewise, consumption of the fermented soy products miso and natto was also inversely associated with reduced risk of high blood pressure.[72] Interestingly, consumption of tofu, a nonfermented soy product, was not associated with this effect.

CLINICAL EVIDENCE OF THE HEALTH BENEFITS OF YOGURT AND OTHER FERMENTED FOODS

According to both tradition and various national and international standards of identity, yogurt is made with a culture containing strains of *S thermophilus* and *L delbrueckii* subsp *bulgaricus*. However, many commercial products are supplemented with probiotic bacteria, particularly strains of *Bifidobacterium* and *Lactobacillus* for added benefits. There are a large number of recent human clinical studies in which these so-called probiotic yogurts and other probiotic-containing cultured milk products have been examined, with specific clinical end points measured.[73–79] The effects of yogurt consumption on risk markers of chronic diseases have been recently reviewed.[80] Fewer studies, however, have considered yogurt and other cultured dairy foods that contain only the fermentation-associated microbes as controls. Several of these studies, which assessed the effect of yogurt consumption on glucose tolerance, are described below.

Results from several randomized, controlled trials have shown that probiotic yogurts are generally more effective than conventional yogurts for improving various health outcomes. In one study of 64 type 2 diabetic patients, the effect of probiotic and conventional yogurt consumption on blood glucose and antioxidant status was determined.[81] Compared with the conventional yogurt, the probiotic yogurt decreased fasting blood glucose and increased several measures of antioxidant status. Similar study designs were used to assess insulin resistance in pregnant women,[82] healthy obese women,[83] and patients with nonalcoholic fatty liver disease.[84] The results from all of these studies showed greater changes in serum insulin levels from baseline among individuals consuming probiotic yogurt compared with those consuming conventional yogurt. However, no differences in other physical or physiological changes, such as weight loss and blood pressure, were observed.

Relatively few human clinical studies that examined the effect of fermented vegetables or other fermented foods on health outcomes have been described in the literature.[71,85] In part, this is because many of these foods (eg, cruciferous vegetables or soybeans) have nutritional properties independent of fermentation and because fermented foods are ordinarily consumed at relatively low levels.[86] As noted above, however, kimchi is widely consumed in Korea. In a randomized, controlled study of 100 healthy Korean young adults, kimchi consumption resulted in improvements in fasting blood glucose and total cholesterol.[87] Another study with 22 overweight and obese adults showed that fermented kimchi consumption improved fasting blood glucose and other health parameters associated with metabolic syndrome.[88] Finally, similar improvements in obesity parameters (eg, decreased plasma triglyceride levels and triglyceride/high-density lipoprotein ratios) in obese adults were observed following daily consumption of a Korean fermented soybean-based red pepper paste called kochujang.[89]

THE SPECIAL CASE OF YOGURT AND LACTOSE MALABSORPTION

Lactose malabsorption is a condition characterized by the inability of certain individuals to digest lactose.[90] The condition is caused by the poor expression of the enzyme β-galactosidase (lactase), which is ordinarily produced and secreted by the enterocytes that line the small intestine. Although β-galactosidase is ordinarily synthesized during infancy in most individuals, expression of the enzyme is reduced after about 2 to 3 years of age,[91] resulting in a lactase-nonpersistence phenotype.[92] When β-galactosidase is not produced in sufficient levels, lactose remains undigested and passes into the large intestine, where it is fermented by colonic organisms, resulting in the formation of gases and acids and an increase in the osmotic load (Figure 3[93]).[91] The resulting symptoms can include diarrhea, gas, and bloating, leading many lactose-intolerant individuals to omit milk and dairy products from their diets.[94] Interestingly, some lactose-intolerant individuals can tolerate modest doses of lactose (up to 12 g), leading some researchers to suggest that the lactose intolerance threshold has been overestimated.[91] Nonetheless, perhaps as much as one-third of the US population and two-thirds of the world population suffer from lactose malabsorption.[95] Lactose digesters, in contrast, express β-galactosidase at sufficient levels such that most of the lactose is hydrolyzed within the jejunum. The resulting glucose and galactose are subsequently absorbed across the epithelial cells and eventually transported into the bloodstream.

Most lactose-intolerant individuals are able to eat yogurt without developing symptoms, and yogurt consumption is often recommended as a suitable dietary strategy for these individuals.[96] That yogurt, but not acidified milk or heat-treated yogurt, is tolerated by lactose-intolerant individuals suggests that the microbes in yogurt have a protective effect against lactose.[97–99] Specifically, the yogurt culture organisms *S thermophilus* and *L delbrueckii* subsp *bulgaricus* produce β-galactosidase as part of their lactose utilization pathway and can potentially improve lactose digestion in vivo.[100] Note that the lactose content is only partially reduced by the actual fermentation of yogurt, with most lactose remaining intact in the finished product. When yogurt is consumed, the live organisms, which contain intracellular β-galactosidase, presumably survive the acidic conditions in the stomach and reach the small intestine. There, they are likely permeabilized by bile acids, releasing β-galactosidase into the lumen.[7,101] Thus, the lactose is hydrolyzed by bacterial β-galactosidase and the monosaccharides are absorbed across the intestinal epithelium.

Several systematic reviews have reported that probiotic microorganisms, including *S thermophilus* and *L delbrueckii* subsp *bulgaricus*, vary in their ability to improve lactose digestion and reduce symptoms of lactose maldigestion.[102–104] The European Food Safety Authority also reviewed human clinical studies that assessed the effectiveness of yogurt in enhancing lactose digestion and reducing symptoms of lactose intolerance.[105] The expert panel reached the following conclusions: (1) there was "strong evidence for the biological plausibility of the effect"; and (2) a cause-and-effect relationship between yogurt consumption and improved lactose digestion was sufficiently established to warrant

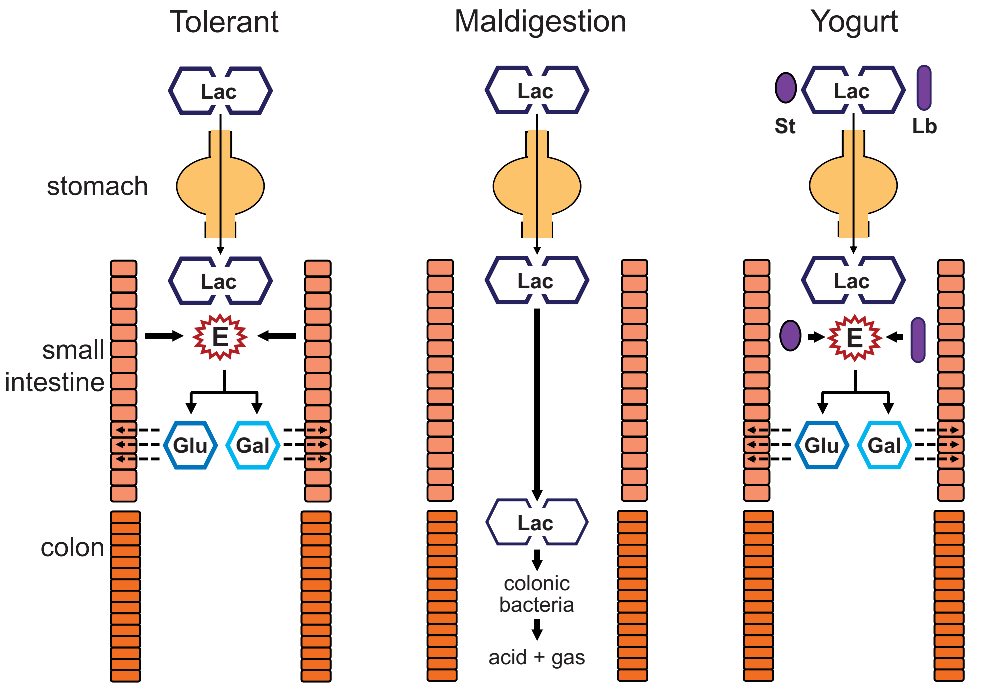

Figure 3 **Lactose digestion in lactose-tolerant individuals and in lactose maldigesters following yogurt consumption.** Lactose-tolerant individuals (left panel) hydrolyze lactose via β-galactosidase secreted in the small intestine, and the end products, glucose and galactose, are absorbed. Lactose maldigesters (center panel) do not secrete sufficient levels of β-galactosidase, and lactose reaches the colon intact, where it causes colonic distress (acid and gas). When yogurt is consumed (right panel), *Streptococcus thermophilus* (St) and *Lactobacillus delbrueckii* subsp *bulgaricus* (Lb) produce β-galactosidase in the small intestine, and lactose hydrolysis is restored. Adapted from Hutkins.[93] *Abbreviations*: E, β-galactosidase; Gal, galactose; Glu, glucose; Lac, lactose; Lb, *Lactobacillus delbrueckii* subsp *bulgaricus*; St, *Streptococcus thermophilus*.

a health claim, provided the yogurt contained at least 10^8 colony-forming units (CFU) per gram.

Interestingly, sour cream and cultured buttermilk contain comparable levels of lactose. These, as well as other fermented dairy products, are made using cultures containing mesophilic species of *Lactococcus* and *Leuconostoc*, yet neither is well tolerated by lactose-intolerant individuals.[106,107] This is evidently because these bacteria do not express β-galactosidase. Instead, lactococci metabolize lactose via a β-galactosidase-independent pathway.[108] Specifically, they express the enzyme phospho-β-galactosidase, whose substrate is lactose phosphate. Lactose phosphate is formed via a phosphotransferase pathway that phosphorylates lactose during its transport across an intact cell membrane. Thus, free lactose is not hydrolyzed by this enzyme.

CONCLUSION

Hygienic lifestyles and diets low in fermented foods are among the factors that have likely reduced exposure to environment- and food-associated microbes and may contribute, in part, to intestinal dysbiosis.[109] The hypothesis that diets rich in fermented foods containing live organisms could redress a dysbiotic intestinal microbiota is an attractive proposition, but it is not new. More than 100 years ago, the Nobel laureate Ilya Metchnikoff wrote the following prescient passage: "The dependence of the intestinal microbes on the food makes it possible to adopt measures to modify the flora in our bodies and to replace the harmful microbes by useful microbes."

However, as Metchnikoff also noted, the absence of suitable methods was a major challenge. "Unfortunately, our actual knowledge of the intestinal flora is still very imperfect because of the impossibility of finding artificial media in which it could be grown. Notwithstanding this difficulty, however, a rational solution of the problem must be sought."

In 2018, these impediments no longer exist, and the microbiomes from gastrointestinal as well as food environments are now routinely surveyed. Indeed, as Veiga et al[18] recently noted, the role of food- or fermentation-derived microbes in promoting gut and systemic health has likely been under-reported because of methodological limitations. Humans have been estimated to ingest as many as 10^9 to 10^{12} CFU per day.[23,110] Although this amount includes microbes from a range of food sources, diets rich in fermented foods likely contribute a large portion of the total.[59] Evidence is accumulating that the allochthonous bacteria in fermented foods, despite their transient occurrence in the gastrointestinal tract, can nonetheless influence the resident microbiome and exert host-specific health benefits.[19,23,59]

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