



HAL
open science

Yogurt: microbiology, organoleptic properties and probiotic potential

Francoise Rul

► **To cite this version:**

Francoise Rul. Yogurt: microbiology, organoleptic properties and probiotic potential. Fermented Foods, Part II: Technological Interventions, CRC Press, 525 p., 2017, Food Biology Series, 9781138637849. <hal-01579303>

HAL Id: hal-01579303

<https://hal.science/hal-01579303v1>

Submitted on 30 Aug 2017

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons CC BY-SA 4.0 - Attribution - ShareAlike - International License



Yogurt

Microbiology, Organoleptic Properties and Probiotic Potential

Françoise Rul

1. Introduction: An Ancestral Fermented Food with an Expanding Contemporary Market

Fermentation has been used for thousands of years to preserve food. Thanks to the acidifying activity of bacteria, the shelf life of milk is increased because the growth of undesirable microorganisms is prevented.

Traces of fermented milk products appear rather quickly after the emergence of agriculture, as early as 8,000 B.C. in Turkey and Eastern Europe. Based on the presence of milk lipids recently discovered on pottery shards, the inhabitants of what is now modern-day Libya were consuming fermented dairy products around 7,000 B.C. (Dunne et al. 2012). Traces of kefir have also been detected on a Bronze Age mummy in China (Yang et al. 2014). Yogurt seems to make an appearance around 5,000 B.C. and was discovered by nomadic peoples living in the Middle East. It has been consumed for thousands of years by different civilizations. “Yogurt” comes from the Turkish word “yogurtmak,” which means to thicken, coagulate, or curdle.

In France, yogurt appears around 1542. King Francis I, who suffered from chronic diarrhea, was cured by eating yogurt. In 1905, Stamen Grigorov, a Bulgarian medical student studying in Geneva, Switzerland, was the first to describe the spherical and rod-shaped lactic acid bacterium that is found in Bulgarian yogurt; the species was named *Bacillus bulgaricus*. Then, in the 20th century, Russian Nobel laureate Elie Metchnikoff, a scientist at the Pasteur Institute in Paris, hypothesized that Bulgarians lived unusually long lives because they regularly consumed yogurt; his research helped make yogurt popular in Europe and served as the foundation for the field of probiotics, which is still growing a century later.

Another major event in yogurt's history was the food's transformation into a commercial product by Isaac Carasso in 1919, in Barcelona, Spain. Yogurt's commercialization was taken further by Danone, a private company, and the food was industrialized and spread throughout Europe starting in the 1960s.

A traditional food that is consumed on a daily basis in the Middle East and Europe, yogurt is currently expanding its market across the globe. Demand has grown dramatically in North and South America, as well as in Asia (>100% between 2000 and 2010 for yogurt and fermented dairy products; Mikkelsen 2013). At present, more than 30% of the world's population eats yogurt, and worldwide yogurt consumption has hit around 15 million tons per year. The global yogurt market was projected to surpass \$65 billion in 2015 (www.strategyr.com). Traditional yogurts—produced at small scales—currently coexist with industrially produced yogurts, and we are seeing renewed interest in homemade foods. Yogurt's nutritional value and healthful properties are universally recognized. The food has a positive market image, attributable to its specific organoleptic properties (fresh taste, sourness, unique aroma), which has improved following the discovery of its probiotic properties and society's movement toward greater health consciousness.

Producing yogurt requires milk to acidify, whereupon curds are formed. This acidification process, which has to be rapid in industrial settings, largely depends on the growth and activity of bacteria that produce lactic acid by fermenting lactose. The association between the two yogurt lactic acid bacteria (LAB) *Streptococcus thermophilus* (*S. thermophilus*) and *Lactobacillus delbrueckii* ssp. *bulgaricus* (*Lb. bulgaricus*) is regarded as a proto-cooperation because it is beneficial for both species, but each bacterium can grow alone in milk (Tamime and Robinson 1999). This proto-cooperation has industrial importance because it can improve yogurt's properties, such as the texture (*via* exopolysaccharide production; Bouzar et al. 1997), the acidification rate (Pette 1950c, Moon and Reinbold 1976, El-Soda et al. 1986, Amoroso et al. 1988, Beal and Corrieu 1991, Bautista et al. 1996), and the flavor (*via* the production of aromatic compounds; Hamdan et al. 1971, Bottazzi et al.

1973, El-Abbassy and Sitohy 1993, Courtin and Rul 2004). This association at least partly relies on metabolite exchanges and involves elements of competition (for the nutrients in the milk) and mutualism (the fellow bacterium synthesizes and hydrolyzes metabolites).

In 1984, the FAO/WHO defined yogurt as “the coagulated milk product obtained by lactic acid fermentation through the action of *Lactobacillus delbrueckii* ssp. *bulgaricus* (*Lb. bulgaricus*) and *Streptococcus thermophilus* from milk and milk products. The microorganisms in the final product must be viable and abundant.” If other bacteria are added, such as probiotics (e.g., *Bifidobacteria*, *Lactobacilli* spp.), the product must be called “fermented milk” and cannot carry the yogurt label. The Codex Alimentarius entry for fermented milk (Codex STAN 243-2003) specifies that yogurt should contain a minimum of 2.7% (m/m) milk proteins, a maximum of 15% milk fat, a minimum of 0.6% titratable acidity (expressed as % of lactic acid), and a minimum of 10^7 CFU/g of microorganisms (total microorganisms in the starter culture). Yogurt has highly attractive nutritional properties—it is low in calories (around 90 kcal per serving) but contains enough macro- and micronutrients (proteins, fatty acids, calcium, phosphorus, and vitamins) to cover a person’s daily needs.

The purpose of this chapter is to provide an overview of the nature of such bacterial associations in yogurts, describe the interactions among the bacteria involved, and detail how bacterial metabolic activities impact the properties of the end product. We will focus on traditional yogurts; yogurts or fermented milk products that contain probiotic species (such as *Bifidobacterium* or *Lactobacillus* spp.), stabilizers, added aromas, or other additives will not be discussed.

2. A Fermented Food Originating in a Mutually Beneficial Association between Two Thermophilic LAB Species

2.1 How Yogurt Bacteria Grow Together in Milk

Typically, yogurts are produced at temperatures around 42°C, which promotes the optimal growth of both *S. thermophilus* and *Lb. bulgaricus*. When milk is inoculated with these two bacteria, they usually grow in succession and *S. thermophilus* presents diauxic growth (Tamime and Robinson 1999, Courtin et al. 2002, Letort et al. 2002, Courtin and Rul 2004, Sieuwerts et al. 2010; Fig. 1). *S. thermophilus* first grows exponentially (for the first 90 to 120 min) and then experiences a short latency period. *Lb. bulgaricus* stays at inoculation levels. *S. thermophilus* subsequently resumes growth, albeit at a reduced rate, and *Lb. bulgaricus* starts to grow exponentially. As the milk becomes acidified, reaching a pH of around 5.2, *S. thermophilus* stops growing. In contrast, the growth of *Lb. bulgaricus* continues until

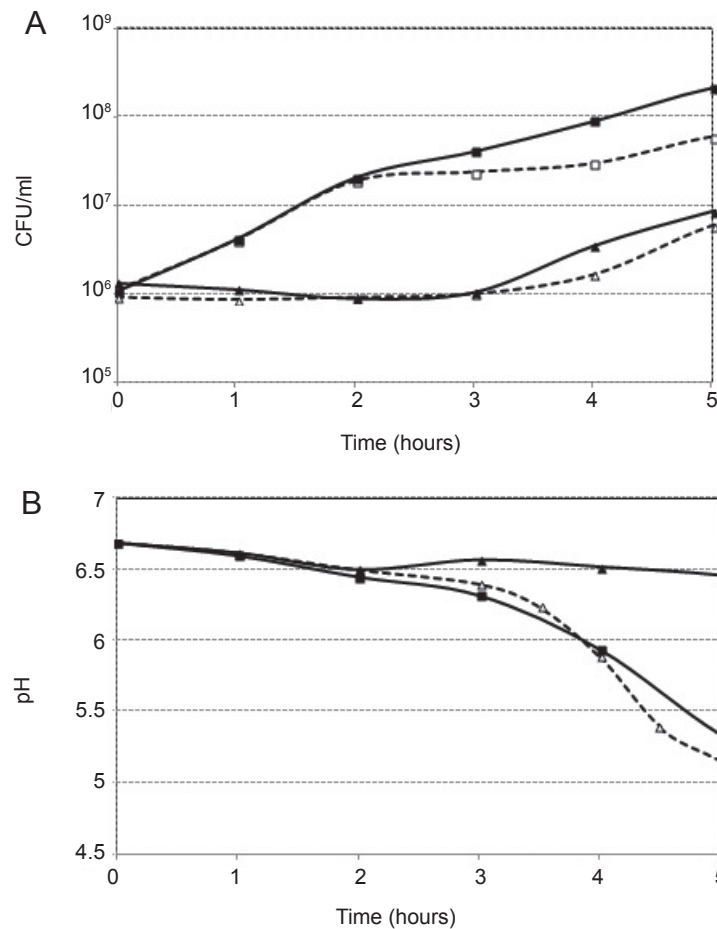


Figure 1. (A) Growth curves of *S. thermophilus* CNRZ385 in pure cultures (□) or co-cultures (■) and of *Lb. bulgaricus* CNRZ398 in pure cultures (▲) or co-cultures (△); cultures were grown in microfiltered milk (Marguerite®).

(B) Acidification curves of milk inoculated with *S. thermophilus* CNRZ385 (■), *Lb. bulgaricus* CNRZ398 (▲), or both bacteria (△).

pH levels drop to around 4.4 (Beal and Corrieu 1991). The acidification curves usually correlate well with these growth patterns (Fig. 1). The first round of acidification corresponds to *S. thermophilus*' period of exponential growth; during the latency period, there is a slowdown in acidification. Then, acidification accelerates with the tandem growth of both bacteria.

Lb. bulgaricus is better than *S. thermophilus* at handling the acidic environment, possibly partly because it can transform ornithine into putrescine, which raises the intracellular pH (Azcarate-Peril et al. 2004).

Despite *S. thermophilus*' greater sensitivity to acidity, this bacterium generally has a numerical advantage over *Lb. bulgaricus* by the end of fermentation (Pette and Lolkema 1950a, Beal et al. 1994, Courtin and Rul 2004, Herve-Jimenez et al. 2008, Ben-Yahia et al. 2012), even when *Lb. bulgaricus* starts off at a higher inoculum level (Béal and Corrieu 1991). This advantage is strain dependent and can be partly explained by the fact that *Lb. bulgaricus* has stricter nutritional requirements. Also, *S. thermophilus* is probably a better competitor than *Lb. bulgaricus* in milk.

2.2 What Genome Analyses Tell us About the (Co)evolution of the Two Yogurt Bacteria?

Growth in yogurt involves several metabolic activities that bacteria have conserved and/or re-enforced over the course of evolution and that are directly related to milk composition. The physiology and metabolic activity of these two LABs have been studied for decades. More recently, the advent of sequencing and post-genomic tools has resulted in a better, more complete picture of how these bacteria evolved and how they have adapted to milk. Analysis of the genomes of *S. thermophilus* and *Lb. bulgaricus* suggests that the two bacteria have coevolved, which has resulted in optimized joint growth. Horizontal gene transfers (HGTs) may be taking place between the two: exopolysaccharide (EPS) genes may be moving from *S. thermophilus* to *Lb. bulgaricus*, and conversely, the *cbs-cblB-cysE* gene cluster—which is involved in sulfur amino acid metabolism—may be moving from *Lb. bulgaricus* or *Lb. helveticus* to *S. thermophilus* (Liu et al. 2009). In the case of *S. thermophilus*, these HGTs could result from the bacterium's natural competence (Gardan et al. 2009) and has allowed the transfer among *S. thermophilus* strains, of the cell-wall protease PrtS, which is essential for growth in milk (see below; Dandoy et al. 2011). In addition, genome analysis suggests that yogurt bacteria have undergone reductive evolution (Bolotin et al. 2004, Makarova et al. 2006): their “domestication” in milk has led to metabolic simplification and specialization. More specifically, among the Lactobacillaceae, the two yogurt LABs have the highest number of pseudogenes, frameshift mutations, nonsense mutations, and deletions (around 10%; Bolotin et al. 2004, Makarova et al. 2006, Goh et al. 2011), leading to a loss of functional genes.

2.3 Yogurt Bacteria are Metabolically Well Adapted to the Composition of Milk

The growth of *S. thermophilus* and *Lb. bulgaricus* in milk largely depends on their ability to efficiently use the medium's major carbon and nitrogen sources (lactose and caseins, respectively), as well as to synthesize any

growth-limiting nucleotide bases that are lacking. These metabolic traits are key for the bacteria's associated growth and thus have a major impact on the properties of the resulting yogurt; they will be discussed further below. Furthermore, *S. thermophilus* produces CO₂ (Driessen et al. 1982, Tinson et al. 1982, Spinnler et al. 1987, Ascon-Reyes et al. 1995), which stimulates the growth of *Lb. bulgaricus*. The CO₂ comes from the decarboxylation of urea—present in milk—by urease (Tinson et al. 1982), which most *S. thermophilus* strains possess (Juillard et al. 1988). Other factors also influence the specifics of this association, such as the production of deleterious compounds like lactate, H₂O₂, or bacteriocins; however, they will not be discussed here.

2.3.1 Lactose metabolism

The main source of carbohydrates in milk is lactose. Because it is still present at high concentrations (around 40 g/L) at the end of fermentation, it is not growth limiting for yogurt bacteria and thus does not directly fuel competition. Yogurt bacteria prefer lactose over other simple sugars, such as glucose or sucrose, as a carbon source (Chervaux et al. 2000, Goh et al. 2011, Thomas et al. 2011), probably because both organisms possess an efficient lactose/galactose antiporter LacS. Lactose is imported into the bacteria and hydrolyzed by β-galactosidase (LacZ) into two compounds: galactose, which is largely exported by LacS permease, and glucose, which feeds the glycolysis pathway. The galactose moiety of lactose is not used by most *S. thermophilus* strains, mainly because they have low galactokinase activity (Vaughan et al. 2001, Vaillancourt et al. 2004) or low levels of induction of the galactose promoter (Van den Bogaard et al. 2004). However, when growth conditions become difficult (e.g., lactose is limited and galactose is present at high concentrations), galactose can be used (Terence and Vaughan 1984, Hutkins et al. 1985, Levander et al. 2002).

Lactose utilization is chromosomally encoded in both yogurt bacteria, which ensures that this trait is maintained. In contrast, it is plasmid encoded in other LABs, such as *Lactococcus lactis*, and is thus less stable. Pyruvate, the end product of glycolysis, is then converted into (L- and D-) lactate, which is excreted, leading to milk acidification. This process is mediated by L-lactate dehydrogenase (L-Ldh) in *S. thermophilus* and by D-lactate dehydrogenase (D-Ldh) in *Lb. bulgaricus*. Even if L-Ldh genes are present in the *Lb. bulgaricus* genome, 90% of pyruvate is nonetheless converted into D-lactate.

2.3.2 Nitrogen metabolism

Optimal bacterial growth depends on efficient protein synthesis and, as a result, on the availability of amino acids (AAs). LABs are auxotrophic

for amino acids: one to several in *S. thermophilus* strains (Hols et al. 2005, Pastink et al. 2009) and 15–20 in *Lb. bulgaricus* strains, which are only able to synthesize 3–4 AAs (Asp, Asn, Thr, +/- Lys; Van de Guchte et al. 2006, Hao et al. 2011).

Milk is poor in nitrogen compounds that can be directly assimilated by LABs (free amino acids and short peptides), but yogurt bacteria possess a complex and efficient proteolytic system that provides them with exogenous nitrogen sources stemming from milk proteins. This multiprotein system has been extensively studied (for reviews, see Christensen et al. 1999, Savijoki et al. 2006, Liu et al. 2010). It is able to hydrolyze caseins—the major proteins in milk. It transports the resulting oligopeptides into the cells and then degrades them into smaller oligopeptides and AAs. The system is composed of a cell-wall protease (Prt), various AA and peptide transporters, and several peptidases, mostly intracellular, the coordinated action of which leads to the recovery of free AAs for protein synthesis (Fig. 2).

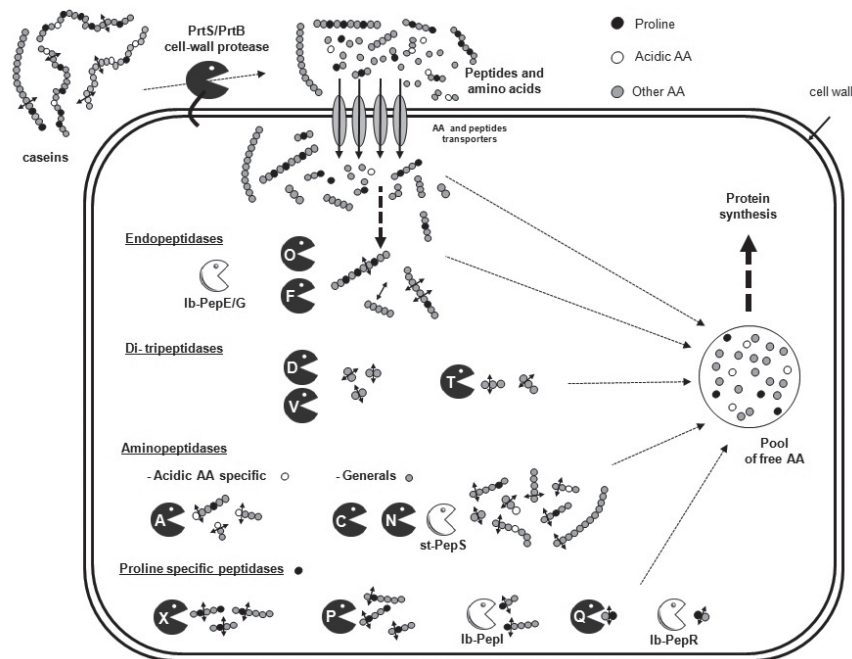


Figure 2. The proteolytic system of *S. thermophilus* and *Lb. bulgaricus*.

●: protease/peptidase common to the two bacteria
 ○: bacterium-specific peptidase; “st” stands for *S. thermophilus* and
 “lb” for *Lb. bulgaricus*

Lb. bulgaricus has higher overall levels of proteolytic activity than *S. thermophilus* (Shankar and Davis 1978, Rajagopal and Sandine 1990, Courtin and Rul 2004). It liberates most of the AAs (Courtin and Rul 2004) that stimulate *S. thermophilus* growth, including valine, histidine, glycine, leucine, isoleucine, methionine, and various dipeptides (Pette and Lolkema 1950b, Bautista et al. 1966, Accolas et al. 1971, Bracquart et al. 1978, 1979, Shankar and Davies 1978, Radke-Mitchell and Sandine 1984, El-Soda et al. 1986, Rajagopal and Sandine 1990, Courtin and Rul 2004). Levels of overall proteolytic activity in *Lb. bulgaricus* vary among strains and differentially promote the growth of *S. thermophilus* when the two bacteria are associated in milk (Courtin and Rul 2004).

Cell-wall protease—PrtB in *Lb. bulgaricus* and PrtS in *S. thermophilus*—plays a major role in stimulating growth in milk because it initiates the breakdown of caseins into various oligopeptides. PrtS is often absent from older strains of *S. thermophilus* (Shahbal et al. 1991) but is frequently found in more recent industrial strains. Prt is particularly important in allowing *Lb. bulgaricus*, which is poorly equipped for AA synthesis (see above), to grow in milk; PrtS- or PrtB-negative mutants develop more slowly than do wild-type strains (Gilbert et al. 1997, Courtin et al. 2002). The PrtS-encoding gene was probably acquired *via* HGT from a species related to *S. suis* (Delorme et al. 2010), and it can be transferred by natural competence to other *S. thermophilus* strains (Dandoy et al. 2011). The expression of PrtS is induced during the latency period (Letort et al. 2002), most probably because available peptides are lacking. In co-cultures, the following are true: (i) PrtB gene expression is probably induced by the presence of *S. thermophilus*, which reduces the peptides available to *Lb. bulgaricus* (as compared to pure cultures; Sieuwerts et al. 2010), and (ii) PrtS is no longer essential to *S. thermophilus* growth if *Lb. bulgaricus* PrtB is present. Indeed, PrtB may be more efficient than PrtS in making nitrogen available because when PrtB-positive *Lb. bulgaricus* strains co-occur with PrtS-negative *S. thermophilus* strains, *S. thermophilus* populations are larger than when PrtS-positive *S. thermophilus* strains co-occur with PrtB-negative *Lb. bulgaricus* strains (Courtin et al. 2002). We also cannot rule out the possibility that the casein-hydrolyzation specificities of PrtB and PrtS are different. For example, the substrate-binding region, which influences Prt specificity, differs between PrtS (Fernandez-Espla et al. 2000) and PrtB (Gilbert et al. 1996).

Yogurt bacteria also possess different transport systems—for AAs, dipeptides, tripeptides, and oligopeptides (the latter have been extensively studied in LABs; for a review, see Savijoki et al. 2006)—that can efficiently target nitrogenous compounds in the medium. *Lb. bulgaricus* lacks the general DtpT di/tri-peptide transporter found in *S. thermophilus*, but its absence may be compensated for by a Dpp transporter that preferentially takes up hydrophobic di/tripeptides. Some *S. thermophilus* transport systems are upregulated in co-cultures, including the oligopeptide carrier

Ami/Opp (Sieuwert et al. 2010) and potential polar AA transporters (Hervé-Jimenez et al. 2009).

S. thermophilus and *Lb. bulgaricus* have a similar number of protease/peptidase genes (44 [Hols et al. 2005] vs. 45–49 [Hao et al. 2011, Zheng et al. 2012], respectively). Around a dozen have been studied to determine their roles in nitrogen metabolism (Fig. 2). They were found to have various peptide hydrolysis specificity and, *a priori*, are sufficient to meet bacterial needs for AAs. There are even peptidases dedicated to hydrolyzing proline-containing peptide bonds, which are difficult to break down but essential for casein degradation as caseins are rich in proline.

One group of AAs is particularly important in allowing yogurt bacteria to grow in milk: branched-chain AAs (BCAAs), arginine, and cysteine (Bracquart and Lorient 1977, Garault et al. 2000). These AAs are predicted to be among the most common in proteins of *S. thermophilus* (Hervé-Jimenez et al. 2009) and *Lb. bulgaricus* (Sieuwert et al. 2010); in contrast, they are largely lacking from caseins and the two bacteria probably compete for these AAs. This fact may explain why *S. thermophilus* and *Lb. bulgaricus* increases BCAA and arginine biosynthesis, and BCAA permease activity, respectively, in co-cultures as compared to in pure cultures. In addition, when the two yogurt bacteria co-occur in milk, there is an increase in activity along the serine-to-methionine and cysteine-conversion pathways, as compared to in pure cultures (Sieuwert et al. 2010). Finally, *S. thermophilus* and *Lb. bulgaricus* possess the necessary peptidolytic and transport pathways for casein exploitation; they hydrolyze caseins into free amino acids, thus fulfilling their protein synthesis needs. When the two bacteria co-occur in milk, they both compete and complement each other in terms of their nitrogen metabolisms.

2.3.3 Formate, folate, and purine metabolism

Some of the first metabolic exchanges described in *S. thermophilus* and *Lb. bulgaricus* associations in milk were interactions involving folic acid (Rao et al. 1984, Sybesma et al. 2003), pyruvic acid (Higashio et al. 1978), formic acid (Veringa et al. 1968), and CO₂ (Driessen et al. 1982). These compounds all fed, directly or indirectly, into the purine biosynthesis pathway (Fig. 3). Formate is necessary for the synthesis of purine bases (i.e., xanthine, adenine, and guanine) that are nucleic acid precursors (Suzuki et al. 1986); both yogurt bacteria require it to grow (Galesloot et al. 1968, Suzuki et al. 1986, Derzelle et al. 2005, Horiuchi and Sasaki 2012, Nishimura et al. 2013).

Depending on the strain, *Lb. bulgaricus* gains a boost in growth at formate concentrations ranging from 0.5 to 27 mM (Galesloot et al. 1968, El-Abbassy et al. 1993, Horiuchi and Sasaki 2012). In addition, Courtin and Rul (2004) showed that formate concentrations decreased more strongly in

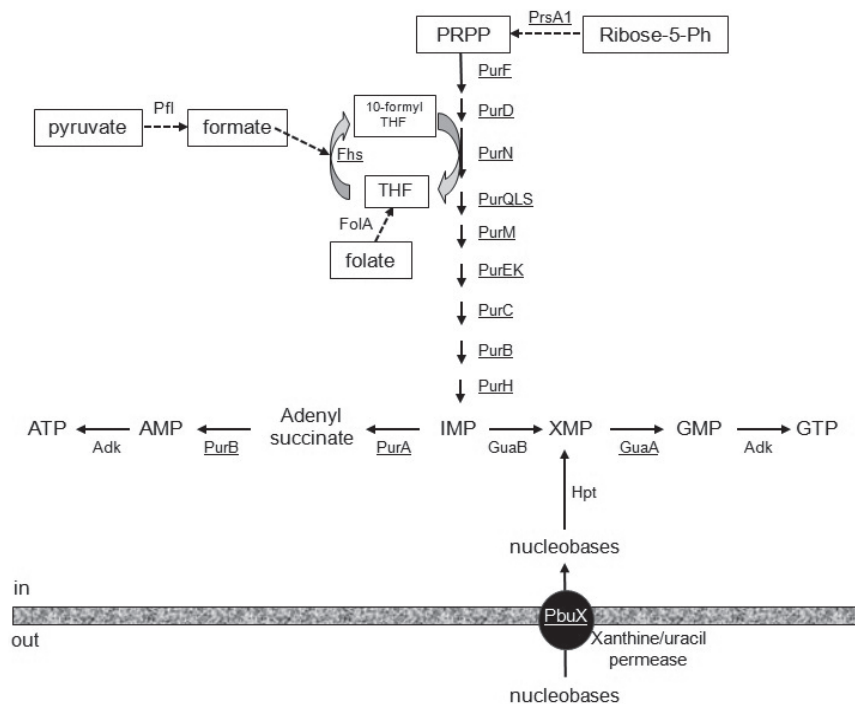


Figure 3. Purine pathway in *S. thermophilus*.

Underlined proteins are proteins or their corresponding genes that were less abundant or repressed during the growth of *S. thermophilus* in co-culture in milk with *Lb. bulgaricus* (data from Hervé-Jimenez et al. 2009).

milk co-cultures than in pure *S. thermophilus* cultures; they differed by a factor of 4 to 8, depending on the *Lb. bulgaricus* strain present and probably because of the latter's consumption of formate.

Pyruvate formate lyase (Pfl), which converts pyruvate into formate, is abundantly expressed in *S. thermophilus* and is induced when the species is grown in milk (as compared to when it is grown in M17-rich medium; Derzelle et al. 2005). If formate (5 mM) or purines (adenine and guanine, 50 μ M) are added to the milk, Pfl is no longer overexpressed, and *S. thermophilus* experiences a boost in growth (Derzelle et al. 2005). In contrast, Pfl is absent from the *Lb. bulgaricus* genome (Van de Guchte et al. 2006). In several bacterial species, Pfl activity is oxygen sensitive (Knappe et al. 1974, Yamada et al. 1985, Sawers and Watson 1998). It has recently been suggested that, in *S. thermophilus*, oxygen conversion by NADH oxidase (NOX) could improve growing conditions, by promoting Pfl activity and, as a consequence, formate synthesis (Horiuchi and Sasaki 2012). Interestingly, when added to milk, formate stimulates EPS production in *Lb. bulgaricus*

by a factor of 4, which may be a mechanism contributing to improved growth as well as to enhanced cell-wall synthesis and bacterial division (Nishuimura et al. 2013).

Thanks to post-genomic approaches, it has been discovered that the purine biosynthesis pathway in *S. thermophilus* slows down in co-cultures; almost all the enzymes involved become less abundant or are expressed at lower levels (Hervé-Jimenez et al. 2009) (Fig. 3). This result was unexpected because the pathway is ramped up when the bacterium is grown in pure cultures (Hervé-Jimenez et al. 2008), confirming that purines are essential for *S. thermophilus*' growth in milk. One might hypothesize that, in co-cultures, purines or purine precursors are supplied by *Lb. bulgaricus*; indeed, a potential xanthine/uracil permease (a transporter of purine precursors) was expressed at higher levels when *S. thermophilus* was associated with *Lb. bulgaricus* (Hervé-Jimenez et al. 2009). However, a more recent post-genomic study of yogurt bacteria associations (Sieuwerts et al. 2010) showed that, when fermentation times were similar (around 5 h), purine synthesis and folate cycling pathways were upregulated in *S. thermophilus*, while folic acid and purine synthesis were downregulated in *Lb. bulgaricus*. These contradictory results underscore the importance of milk type and strain identity, as they differed in the two studies (skim milk vs. μ -filtered milk and strains CNRZ1066-ATCC BAA-65 vs. LMG18311-ATCC11842, respectively). However, yogurt bacteria need to utilize purines to grow in milk, and the process can be modulated. It is assumed that *S. thermophilus* supplies *Lb. bulgaricus* with the compounds needed for purine biosynthesis, such as formate, a precursor, and folic acid, which is a co-factor and produced in co-cultures (Crittenden et al. 2002). In turn, *Lb. bulgaricus* may provide *S. thermophilus* with other purine precursors.

The proto-cooperative association of the two yogurt bacteria has been studied for years (for a review see Sieuwerts et al. 2008), but new genomic and post-genomic approaches have made it possible to gather more detailed knowledge about the general and specific metabolic mechanisms involved (Fig. 4). They have revealed new, entirely unexpected interactions and exchanges. For instance, iron metabolism in *S. thermophilus* (Hervé-Jimenez et al. 2009) and fatty acid metabolism in *Lb. bulgaricus* (Sieuwerts et al. 2010) are modulated when the bacteria are grown in milk co-cultures, but not when they are grown in pure cultures. It has become clear that the association is the sum of a variety of bacterial interactions, both positive ones, such as mutualism and commensalism, as well as negative ones, such as competition and amensalism.

These new findings are crucial when it comes to designing and selecting novel compatible and complementary strains and strain cocktails with specific properties, with a view to creating tailored dairy products or developing entirely new foods.

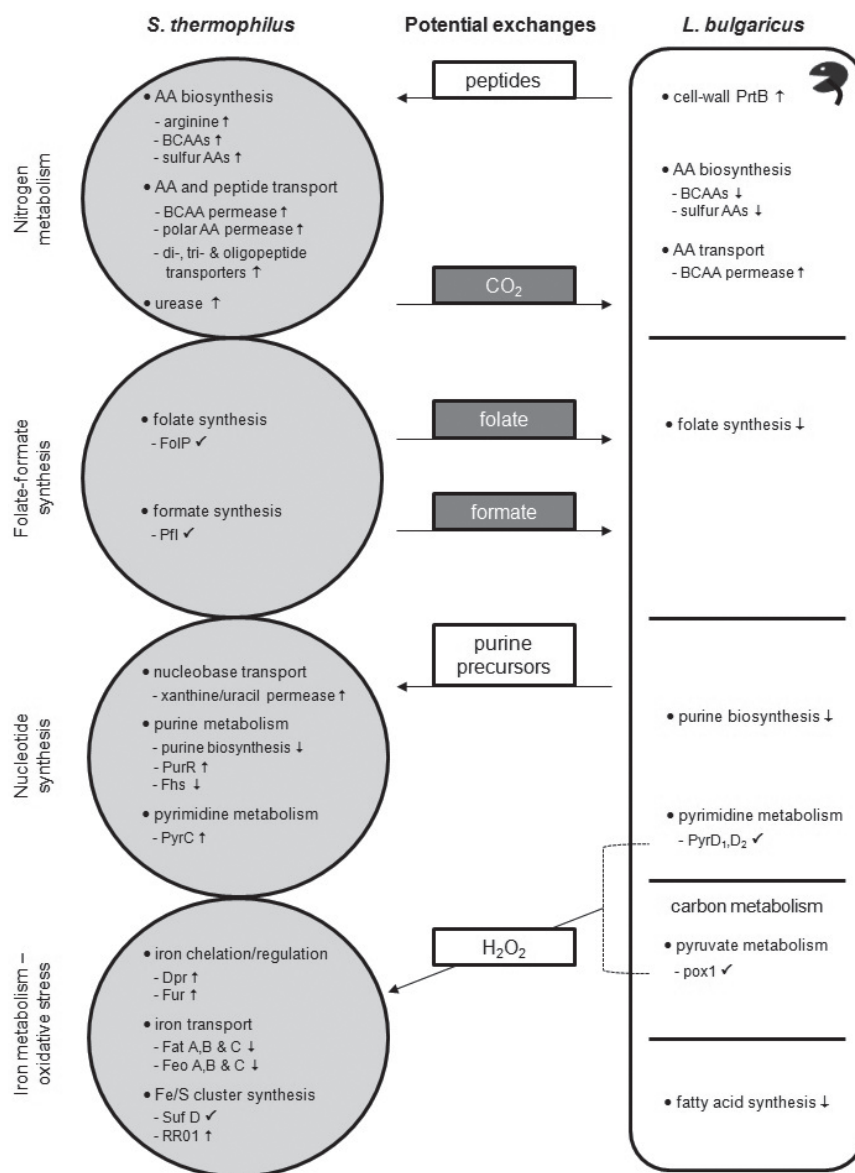


Figure 4. Metabolite exchanges between the two yoghurt bacteria, in particular regarding the metabolism pathways that were modulated during their co-culture in milk.

↑, ↓: Proteins or genes that, respectively, were more or less abundant or expressed during the co-culture.

✓: Proteins or genes that were present or expressed without quantitative variation during the co-culture.

3. A Fermented Food with Typical Organoleptic Characteristics

3.1 The Flavor of Yogurt Arises from a Complex Mix of Aroma Compounds Produced by LABs

More than 100 different aroma compounds have been identified in yogurt (Ott et al. 1997, Cheng 2010), as a result of GC (gas chromatography) and GC-MS (gas chromatography-mass spectrometry) analyses, which are sometimes coupled with human olfactory assays (GC-sniffing or GC-olfactory detection) (Ott et al. 1997, Friedrich and Acree 1998). However, most are present at very low concentrations; only a few occur at significant levels. The flavor we typically associate with yogurt comes from its acidity (i.e., the presence of lactic acid) (Ott et al. 2000b). It is also influenced by different carbonyl compounds that were identified quite some time ago and that result from the proteolysis and degradation of amino acids into alcohol, aldehydes, and esters. These compounds are mainly acetaldehyde, acetoin, diacetyl, and 2,3-pentanedione, which are, for the most part, produced by bacterial metabolic activity (Fig. 5). Their production and/or accumulation in milk in co-cultures is strain dependent because, for

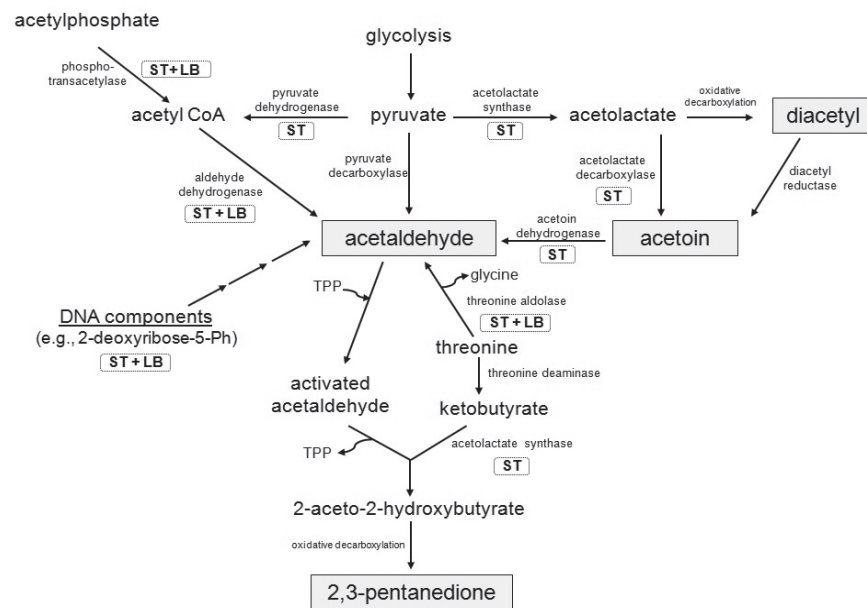


Figure 5. Production pathways of the main aroma compounds found in yogurt bacteria. ST, LB, and ST + LB indicate that the gene or enzyme is present in *S. thermophilus*, *Lb. bulgaricus*, and *S. thermophilus* and *Lb. bulgaricus* together, respectively.

example, when a given strain of *S. thermophilus* co-occurs with different strains of *Lb. bulgaricus*, different levels of acetaldehyde, acetoin, or diacetyl are generated (Courtin and Rul 2004). Their levels do not vary significantly when yogurt is stored at 4°C.

Acetaldehyde is the most typical yogurt flavor component (Pette and Lolkema 1950c, Dumont and Adda 1973, Law 1981) and is responsible for the food's fresh and fruity notes (e.g., hints of green apple and nuts). It is usually found at concentrations of 1 to 25 mg/L (Hamdan et al. 1971, Bottazzi et al. 1973, Rysstad and Abrahamsen 1987, Kneifel et al. 1992, Beshkova et al. 1998). The accumulation of acetaldehyde as yogurt fermentation progresses could be related to the bacteria's limited ability to use it (as hypothesized by Manca de Nadra et al. [1988]) and convert it into ethanol, as other LABs do (Lees and Jago 1976, Chaves et al. 2002).

Acetaldehyde can be produced in several ways: via pyruvate decarboxylation (from DNA) and via alcohol dehydrogenation (Fig. 5). However, the acetaldehyde found in yogurt bacteria probably mainly stems from the transformation of the amino acid threonine (Thr) into glycine (Gly) and acetaldehyde by threonine aldolase (Lees and Jago 1976, Raya et al. 1986, Ott et al. 2000a, Chaves et al. 2002). A threonine aldolase has been purified and characterized in *Lb. bulgaricus* (Manca de Nadra et al. 1987), and there is evidence for its involvement in flavor development (Marshall and Cole 1983). It is inhibited by the presence of glycine, via pH dependent way (Manca de Nadra et al. 1987), similarly to the threonine aldolase found in *S. thermophilus* (Marranzini et al. 1989). When threonine is added to milk, acetaldehyde production in *S. thermophilus* increases (Chaves et al. 2002, Ozer and Atasoy 2002); additionally, the higher Thr to Gly ratio generally enhances acetaldehyde production by both bacteria (Marranzini et al. 1989). Depending on the strain, decarboxylase or aldehyde dehydrogenase activity, which results in acetaldehyde production (Fig. 5), may or may not be present (Lees and Jago 1976 and Raya et al. 1986, respectively).

Apart from acetaldehyde, the other essential aroma compounds are diacetyl, acetoin, and 2–3 pentanedione, which give yogurt its buttery note. Diacetyl is also responsible for yogurt's full, delicate flavor (Rasic and Kurmann 1978); it occurs at concentrations of 0.2 to 3 mg/L (Cheng 2010) and is produced by both yogurt bacteria (Dutta et al. 1973, Rasic and Kurmann 1978). Production of 2–3 pentanedione is ramped up 3 to 5 fold in co-cultures, as compared to its combined production by each bacterium considered separately (1 mg/kg; Imhof et al. 1995).

While diacetyl and acetadehyde are the main compounds that define yogurt's flavor (Ott et al. 1997, Friedrich and Acree 1998), the ratio between the different aromatic compounds matters more than their individual concentrations (Pette and Lolkelma 1950c, Bottazzi and Vescoso 1969). For example, Bottazzi and Vescoso (1969) observed that a stronger flavor was

obtained when the acetaldehyde-to-acetone ratio was 2.8:1 but not when it was 0.4:1. Diacetyl takes on greater importance when the acetaldehyde concentration is low (Groux 1973, Rysstad and Abrahamsen 1987). Although a 1:1 ratio of acetaldehyde to diacetyl yields the preferred, typical yogurt's flavor associated with yogurt (Bottazzi and Dellaglio 1967, Zourari and Desmazeaud 1991), ratios of 7–10:1 can nonetheless create a “good” flavor (Beshkova et al. 1988). In addition, some low-acetaldehyde yogurts present a typical aroma (Hamdan et al. 1971, Groux 1973), possibly thanks to the presence of diacetyl (Kneifel et al. 1992).

Genome analysis has revealed that *Lb. bulgaricus* is probably poorly equipped to produce the aroma compounds mentioned above (Hao et al. 2011). *S. thermophilus* possesses several aminotransferases that convert Asp, aromatic AAs, or BCAAs into flavor compounds and produces alpha ketoglutarate from glutamate dehydrogenase, thus helping generate different volatiles (Pastink et al. 2009).

Finally, yogurt flavor results from a subtle balance between the main flavor compounds, which stem from bacterial proteolytic processes, and from fatty-acid derivatives (Turcic et al. 1969, Dumont and Adda 1973, Beshkova et al. 1998).

3.2 The Texture of Yogurt Results from the Acidification Capacity and Exopolysaccharide Production of LABs

In addition to its unique flavor, yogurt also has a very specific texture, which plays an important role in gustative quality. This texture is largely a function of bacterial activities: the acidification of milk leads to the formation of a coagulated gel and the production of EPSs creates a matrix which participates in shaping yogurt texture.

During milk fermentation, pH drops, and when it reaches the isoelectric point of the caseins (pH of 4.6), the latter precipitate and then aggregate, generating a gel network in which water and fat are embedded. The firmness and viscosity of the curd ultimately depend on the final pH, as well as on bacterial proteolytic activity, which can result in syneresis (Marshall 1987) and change the structure or microstructure of the yogurt.

S. thermophilus and *Lb. bulgaricus* both produce EPSs (Cerning et al. 1986, 1988, Cerning 1990, Laws et al. 2001). These polysaccharides are key players in the development of yogurt's rheological properties and help determine yogurt firmness, unctuousity, stickiness, and mouthfeel (Broadbent et al. 2003, Vanindegem et al. 2004, Purwandari et al. 2007, Qin et al. 2011). Polysaccharides can bind to casein micelles and thus both increase water retention in the curd and reduce whey exudation at the yogurt's surface (Amatayakul et al. 2006a,b, Purohit et al. 2009). *S. thermophilus* EPSs also act to protect *Lb. bulgaricus* (Ramchandran and Shah 2009).

Fermentation conditions (e.g., temperature, time of incubation), the composition of the medium (e.g., carbon and nitrogen sources, the carbon-to-nitrogen ratio), the level of acidity, and the identity of the strain affect EPS quantity and sugar composition (De Vuyst et al. 1998, Degeest and De Vuyst 1999, Tamime and Robinson 1999, Zisu and Shah 2003, Vaningelgem et al. 2004, Zhang et al. 2014). Depending on the strain and culture conditions, *S. thermophilus* and *Lb. bulgaricus* produce EPSs either during the exponential growth phase (De Vuyst et al. 1998) or late fermentation (Petry et al. 2000, Broadbent et al. 2003, Sieuwerts et al. 2010). Production levels are higher in co-cultures than in pure cultures (Cerning 1990, Frengova et al. 2000, Sieuwerts et al. 2010), possibly because the drop in pH favors EPS production by *Lb. bulgaricus*. EPS production by *Lb. bulgaricus* can be stimulated by formate and other compounds such as vitamins or nucleobases.

EPSs are synthesized in the cytoplasm by polymerization of repeating sugar units that are attached to a lipid carrier. They are translocated to the membrane before being secreted, which is what distinguishes them from capsular polysaccharides (which are permanently attached to the cellular surface). LAB EPSs comprise multiple copies of an oligosaccharide that contains several residues linked in different patterns. All the EPSs characterized in yogurt bacteria up until now are mainly composed of galactose. Galactose's omnipresence is probably a consequence of the ubiquity of lactose in milk—it is the main carbon source and, when hydrolyzed, forms (i) glucose, which is preferentially used for glycolysis-based energy production and (ii) galactose, which can be used to synthesize nucleotide sugars for EPS production.

In *S. thermophilus*, EPSs are most commonly composed of galactose and glucose (De Vuyst et al. 1988, Petit et al. 1991, Laws et al. 2001, Marshall et al. 2001, Nordmark et al. 2005, Sawen et al. 2010, Qin et al. 2011). In some strains, additional mannose (Cerning et al. 1986) or rhamnose (Cerning et al. 1986, Escalante et al. 1998) are also included; in others, it is small amounts of xylose, arabinose, and mannose (Cerning et al. 1988). Alternatively, EPSs can also be solely composed of rhamnose and galactose (Ariga et al. 1992, Faber et al. 1998, 2001) or contain sugar derivatives such as acetylgalactosamine and/or fucose (Doco et al. 1990, Stingle et al. 1996, Laws et al. 2001), D-galactopyranose and L-rhamnopyranose residues (Bubb et al. 1997), or N-acetylglucosamine and glucuronic acid, which are components of hyaluronic acid (Izawa et al. 2009). In *Lb. bulgaricus*, most of EPSs described to date contain galactose, glucose, and rhamnose (Cerning et al. 1986, Zourari et al. 1992, Gruter et al. 1993, Grobber et al. 1995, Petry et al. 2000, Marshall et al. 2001, Lamothe et al. 2002) and occasionally traces of mannose (Petry et al. 2000). However, some *Lb. bulgaricus* EPSs are composed of galactose and glucose (Petry et al. 2000, Faber et al. 2001); galactose,

glucose, and traces of mannose (Bouzar et al. 1996); or xylose and arabinose (Cerning et al. 1988). Even if both bacteria produce EPSs containing similar sugars, the proportions of these sugars differ, generating EPS diversity and shaping yogurt viscosity in different ways (Faber et al. 1998). In addition, EPS composition can vary during fermentation (Bouzar et al. 1997).

Several EPS gene clusters have been described in different yogurt bacterial strains, which often possess two of said clusters. The *eps* clusters usually exhibit a modular organization and a chimeric structure; they are highly diverse in terms of sequence and genetic context across clusters, both within and among strains (Stingele et al. 1996, Bourgoin et al. 1999, Jolly and Stingele 2001, Broadbent et al. 2003, Rasmussen et al. 2008, Goh et al. 2011, Hao et al. 2011). Sequence divergence ranges from 10 to 50% for *S. thermophilus* EPSs (Bourgoin et al. 1999). The diversity of these genes suggests that HGTs are being acquired from other bacteria in the environment. For instance, *S. thermophilus* strain LMD-9 contains some *eps* genes that are very similar to those found in *Lactococcus lactis* (Bourgoin et al. 1999, Goh et al. 2011). In addition, Wu et al. (2014) has proposed that *S. thermophilus* may produce EPSs of different molecular sizes because the researchers detected the presence of two gene pairs that are involved in chain-length determination.

4. A Fermented Food with Probiotic Potential

Yogurt can also be considered to be a probiotic food (Guarner et al. 2005). Indeed, yogurt starters clearly meet the definition of probiotics—“Live microorganisms [that] when administered in adequate amounts confer a health benefit on the host”—proposed by the Joint Food and Agriculture Organization/World Health Organization Working Group (2002) and adopted by the International Scientific Association for Probiotics and Prebiotics (Reid et al. 2003). In addition, yogurt possesses well-documented healthful properties, including the ability to help alleviate lactose intolerance. This latter characteristic is the basis of a health claim recently accepted by EFSA (Section 4.1, 2010).

There are numerous examples in the literature of the probiotic effects of LAB, when delivered in capsules, sprays, or via yogurt. However, the goal here is to focus exclusively on the probiotic effects of traditional yogurt, which includes both and only *S. thermophilus* and *Lb. bulgaricus*.

4.1 Bacterial β -galactosidase Participates in Lactose Digestion in the Gastrointestinal Tract

Lactose maldigestion/intolerance is the main cause of milk intolerance in adults. Yogurt’s ability to alleviate the symptoms of lactose maldigestion

is well documented and recognized at the regulatory level (FAO/WHO 2001, 2002, EFSA 2010). Lactose maldigestion results from reduced or absent lactase activity (the hydrolysis of lactose into glucose and galactose) in the brush border membrane of the small intestine. Undigested lactose travels to the colon, where it is subject to fermentation by resident microbiota, leading to excessive gas production (i.e., methane, carbonic gas, hydrogen) and, consequently, symptoms such as abdominal pain, bloating, cramps, or diarrhea. Lactose intolerance/maldigestion can be diagnosed by the breath-hydrogen concentration test. It measures the quantity of exhaled hydrogen, which is proportional to the quantity of ingested lactose reaching the colon and is thus inversely proportional to the level of lactose digestion in the intestine (Savaiano 2014). Hypolactasia (lactase deficiency) is a physiological condition and is affected by age, sex, and ethnic origin. For instance, lactase activity rapidly decreases after weaning in the majority of children. Hypolactasia prevalence is over 50% in adult Africans, American Hispanics, and American Indians, and close to 100% in some Asian populations (Wilt et al. 2010, Lember 2012), because of a genetically programmed loss of lactase after weaning.

Though the lactose concentration in yogurt is similar to that in milk (around 40 g/L), yogurt consumption is recommended for people suffering from lactose intolerance because it alleviates the symptoms of the disorder. For example, lactose intolerance/maldigestion is more severe in young children (e.g., causing acidic diarrhea), but yogurt consumption appears to help (i.e., is associated with a decrease in acidic feces occurrence and volume) (Dewit et al. 1987, Shermak et al. 1995). These benefits can only be obtained if the product contains live yogurt bacteria; they are lost if the yogurt is thermized and the bacteria are killed (Goodenough and Kelyn 1975, Gilliland and Kim 1984, Savaiano et al. 1984, Lerebours et al. 1989, Pochart et al. 1989, de Vrees et al. 2001).

Older work by Alm et al. (1982) suggested that the lactase produced by yogurt bacteria (β -galactosidase, see above)—which all strains of yogurt bacteria have—could promote lactose hydrolysis in the digestive tract. This hypothesis was later experimentally supported in mice by Douault et al. (2002). In lactase-deficient subjects, more than 90% of the lactose found in the small intestine was hydrolyzed by the β -galactosidase of yogurt starters (Marteau et al. 1990). The results were dependent on the size of the bacterial population present in the yogurt; total hydrolysis occurred when 10^8 UFC/g yogurt were present but was limited when only 10^6 UFC/g were present (Pelletier et al. 2001).

It has been suggested that lactose could enter yogurt bacteria as a result of the permeabilization of their envelopes by bile (Noh and Gilliland 1994), or that bacteria lyse and release their β -galactosidase into the lumen (Marteau et al. 1997). Yogurt's texture—which is more viscous and

thicker than that of milk—could also slow down gastric emptying and gastrointestinal transit times (Marteau et al. 1990), thus favoring the action of residual intestinal lactase on enterocytes by favoring contact with lactose in the lumen. In rats, intestinal lactase activity was higher in animals fed yogurt than in animals fed pasteurized yogurt or milk (Goodenough and Kleyn 1975, Besnier et al. 1983, Garvie et al. 1984).

4.2 Yogurt Consumption Can Have Beneficial Effects on Infections, Inflammatory Diseases, and Cancers

Infections, antibiotic treatments, and tube feeding are major causes of diarrhea. In developing countries, bacterial enteropathogens, such as enterotoxigenic *E. coli*, are frequently responsible for diarrhea in children and travellers (Narayan et al. 2010). The WHO (1995) has recommended using yogurt to treat acute diarrhea because yogurt is associated with the production of antimicrobial compounds (H_2O_2 , bacteriocins, or organic acids such as lactic acid), acts via immunomodulation, and inhibits pathogen adhesion to the intestinal epithelium. In particular, yogurt helps limit chronic diarrhea in children (Boudraa et al. 1990, Touhami et al. 1992), by reducing both its frequency and duration (Boudraa et al. 2001).

Maintaining microbial equilibrium is an important part of intestinal physiological health and homeostasis; it also helps eliminate pathogenic enteric bacteria. For patients with chronic liver disease, consuming yogurt can decrease microbiota imbalances (Liu et al. 2010), and in patients with inflammatory bowel disease (IBS), yogurt consumption has been linked to a decline in the pathogen *Bilophila wadsworthia* (Veiga et al. 2014). The feces of subjects that have consumed yogurt have higher microbial densities and contain larger amounts of LABs as compared to *Bacteroides* species (Garcia-Albiach et al. 2008). Yogurt consumption resulted in lower *E. coli* counts in patients suffering from chronic liver disease (Liu et al. 2010). It also led to lower levels of *Clostridium* in the elderly, which is beneficial because Clostridia generate putrefactive products that are potentially toxic for the colic mucosa (Canzi et al. 2002). Interestingly, a recent meta-analysis looking at the influence of diet on tooth erosion in children and adolescents has indicated that yogurt has protective effects (Salas et al. 2015). *In vitro* experiments suggest they may stem from bactericidal effects on cariogenic *S. mutans* species (Petti et al. 2008).

In the 1990s, research began to suggest that the administration of live LABs could modify immune responses. The effects of each of the two yogurt bacteria on inflammatory and immune responses have been documented, but a few studies have also shown that yogurt containing both bacteria can have beneficial impacts. Yogurt consumption stimulates the immune system and decreases allergies in young adults (20–40 years old) and older

adults (55–70 years old) (Trapp et al. 1993, Van de Water et al. 1999) and is recommended for the immunocompromised (Meydani and Ha 2000). Based on the results of *in vitro* and *in vivo* studies, one could hypothesize that the immunomodulatory and anti-inflammatory effects of yogurt could stem from the induction of cytokines (γ -interferon, TNF α , IL-12), the production of immunoglobulins (IgA in particular), and an improved barrier effect due to increased mucosa thickness.

Furthermore, in animal models with induced cancers, yogurt consumption reduces tumor number (Narushima et al. 2010); it also inhibits tumor progression and spread of colon cancer by increasing apoptosis (De Moreno de Leblanc and Perdigon 2004), by decreasing the inflammatory immune response (mediated by increases in IgA), and increasing IL-10 expression (Perdigon et al. 2002). In humans, yogurt consumption is associated with a reduction in colorectal cancer (Pala et al. 2011) and may also reduce the risk of breast cancer (Le et al. 1986, Van't Veer et al. 1989). Again, yogurt's cancer-fighting properties are lost if the food is thermized (Pool-Zabel et al. 1993), underscoring that the benefits are due to the presence of live bacteria.

4.3 The Proteolytic Activity of Yogurt Bacteria Contributes to Yogurt's Antihypertensive Potential

The proteolytic activity of yogurt starters is essential for bacterial growth in milk (see above), as well as for the production of peptides that possess varying degrees of functional activity. Several casein-derived peptides produced by yogurt LABs have been identified, and their biological activity has been demonstrated *in vitro*. *In vivo*, following their ingestion, these yogurt peptides must confront the proteolytic enzymes of the gastrointestinal tract (i.e., pepsin, trypsin, chymotrypsin, as well as carbo-, amino- and membrane endopeptidases), which can hydrolyze them and thus prevent them from reaching their target within the host. Nevertheless, proline-rich peptides can withstand the gauntlet of gastrointestinal hydrolysis (Korhonen and Pihlanto 2003) because peptide bonds containing proline can only be hydrolyzed with specific enzymes. Consequently, the tripeptides IPP (Ile-Pro-Pro) and VPP (Val-Pro-Pro), which are produced in yogurt (Donkor et al. 2007) and have antihypertensive properties (Hirota et al. 2007), resist *in vivo* degradation; a product containing these two peptides has been commercialized. The antihypertensive effects of such peptides results from their inhibition of angiotensin-converting enzyme (ACE), which plays a crucial role in regulating blood pressure by modulating the levels of the vasoconstricting peptide angiotensin II and those of the vasodilatory peptide bradykinin. More recently, β -casein(94–123)-derived peptides, which are present in yogurt, have been shown to enhance the expression

of mucin-encoding genes and the number of goblet and Paneth cells in the small intestine (Plaisancié et al. 2013); they may thus play a role in protecting the intestinal epithelium and maintaining its homeostasis. More generally, bioactive peptides with diverse functional properties have been isolated from dairy products (Madureira et al. 2010, Muro Urista et al. 2011).

Apart from the extensive data provided above that demonstrate yogurt's probiotic effects, other findings indicate that yogurt could have promise in treating prevalent pathologies—such as obesity, diabetes II (Margolis et al. 2011), and cardiovascular diseases (Sonestedt et al. 2011)—and maintaining better general health in aging populations (El-Abbadi et al. 2014). Furthermore, the lactate present in yogurt not only acts as an antibacterial agent, but also helps define the food's organoleptic properties (see above) and has bioactive properties (Garrote et al. 2015). It functions as a signaling molecule between bacteria and the host and, in particular, modulates the physiology of the colon epithelium (Rul et al. 2011, Thomas et al. 2011). Recently, Tsilingiri and Rescigno (2013) have proposed the concept of "postbiotic" factors, which are "soluble factors produced by probiotics [that] are sufficient to elicit the desired response" and that "could be a safe alternative for clinical applications, especially in chronic inflammatory conditions like inflammatory bowel disease." However, clinical trials in humans are still lacking, and most of the potential mechanisms involved remain to be specifically elucidated.

5. Conclusions

Yogurt, a healthful, traditional food that has been consumed for millenia, has modern relevance because its combination of nutritional and probiotic proprieties result in unique benefits. It is an interesting food ecosystem which has recently been rediscovered using post-genomic tools. We now have a better understanding of yogurt microbiology, and especially of the metabolic processes that are essential for yogurt production. Nevertheless, data are lacking on some key technical aspects (e.g., the nature of optimal bacterial combinations, the regulation of EPS production) and the factors responsible for yogurt's healthful effects. Research has yet to fully clarify yogurt's probiotic potential and the underlying mechanisms. Indeed, the list of yogurt's possible probiotic properties in the face of various pathologies continues to grow as various animal models are explored. However, findings in humans, particularly in healthy populations, are still needed.

The emergence of new food consumption patterns and of health consciousness on the part of consumers, as well as the global aging of the population, are reasons for continuing to promote fermented foods, such as yogurt, and to develop new ones. For example, vitamin- and/or iron-fortified yogurts, thermized yogurts, and dairy snacks are now available,

and it is easy to imagine that these products will continue to be developed and adapted to different populations (e.g., varying in age, sex, ethnic origin, and geographical location) and different nutritional habits. Traditional yogurt probably has benefits that remain to be identified, and exploring its characteristics in greater detail may yield new probiotic applications. Yogurt bacteria EPSs provide a good example: older studies focused on describing these texturing agents of yogurts, and more recent studies have suggested that texturing agents could be involved in inflammatory diseases (Sengul et al. 2006) and have immunostimulating (Makino et al. 2006), antiviral (Nagai et al. 2011), and antibacterial (Aslim et al. 2007) effects.

Acknowledgements

We are very grateful to Jessica Pearce-Duvet for language editing in the manuscript.

Keywords: Acidification, aroma, carbohydrate metabolism, exopolysaccharide, flavor, lactic acid bacteria, *Lactobacillus bulgaricus*, lactose, nitrogen metabolism, probiotics, proteolysis, proto-cooperation, *Streptococcus thermophilus*, texture, yogurt

References

- Accolas, J.P., Veaux, M. and Auclair, J. (1971). Etude des interactions entre diverses bactéries lactiques thermophiles et mésophiles, en relation avec la fabrication des fromages à pâte cuite. *Lait* 505-506: 249-272.
- Alm, L. (1982). Effect of fermentation on lactose, glucose, and galactose content in milk and suitability of fermented milk products for lactose intolerant individuals. *Journal of Dairy Science* 65: 346-352.
- Amatayakul, T., Sherkat, F. and Shah, N.P. (2006b). Syneresis in set yogurt as affected by EPS starter cultures and levels of solids. *International Journal of Dairy Technology* 59: 216-221.
- Amatayakul, T., Sherkat, F. and Shah, N.P. (2006a). Physical characteristics of set yoghurt made with altered casein to whey protein ratios and EPS-producing starter cultures at 9 and 14% total solids. *Food Hydrocolloids* 20: 314-324.
- Amoroso, M.J., Manca de Nadra, M.C. and Oliver, G. (1988). Glucose, galactose, fructose, lactose and sucrose utilization by *Lactobacillus bulgaricus* and *Streptococcus thermophilus* isolated from commercial yoghurt. *Milchwissenschaft* 43: 626-631.
- Ariga, H., Urashima, T., Michihata, E., Ito, M., Morizono, N., Kimura, T. and Takahashi, S. (1992). Extracellular polysaccharide from encapsulated *Streptococcus salivarius* subsp. *thermophilus* OR-901 isolated from commercial yogurt. *Journal of Food Science* 57: 625-628.
- Ascon-Reyes, D.B., Ascon-Cabrera, M.A., Cochet, N. and Lebeault, J.M. (1995). Indirect conductance for measurements of carbon dioxide produced by *Streptococcus salivarius* ssp. *thermophilus* TJ 160 in pure and mixed cultures. *Journal of Dairy Science* 48: 8-16.
- Aslim, B., Onal, D. and Beyatli, Y. (2007). Factors influencing autoaggregation and aggregation of *Lactobacillus delbrueckii* subsp. *bulgaricus* isolated from handmade yogurt. *Journal of Food Protection* 70(1): 223-237.
- Azcarate-Peril, M.A., Altermann, E., Hoover-Fitzula, R.L., Cano, R.C. and Klaenhammer, T.R. (2004). Identification and inactivation of genetic loci involved with *Lactobacillus acidophilus* Acid tolerance. *Applied and Environmental Microbiology* 70: 5315-5322.

- Bautista, E.S., Dahiya, R.S. and Speck, M.L. (1966). Identification of compounds causing symbiotic growth of *Streptococcus thermophilus* and *Lactobacillus bulgaricus* in milk. *Journal of Dairy Research* 33: 299–307.
- Beal, C., Spinnler, H.E. and Corrieu, G. (1994). Comparison of growth, acidification and productivity of pure and mixed cultures of *Streptococcus salivarius* subsp. *thermophilus* 404 and *Lactobacillus delbrueckii* subsp. *bulgaricus* 398. *Microbiology and Biotechnology* 41: 95–98.
- Beal, C. and Corrieu, G. (1991). Influence of pH, temperature, and inoculum composition on mixed cultures of *Streptococcus thermophilus* 404 and *Lactobacillus* 398. *Biotechnology and Bioengineering* 38: 90–98.
- Ben-Yahia, L., Mayeur, C., Rul, F. and Thomas, M. (2012). Growth advantage of *Streptococcus thermophilus* over *Lactobacillus bulgaricus* *in vitro* and in the gastrointestinal tract of gnotobiotic rats. *Beneficial Microbes* 3: 211–219.
- Beshkova, D., Simova, E., Frengova, G. and Simov, Z. (1998). Production of flavour compounds by yogurt starter cultures. *Journal of Industrial Microbiology and Biotechnology* 20: 180–186.
- Besnier, M.O., Bourlioux, P., Fourniat, J., Ducluzeau, R. and Aumaitre, A. (1983). Effect of yogurt ingestion on the intestinal lactase activity in axenic or holoxenic mice. *Annals of Microbiology (Paris)* 134A: 219–230.
- Bolotin, A., Quinquis, B., Renault, P., Sorokin, A., Ehrlich, S.D., Kulakauskas, S., Lapidus, A., Goltsman, E., Mazur, M., Pusch, G.D., Fonstein, M., Overbeek, R., Kyprides, N., Purnelle, B., Prozzi, D., Ngui, K., Masuy, D., Hancy, F., Burteau, S., Boutry, M., Delcour, J., Goffeau, A. and Hols, P. (2004). Complete sequence and comparative genome analysis of the dairy bacterium *Streptococcus thermophilus*. *Nature Biotechnology* 22: 1554–1558.
- Bottazzi, V., Battistotti, B. and Montescani, G. (1973). Influence des souches seules et associées de *Lb. bulgaricus* et *Str. thermophilus* ainsi que des traitements du lait sur la production d'aldéhyde acétique dans la yaourt. *Lait* 525-526: 295–308.
- Bottazzi, V. and Vescovo, M. (1969). Carbonyl compounds produced by yoghurt bacteria. *Netherlands Milk and Dairy Journal* 23: 71–78.
- Bottazzi, V. and Dellaglio, F. (1967). Acetaldehyde and diacetyl production by *Streptococcus thermophilus* and other lactic streptococci. *Journal of Dairy Research* 34: 109–113.
- Boudraa, G., Benbouabdellah, M., Hachelaf, W., Boisset, M., Desjeux, J.F. and Touhami, M. (2001). Effect of feeding yogurt versus milk in children with acute diarrhea and carbohydrate malabsorption. *Journal of Pediatric Gastroenterology and Nutrition* 33: 307–313.
- Boudraa, G., Touhami, M., Pochart, P., Soltana, R., Mary, J.Y. and Desjeux, J.F. (1990). Effect of feeding yogurt versus milk in children with persistent diarrhea. *Journal of Pediatric Gastroenterology Nutrition* 11: 509–512.
- Bourgoin, F., Pluvinet, A., Gintz, B., Decaris, B. and Guédon, G. (1999). Are horizontal transfers involved in the evolution of the *Streptococcus thermophilus* exopolysaccharide synthesis loci? *Gene* 233: 151–61.
- Bouzar, F., Cerning, J. and Desmazeaud, M. (1997). Exopolysaccharide production and texture-promoting abilities of mixed-strain starter cultures in yogurt production. *Journal of Dairy Science* 80: 2310–2317.
- Bouzar, F., Cerning, J. and Desmazeaud, M. (1996). Exopolysaccharide production in milk by *Lactobacillus delbrueckii* ssp. *bulgaricus* CNRZ 1187 and by two colonial variants. *Journal of Dairy Science* 79: 205–211.
- Bracquart, P. and Lorient, D. (1979). Effet des acides aminés et peptides sur la croissance de *Streptococcus thermophilus*. III. Peptides comportant Glu, His et Met. *Milchwissenschaft* 34: 679–679.
- Bracquart, P., Lorient, D. and Alais, C. (1978). Effet des acides aminés sur la croissance de *Streptococcus thermophilus*. II: Etude sur cinq souches. *Milchwissenschaft* 33: 341–344.
- Bracquart, P. and Lorient, D. (1977). Effet des acides aminés sur la croissance de *Streptococcus thermophilus*. *Milchwissenschaft* 32: 221–224.

- Broadbent, J.R., Mc Mahon, D.J., Oberg, W.C. and Moineau, S. (2003). Biochemistry, genetics, and applications of exopolysaccharide production in *Streptococcus thermophilus*: a review. *Journal of Dairy Science* 86: 407–423.
- Bubb, W.A., Urashima, T., Fujiwara, R., Shinnai, T. and Ariga, H. (1997). Structural characterisation of the exocellular polysaccharide produced by *Streptococcus thermophilus* OR 901. *Carbohydrate Research* 301(1-2): 41–50.
- Canzi, E., Casiraghi, M.C., Zanchi, R., Gandolfi, R., Ferrari, A., Brighenti, F., Bosia, R., Crippa, A., Maestri, P., Vesely, R. and Bianchi Salvadori, B. (2002). Yogurt in the diet of the elderly: a preliminary investigation into its effect on the gut ecosystem and lipid metabolism. *Lait* 82: 713–723.
- Cerning, J. (1990). Exocellular polysaccharides produced by lactic acid bacteria. *FEMS Microbiological Reviews* 7: 113–130.
- Cerning, J., Bouillanne, C., Desmazeaud, M.J. and Landon, M. (1988). Exocellular polysaccharide production by *Streptococcus thermophilus*. *Biotechnology Letters* 10: 255–260.
- Cerning, J., Bouillanne, C., Desmazeaud, M.J. and Landon, M. (1986). Isolation and characterization of exopolysaccharide produced by *Lactobacillus bulgaricus*. *Biotechnology Letters* 8: 625–628.
- Chaves, A.C.S.D., Fernandez, M., Lerayer, A.L.S., Mierau, I., Kleerebezem, M. and Hugenholz, J. (2002). Metabolic engineering of acetaldehyde production by *Streptococcus thermophilus*. *Applied and Environmental Microbiology* 68: 5656–5662.
- Cheng, H. (2010). Volatile flavor compounds in yogurt: a review. *Critical Reviews in Food Science and Nutrition* 50(10): 938–950.
- Chervaux, C., Ehrlich, S.D. and Maguin, E. (2000). Physiological study of *Lactobacillus delbrueckii* subsp. *bulgaricus* strains in a novel chemically defined medium. *Applied Environmental Microbiology* 66: 5306–5311.
- Christensen, J.E., Dudley, E.G., Pederson, J.A. and Steele, J.L. (1999). Peptidases and amino acid catabolism in lactic acid bacteria. *Antonie van Leeuwenhoek* 76: 217–246.
- Courtin, P. and Rul, F. (2004). Interactions between microorganisms in a simple ecosystem: yogurt bacteria as a study model. *Lait* 84(1-2): 125–134.
- Courtin, P., Monnet, V. and Rul, F. (2002). Cell-wall proteinases PrtS and PrtB have a different role in *Streptococcus thermophilus*/*Lactobacillus bulgaricus* mixed cultures in milk. *Microbiology* 148: 3413–3421.
- Crittenden, R.G., Martinez, N.R. and Playne, M.J. (2002). Synthesis and utilisation of folate by yoghurt starter cultures and probiotic bacteria. *International Journal of Food Microbiology* 80: 217–222.
- Dandoy, D., Fremaux, C., Henry de Frahan, M. and Horvath, P., Boyaval, P., Hols, P. and Fontaine, L. (2011). The fast milk acidifying phenotype of *Streptococcus thermophilus* can be acquired by natural transformation of the genomic island encoding the cell-envelope proteinase PrtS. *Microbial Cell Factories* 10(suppl 1): 521.
- De Moreno de Leblanc, A. and Perdigón, G. (2004). Yogurt feeding inhibits promotion and progression of experimental colorectal cancer. *Medical Science Monitor Journal* 10: BR96–104.
- de Vrese, M., Stegelmann, A., Richter, B., Fenselau, S., Laue, C. and Schrezenmeir, J. (2001). Probiotics—compensation for lactase insufficiency. *The American Journal of Clinical Nutrition* 73(2): 421s–429s.
- De Vuyst, L., Vanderveken, F., Van de Ven, S. and Degeest, B. (1998). Production by and isolation of exopolysaccharides from *Streptococcus thermophilus* grown in a milk medium and evidence for their growth-associated biosynthesis. *Journal of Applied Microbiology* 84: 1059–1068.
- Degeest, B. and De Vuyst, L. (1999). Indication that the nitrogen source influences both amount and size of exopolysaccharides produced by *Streptococcus thermophilus* LY03 and modelling of the bacterial growth and exopolysaccharide production in a complex medium. *Applied and Environmental Microbiology* 65(7): 2863–2870.

- Delorme, C., Bartholini, C., Bolotine, A., Ehrlich, S.D. and Renault, P. (2010). Emergence of a Cell Wall Protease in the *Streptococcus thermophilus* Population. *Applied and Environmental Microbiology* 76: 451–460.
- Derzelle, S., Bolotin, A., Mistou, M.-Y. and Rul, F. (2005). Proteome analysis of *Streptococcus thermophilus* grown in milk reveals pyruvate formate-lyase as the major upregulated protein. *Applied and Environmental Microbiology* 71: 8597–8605.
- Dewit, O., Boudraa, G., Touhami, M. and Desjeux, J.F. (1987). Breath hydrogen test and stools characteristics after ingestion of milk and yogurt in malnourished children with chronic diarrhoea and lactase deficiency. *Journal of Tropical Pediatrics* 33: 177–180.
- Doco, T., Wieruszkeski, J.-M., Fournet, B., Carcano, D., Ramos, P. and Loones, A. (1990). Structure of an exocellular polysaccharide produced by *Streptococcus thermophilus*. *Carbohydrate Research* 198: 313–321.
- Donkor, O.N., Henriksson, A., Singh, T.K., Vasiljevic, T. and Shah, N.P. (2007). ACE-inhibitory activity of probiotic yoghurt. *International Dairy Journal* 17: 1321–1331.
- Driessen, F.M., Kingma, F. and Stadhouders, J. (1982). Evidence that *Lactobacillus bulgaricus* in yogurt is stimulated by carbon dioxide produced by *Streptococcus thermophilus*. *Netherlands Milk and Dairy Journal* 36: 135–144.
- Drouault, S., Anba, J. and Corthier, G. (2002). *Streptococcus thermophilus* is able to produce a b-galactosidase active during its transit in the digestive tract of germ-free mice. *Applied and Environmental Microbiology* 68: 938–941.
- Dumont, J. and Adda, J. (1973). Méthode rapide d'étude des composés très volatils de l'arôme des produits laitiers. Application au yoghurt. *Dairy Science and Technology* 53: 12–22.
- Dunne, J., Evershed, R.P., Salque, M., Cramp, L., Bruni, S., Ryan, K., Biagetti, S. and di Lernia, S. (2012). First dairying in green Saharan Africa in the fifth millennium bc. *Nature* 486: 390–394.
- Dutta, S., Kuila, R. and Ranganathan, B. (1973). Effect of different heat treatments of milk on acid and flavour production by five single strain cultures. *Milchwissenschaft* 28: 321–323.
- El-Abbadi, N.H., Dao, M.C. and Meydani, S.N. (2014). Yogurt: role in healthy and active aging. *The American Journal of Clinical Nutrition* 99: 1263S–1270S.
- El-Abbassy, M.Z. and Sitohy, M. (1993). Metabolic interaction between *Streptococcus thermophilus* and *Lactobacillus bulgaricus* in single and mixed starter yogurts. *Nahrung* 37(1): 53–58.
- El-Soda, M.A., Abou-Donia, S.A., El-Shafy, H.K., Mashaly, R. and Ismail, A.A. (1986). Metabolic activities and symbiosis in zabady isolated cultures. *Egyptian Journal of Dairy Science* 14: 1–10.
- Escalante, A., WachterRodarte, C., GarciaGaribay, M. and Farres, A. (1998). Enzymes involved in carbohydrate metabolism and their role on exopolysaccharide production in *Streptococcus thermophilus*. *Journal of Applied Microbiology* 84: 108–114.
- European and Food Safety Authority. (2010). Scientific opinion on the substantiation of health claims related to live yogurt cultures and improved lactose digestion. *EFSA Journal* 8: 1763.
- Faber, E.J., Kamerling, J.P. and Vliegthart, J.F. (2001). Structure of the extracellular polysaccharide produced by *Lactobacillus delbrueckii* subsp. *bulgaricus* 291. *Carbohydrate Research* 331: 183–194.
- Faber, E.J., Zoon, P.J., Kamerling, P. and Vliegthart, J.F.G. (1998). The exopolysaccharides produced by *Streptococcus thermophilus* Rs and Sts have the same repeating unit but differ in viscosity of their milk cultures. *Carbohydrate Research* 310(4): 269–276.
- FAO/WHO. (2001). Report of a joint FAO/WHO Expert Consultation on evaluation of health and nutritional properties of probiotics in food including power milk with lactic acid bacteria. ftp.fao.org/es/esn/food/probio_report_en.pdf.
- FAO/WHO. (2002). Report of a joint FAO/WHO Working Group on drafting guidelines for the evaluation of probiotics in food. <ftp.fao.org/es/esn/food/wgreport2.pdf>.
- Fernandez-Espla, M.-D., Garault, P., Monnet, V. and Rul, F. (2000). *Streptococcus thermophilus* cell wall-anchored proteinase: release, purification, and biochemical and genetic characterization. *Applied and Environmental Microbiology* 66: 4772–4778.

- Frengova, G.I., Simova, E.D., Beshkova, D.M. and Simov, Z.I. (2000). Production and monomer composition of exopolysaccharides by yogurt starter cultures. *Canadian Journal of Microbiology* 46: 1123–1127.
- Friedrich, J.E. and Acree, T.E. (1998). Gas chromatography olfactometry (GC/O) of dairy products. *International Dairy Journal* 8: 235–241.
- Galesloot, T.E., Hassing, F. and Veringa, H.A. (1968). Symbiosis in yoghurt(I). Stimulation of *Lactobacillus bulgaricus* by a factor produced by *Streptococcus thermophilus*. *Netherland Milk Dairy Journal* 22: 50–63.
- Garault, P., Letort, C., Juillard, V. and Monnet, V. (2000). Branched-chain amino acid biosynthesis is essential for optimal growth of *Streptococcus thermophilus* in milk. *Applied and Environmental Microbiology* 66: 5128–5133.
- García-Albiach, R., José, M., de Felipe, P., Angulo, S., Morosini, M.I., Bravo, D., Baquero, F. and del Campo, R. (2008). Molecular analysis of yogurt containing *Lactobacillus delbrueckii* subsp. *bulgaricus* and *Streptococcus thermophilus* in human intestinal microbiota. *American Journal of Clinical Nutrition* 87: 91–6.
- Gardan, R., Besset, C., Guillot, A., Gitton, C. and Monnet, V. (2009). The oligopeptide transport system is essential for the development of natural competence in *Streptococcus thermophilus* Strain LMD-9. *Journal of Bacteriology* 191: 4647–4655.
- Garrote, G., Abraham, A.G. and Rumbo, M. (2015). Is lactate an undervalued functional component of lactic acid bacteria-fermented food products? *Frontiers in Microbiology* 6.
- Garvie, E.I., Cole, C.B., Fuller, R. and Hewitt, D. (1984). The effect of yoghurt on some components of the gut microflora and on the metabolism of lactose in the rat. *Journal of Applied Bacteriology* 56: 237–245.
- Gilbert, C., Blanc, B., Frot-Coutaz, J., Portalier, R. and Atlan, D. (1997). Comparison of cell surface proteinase activities within the *Lactobacillus* genus. *Journal of Dairy Research* 64: 561–571.
- Gilbert, C., Atlan, D., Blanc, B., Portalier, R., Germond, J.E., Lapierre, L. and Mollet, B. (1996). A new cell surface proteinase: sequencing and analysis of the *prtB* gene from *Lactobacillus delbrueckii* subsp. *bulgaricus*. *Journal of Bacteriology* 178: 3059–3065.
- Gilliland, S.E. and Kim, H.S. (1984). Effect of viable starter culture bacteria in yogurt on lactose utilization in humans. *Journal of Dairy Science* 67: 1–6.
- Goh, Y., Goin, C., O'Flaherty, S., Altermann, E. and Hutkins, R. (2011). Specialized adaptation of a lactic acid bacterium to the milk environment: the comparative genomics of *Streptococcus thermophilus* LMD-9. *Microbial Cell Factories* 10(Suppl 1): S22.
- Goodenough, E.R. and Kleyn, D.H. (1975). Influence of viable yoghurt microflora on digestion of lactose by the rat. *Journal of Dairy Science* 59: 601–606.
- Grobben, G.J., Sikkema, J., Smith, M.R. and de Bont, J.A.M. (1995). Production of extracellular polysaccharides by *Lactobacillus delbrueckii* ssp. *bulgaricus* NCFB 2772 grown in a chemically defined medium. *Journal of Applied Bacteriology* 79: 103–107.
- Groux, M. (1973). Etude des composants de la flaveur du yoghourt. *Lait* 523-524: 146–153.
- Gruter, M., Leeflang, B.R., Kuiper, J., Kamerling, J.P. and Vliegthart, J.E. (1993). Structural characterization of the exopolysaccharide produced by *Lactobacillus delbrueckii* subspecies *bulgaricus* rr grown in skimmed milk. *Carbohydrate Research* 239: 209–226.
- Guarner, F., Perdigon, G., Corthier, G., Salminen, S., Koletzjo, B. and Morelli, L. (2005). Should yoghurt cultures be considered probiotic? *British Journal of Nutrition* 93: 783–786.
- Hamdan, I.Y., Kunsman, J.E. and Deane, D.D. (1971). Acetaldehyde production by combined yogurt cultures. *Journal of Dairy Science* 54(7): 1080–1082.
- Hao, P., Zheng, H., Yu, Y., Ding, G., Gu, W., Chen, S., Yu, Z., Ren, S., Oda, M., Konno, T., Wang, S., Li, X., Ji, Z.S. and Zhao, G. (2011). Complete sequencing and pan-genomic analysis of *Lactobacillus delbrueckii* subsp. *bulgaricus* reveal its genetic basis for industrial yogurt production. *PLoS One* 6: e15964.
- Herve-Jimenez, L., Guillouard, I., Guedon, E., Boudebouze, S., Hols, P., Monnet, V., Maguin, E. and Rul, F. (2009). Postgenomic analysis of *Streptococcus thermophilus* cocultivated in

- milk with *Lactobacillus delbrueckii* subsp. *bulgaricus*: involvement of nitrogen, purine, and iron metabolism. *Applied and Environmental Microbiology* 75: 2062–2073.
- Herve-Jimenez, L., Guillouard, I., Guedon, E., Gautier, C., Boudebbouze, S., Hols, P., Monnet, V., Rul, F. and Maguin, E. (2008). Physiology of *Streptococcus thermophilus* during the late stage of milk fermentation with special regard to sulfur amino-acid metabolism. *Proteomics* 8: 4273–4286.
- Higashio, K., Kikuchi, T. and Furuichi, E. (1978). Symbiose entre *Lactobacillus bulgaricus* et *Streptococcus thermophilus* dans le yoghourt. XX congrès international de laiterie, Paris.
- Hirota, T., Ohki, K., Kawagishi, R., Kajimoto, Y., Mizuno, S., Nakamura, Y. and Kitakaze, M. (2007). Casein hydrolysate containing the antihypertensive tripeptides Val-Pro-Pro and Ile-Pro-Pro improves vascular endothelial function independent of blood pressure-lowering effects: contribution of the inhibitory action of angiotensin-converting enzyme. *Hypertension Research* 30: 489–496.
- Hols, P., Hancy, F., Fontaine, L., Grossiord, B., Prozzi, D., Leblond-Bourget, N., Decaris, B., Bolotin, A., Delorme, C., Ehrlich, S.D., Guédon, E., Monnet, V., Renault, P. and Kleerebezem, M. (2005). New insights in the molecular biology and physiology of *Streptococcus thermophilus* revealed by comparative genomics. *FEMS Microbiology Reviews* 29: 435–463.
- Horiuchi, H. and Sasaki, Y. (2012). Effect of oxygen on symbiosis between *Lactobacillus bulgaricus* and *Streptococcus thermophilus*. *Journal of Dairy Science* 95: 2904–2909.
- Hutkins, R., Morris, H.A. and McKay, L.L. (1985). Galactokinase activity in *Streptococcus thermophilus*. *Applied and Environmental Microbiology* 50: 777–780.
- Imhof, R., Glättli, H. and Bosset, J.O. (1995). Volatile organic compounds produced by thermophilic and mesophilic single strain dairy starter cultures. *Lebensmittel-Wissenschaft und Technologie* 28: 78–86.
- Izawa, N., Hanamizu, T., Iizuka, R., Sone, T., Mizukoshi, H., Kimura, K. and Chiba, K. (2009). *Streptococcus thermophilus* produces exopolysaccharides including hyaluronic acid. *Journal of Bioscience and Bioengineering* 107: 119–123.
- Jolly, L. and Stingle, F. (2001). Molecular organization and functionality of exopolysaccharide gene clusters in lactic acid bacteria. *International Dairy Journal* 11: 733–745.
- Juillard, V., Desmazeaud, M.J. and Spinnler, H.E. (1988). Mise en évidence d'une activité uréasique chez *Streptococcus thermophilus*. *Canadian Journal of Microbiology* 34: 818–822.
- Korhonen, H. and Pihlanto, A. (2003). Food-derived bioactive peptides—opportunities for designing future foods. *Current Pharmaceutical Design* 9: 1297–1308.
- Knappe, J., Blaschkowski, H.P., Gröbner, P. and Schmitt, T. (1974). Pyruvate Formate-Lyase of *Escherichia coli*: the Acetyl-Enzyme Intermediate. *European Journal of Biochemistry* 50: 253–263.
- Kneifel, W., Ulberth, F., Erhard, F. and Jaros, D. (1992). Aroma profiles and sensory properties of yogurt and yogurt-related products. I Screening of commercially available stater cultures. *Milchwissenschaft* 47: 362–365.
- Lamothe, G.T., Jolly, L., Mollet, B. and Stingle, F. (2002). Genetic and biochemical characterization of exopolysaccharide biosynthesis by *Lactobacillus delbrueckii* subsp. *bulgaricus*. *Archives of Microbiology* 178: 218–228.
- Law, B. (1981). The formation of aroma and flavour compounds in fermented dairy products. *Dairy Science Abstracts* 43: 143–154.
- Laws, A., Gu, Y. and Marshall, V. (2001). Biosynthesis, characterization, and design of bacterial exopolysaccharides from lactic acid bacteria. *Biotechnol Advances* 19: 597–625.
- Lê, M.G., Moulton, L.H., Hill, C. and Kramar, A. (1986). Consumption of dairy produce and alcohol in a case-control study of breast cancer. *Journal of the National Cancer Institute* 77: 633–636.
- Lees, G.J. and Jago, G.R. (1976). Formation of acetaldehyde from threonine by lactic acid bacteria. *Journal of Dairy Research* 43: 75–83.
- Lember, M. (2012). Hypolactasia: a common enzyme deficiency leading to lactose malabsorption and intolerance. *Polish Archives of Internal Medicine* 122: 60–64.

- Lerebours, E., N'Djitoyp Ndam, N.C., Lavoine, A., Hellot, M.F., Antoine, J.M. and Colin, R. (1989). Yogurt and fermented-then-pasteurized milk: effects of short-term and long-term ingestion on lactose absorption and mucosal lactase activity in lactase-deficient subjects. *The American Journal of Clinical Nutrition* 49: 823–827.
- Letort, C., Nardi, M., Garault, P., Monnet, V. and Juillard, V. (2002). Casein utilization by *Streptococcus thermophilus* results in a diauxic growth in milk. *Applied and Environmental Microbiology* 68: 3162–3165.
- Levander, F., Svensson, M. and Rådström, P. (2002). Enhanced exopolysaccharide production by metabolic engineering of *Streptococcus thermophilus*. *Applied and Environmental Microbiology* 68: 784–790.
- Liu, M., Siezen, R.J. and Nauta, A. (2009). *In silico* prediction of horizontal gene transfer events in *Lactobacillus bulgaricus* and *Streptococcus thermophilus* reveals proto-cooperation in yogurt manufacture. *Applied and Environmental Microbiology* 75: 4120–4129.
- Liu, J.E., Zhang, Y., Zhang, J., Dong, P.L., Chen, M. and Duan, Z.P. (2010). Probiotic yogurt effects on intestinal flora of patients with chronic liver disease. *Nursing Research* 59: 426–432.
- Madureira, A.R., Tavares, T.A., Gomes, M.P., Pintado, M.E. and Malcata, F.X. (2010). Invited review: Physiological properties of bioactive peptides obtained from whey proteins. *Journal of Dairy Science* 93: 437–455.
- Makarova, K., Slesarev, A., Wolf, Y., Sorokin, A., Mirkin, B., Koonin, E., Pavlov, A., Pavlova, N., Karamychev, V., Polouchine, N., Shakhova, V., Grigoriev, I., Lou, Y., Rohksar, D., Lucas, S., Huang, K., Goodstein, D.M., Hawkins, T., Plengvidhya, V., Welker, D., Hughes, J., Goh, Y., Benson, A., Baldwin, K., Lee, J.H., Díaz-Muñiz, I., Dosti, B., Smeianov, V., Wechter, W., Barabote, R., Lorca, G., Altermann, E., Barrangou, R., Ganesan, B., Xie, Y., Rawsthorne, H., Tamir, D., Parker, C., Breidt, F., Broadbent, J., Hutkins, R., O'Sullivan, D., Steele, J., Unlu, G., Saier, M., Klaenhammer, T., Richardson, P., Kozyavkin, S., Weimer, B. and Mills, D. (2006). Comparative genomics of the lactic acid bacteria. *Proceedings of the National Academy of Sciences* 103: 15611–15616.
- Makino, S., Ikegami, S., Kano, H., Sashihara, T., Sugano, H., Horiuchi, H., Saito, T. and Oda, M. (2006). Immunomodulatory effects of polysaccharides produced by *Lactobacillus delbrueckii* ssp. *bulgaricus* OLL1073R-1. *Journal of Dairy Science* 89: 2873–2881.
- Manca de Nadra, M.C., Amoroso, M.J. and Oliver, G. (1988). Acetaldehyde metabolism in *Lactobacillus bulgaricus* and *Streptococcus thermophilus* isolated from market yogurt. *Microbiologie, Aliments Nutrition* 6: 269–272.
- Manca de Nadra, M.C., Raya, R.R., Pesce de Ruiz Holgadi, A. and Oliver, G. (1987). Isolation and properties of threonine aldolase of *Lactobacillus bulgaricus* YOP12. *Milchwissenschaft* 42: 92–94.
- Margolis, K.L., Wei, F., de Boer, I.H., Howard, B.V., Liu, S., Manson, J.E., Mossavar-Rahmani, Y., Phillips, L.S., Shikany, J.M., Tinker, L.F. and for the Women's Health Initiative Investigators. (2011). A diet high in low-fat dairy products lowers diabetes risk in postmenopausal women. *The Journal of Nutrition* 141: 1969–1974.
- Marranzini, R.M., Schmidt, R.H., Shireman, R.B., Marshall, M.R. and Cornell, J.A. (1989). Effect of threonine and glycine concentrations on threonine aldolase activity of yogurt microorganisms during growth in a modified milk prepared by ultrafiltration. *Journal of Dairy Science* 72: 1142–1148.
- Marshall, V.M. (1987). Lactic acid bacteria: starters for flavour. *FEMS Microbiological Reviews* 46: 327–336.
- Marshall, V.M., Laws, A.P., Gu, F., Levander, Y., Radstrom, P., DeVuyst, L., Degeest, B., Vaningelgem, F., Dunn, H. and Elvin, M. (2001). Exopolysaccharide-producing strains of thermophilic lactic acid bacteria cluster into groups according to their EPS structure. *Letters in Applied Microbiology* 32: 433–437.
- Marshall, V.M. and Cole, W.M. (1983). Threonine aldolase and alcohol dehydrogenase activities in *Lactobacillus bulgaricus* and *Lactobacillus acidophilus* and their contribution to flavour production in fermented milks. *Journal of Dairy Research* 50: 375–379.

- Marteau, P., Minekus, M., Havenaar, R. and Huis In't Veld, J.H.J. (1997). Survival of lactic acid bacteria in a dynamic model of the stomach and small intestine: Validation and the effects of bile. *Journal of Dairy Science* 80: 1031–1037.
- Marteau, P., Flourie, B., Pochart, P., Chastang, C., Desjeux, J.F. and Rambaud, J.C. (1990). Effect of the microbial lactase (EC 3.2.1.23) activity in yoghurt on the intestinal absorption of lactose: an *in vivo* study in lactase-deficient humans. *British Journal of Nutrition* 64: 71–79.
- Meydani, S.N. and Ha, W.-K. (2000). Immunologic effects of yogurt. *The American Journal of Clinical Nutrition* 71: 861–872.
- Mikkelsen, P. (2013). The world demands more yoghurts. *International dairy magazine* 11/12.
- Moon, N.J. and Reinbold, G.W. (1976). Commensalism and competition in mixed cultures of *Lactobacillus bulgaricus* and thermophilus. *Journal of Milk and Food Technology* 39: 337–341.
- Muro Urista, C., Álvarez Fernández, R., Riera Rodriguez, F., Arana Cuenca, A. and Téllez Jurado, A. (2011). Review: Production and functionality of active peptides from milk. *Food Science and Technology International* 17: 293–317.
- Nagai, T., Makino, S., Ikegami, S., Itoh, H. and Yamada, H. (2011). Effects of oral administration of yogurt fermented with *Lactobacillus delbrueckii* ssp. *bulgaricus* OLL1073R-1 and its exopolysaccharides against influenza virus infection in mice. *International Immunopharmacology* 11: 2246–2250.
- Narayan, S.S., Jalgaonkar, S., Shahani, S. and Kulkarni, V.N. (2010). Probiotics: current trends in the treatment of diarrhoea. *Hong Kong Medical Journal* 16: 213–218.
- Narushima, S., Sakata, T., Hioki, K., Itoh, T., Nomura, T. and Itoh, K. (2010). Inhibitory effect of yogurt on aberrant crypt foci formation in the rat colon and colorectal tumorigenesis in RasH2 mice. *Experimental Animals* 59: 487–94.
- Nishimura, J., Kawai, Y., Aritomo, R., Ito, Y., Makino, S., Ikegami, S., Isogai, E. and Saito, T. (2013). Effect of formic acid on exopolysaccharide production in skim milk fermentation by *Lactobacillus delbrueckii* subsp. *bulgaricus* OLL1073R-1. *Bioscience of Microbiota, Food and Health* 32: 23–32.
- Noh, D.O. and Gilliland, S.E. (1994). Influence of Bile on β -Galactosidase Activity of Component Species of Yogurt Starter Cultures. *Journal of Dairy Science* 77: 3532–3537.
- Nordmark, E.L., Yang, Z., Huttunen, E. and Radstrom, P. (2005). Structural studies of an exopolysaccharide produced by *Streptococcus thermophilus* THS. *Biomacromolecules* 6: 105–108.
- Ott, A., Hugli, A., Baumgartner, M. and Chaintreau, A. (2000b). Sensory investigation of yogurt flavor perception: mutual influence of volatiles and acidity. *Journal of Agricultural and Food Chemistry* 48: 441–450.
- Ott, A., Germond, J.E. and Chaintreau, A. (2000a). Origin of acetaldehyde during milk fermentation using C-13-labeled precursors. *Journal of Agricultural and Food Chemistry* 48: 1512–1517.
- Ott, A., Fay, L.B. and Chaintreau, A. (1997). Determination and origin of the aroma impact compounds of yogurt flavor. *Journal of Agricultural and Food Chemistry* 45: 850–858.
- Ozer, B. and Atasoy, F. (2002). Effect of addition of amino acids, treatment with β -galactosidase and use of heat-shocked cultures on the acetaldehyde level in yoghurt. *International Journal of Dairy Technology* 55: 166–170.
- Pala, V., Sieri, S., Berrino, F., Vineis, P., Sacerdote, C., Palli, D., Masala, G., Panico, S., Mattiello, A., Tumino, R., Giurdanella, M.C., Agnoli, C., Grioni, S. and Vittorio, K. (2011). Yogurt consumption and risk of colorectal cancer in the Italian European prospective investigation into cancer and nutrition cohort. *International Journal of Cancer* 129: 2712–2719.
- Pastink, M.I., Teusink, B., Hols, P., Visser, S., de Vos, W.M. and Hugenholtz, J. (2009). Genome-scale model of *Streptococcus thermophilus* LMG18311 for metabolic comparison of lactic acid bacteria. *Applied and Environmental Microbiology* 75: 3627–3633.
- Pelletier, X., Laure-Boussage, S. and Donazzolo, Y. (2001). Hydrogen excretion upon ingestion of dairy products in lactose-intolerant male subjects: importance of the live flora. *European Journal of Clinical Nutrition* 55: 509–512.

- Perdigón, G., de Moreno de LeBlanc, A., Valdez, J. and Rachid, M. (2002). Role of yoghurt in the prevention of colon cancer. *European Journal of Clinical Nutrition* 56(Suppl 3): S65–S68.
- Petit, C., Grill, J.P., Maazouzo, N. and Marczak, R. (1991). Regulation of polysaccharide formation by *Streptococcus thermophilus* in batch and in fed-batch cultures. *Applied Microbiology and Biotechnology* 36: 216–221.
- Petry, S., Furlan, S., Crepeau, M.-J., Cerning, J. and Desmazeaud, M. (2000). Factors affecting exocellular polysaccharide production by *Lactobacillus delbrueckii* subsp. *bulgaricus* grown in a chemically defined medium. *Applied and Environmental Microbiology* 66: 3427–3431.
- Pette, J.W. and Lolkema, H. (1950c). Acid formation and aroma formation in yoghurt. *Netherlands Milk and Dairy Journal* 4: 261–273.
- Pette, J.W. and Lolkema, H. (1950b). Growth stimulating factors for *Sc. thermophilus*. *Netherlands Milk and Dairy Journal* 4: 209–224.
- Pette, J.W. and Lolkema, H. (1950a). Symbiosis and antibiosis in mixed cultures *Lb. bulgaricus* and *S. thermophilus*. *Netherlands Milk and Dairy Journal* 4: 197–208.
- Petti, S., Tarsitani, G. and Simonetti D'Arca, A. (2008). Antibacterial activity of yoghurt against viridans streptococci *in vitro*. *Archives of Oral Biology* 53: 985–990.
- Plaisancié, P., Claustre, J., Estienne, M., Henry, G., Boutrou, R., Paquet, A. and Léonil, J. (2013). A novel bioactive peptide from yoghurts modulates expression of the gel-forming MUC2 mucin as well as population of goblet cells and Paneth cells along the small intestine. *Journal of Nutritional Biochemistry* 24: 213–221.
- Pochart, P., Dewit, O., Desjeux, J. and Bourlioux, P. (1989). Viable starter culture, beta-galactosidase activity, and lactose in duodenum after yogurt ingestion in lactase-deficient humans. *American Journal of Clinical Nutrition* 49: 828–831.
- Pool-Zobel, B.L., Münzner, R. and Holzapfel, W.H. (1993). Antigenotoxic properties of lactic acid bacteria in the *S. typhimurium* mutagenicity assay. *Nutrition and Cancer* 20: 261–270.
- Purohit, D.H., Hassan, A.N., Bhatia, E., Zhang, X. and Dwivedi, C. (2009). Rheological, sensorial, and chemopreventive properties of milk fermented with exopolysaccharide-producing lactic cultures. *Journal of Dairy Science* 92: 847–856.
- Purwandari, U., Shah, N.P. and Vasiljevic, T. (2007). Effects of exopolysaccharide-producing strains of *Streptococcus thermophilus* on technological and rheological properties of set-type yoghurt. *International Dairy Journal* 17: 1344–1352.
- Qin, Q.Q., Xia, B.S., Xiong, Y., Zhang, S.X., Lou, Y.B. and Hao, Y.L. (2011). Structural characterization of the exopolysaccharide produced by *Streptococcus thermophilus* 05-34 and its application in yogurt. *Journal of Food Science* 76: C1226–1230.
- Radke-Mitchell, L. and Sandine, W.E. (1984). Associative growth and differential enumeration of *Streptococcus thermophilus* and *Lactobacillus bulgaricus*: a review. *Journal of Food Protection* 47(3): 245–248.
- Rajagopal, S.N. and Sandine, W.E. (1990). Associative growth and proteolysis of *Streptococcus thermophilus* and *Lactobacillus bulgaricus* in skim milk. *Journal of Dairy Science* 73: 894–899.
- Ramchandran, L. and Shah, N.P. (2009). Effect of exopolysaccharides on the proteolytic and angiotensin-I converting enzyme-inhibitory activities and textural and rheological properties of low-fat yogurt during refrigerated storage. *Journal of Dairy Science* 92: 895–906.
- Rao, D.R., Reddy, A.V., Pulusani, S.R. and Cornwell, P.E. (1984). Biosynthesis and utilization of folic acid and vitamin B by lactic cultures in skim milk. *Journal of Dairy Science* 67: 1169–1174.
- Rasic, J. and Kurmann, J.A. (1978). Flavour and aroma in yoghurt. pp. 90–98. *In*: Rasic and Kurmann (eds.). *Yoghurt Scientific Grounds, Technology, Manufacture and Preparations*. Copenhagen.
- Rasmussen, T.B., Danielsen, M., Valina, O., Garrigues, C., Johansen, E. and Pedersen, M.B. (2008). *Streptococcus thermophilus* core genome: comparative genome hybridization study of 47 strains. *Applied and Environmental Microbiology* 74: 4703–10.
- Raya, R.R., Manca de Nadra, M.C., Pesce de Ruiz Holgado, A. and Oliver, G. (1986). Acetaldehyde metabolism in lactic acid bacteria. *Milchwissenschaft* 41: 397–399.

- Reid, G., Sanders, M.E., Gaskins, H.R., Gibson, G.R., Mercenier, A., Rastall, R., Roberfroid, M., Rowland, I., Cherbut, C. and Klaenhammer, T.R. (2003). New scientific paradigms for probiotics and prebiotics. *Journal of Clinical Gastroenterology* 37: 105–108.
- Rul, F., Ben-Yahia, L., Chegdani, F., Wrzosek, L., Thomas, S., Noordine, M.-L., Gitton, C., Cherbuy, C., Langella, P. and Thomas, M. (2011). Impact of the Metabolic Activity of *Streptococcus thermophilus* on the colon epithelium of gnotobiotic rats. *Journal of Biological Chemistry* 286: 10288–10296.
- Rysstad, G. and Abrahamsen, R.K. (1987). Formation of volatile aroma compounds and carbon dioxide in yogurt starter grown in cow's and goat's milk. *Journal of Dairy Research* 54: 257–266.
- Salas, M.M., Nascimento, G.G., Vargas-Ferreira, F., Tarquinio, S.B., Huysmans, M.C. and Demarco, F.F. (2015). Diet influenced tooth erosion prevalence in children and adolescents: Results of a meta-analysis and meta-regression. *Journal of Dentistry* 43: 865–875.
- Savaiano, D.A. (2014). Lactose digestion from yogurt: mechanism and relevance. *The American Journal of Clinical Nutrition* 99: 1251S–1255S.
- Savaiano, D.A., Abou El Anouar, A., Smith, D.E. and Levitt, M.D. (1984). Lactose malabsorption from yogurt, pasteurized yogurt, sweet acidophilus milk, and cultured milk in lactase-deficient individuals. *The American Journal of Clinical Nutrition* 40: 1219–1223.
- Savijoki, K., Ingmer, H. and Varmanen, P. (2006). Proteolytic systems of lactic acid bacteria. *Applied Microbiology and Biotechnology* 71: 394–406.
- Säwén, E., Huttunen, E., Zhang, X., Yang, Z. and Widmalm, G. (2010). Structural analysis of the exopolysaccharide produced by *Streptococcus thermophilus* ST1 solely by NMR spectroscopy. *Journal of Biomolecular NMR* 47: 125–134.
- Sawers, G. and Watson, G. (1998). A glycy radical solution: oxygen-dependent interconversion of pyruvate formate-lyase. *Molecular Microbiology* 29: 945–954.
- Sengül, N., Aslım, B., Uçar, G., Yücel, N., Işık, S., Bozkurt, H., Sakaoğullari, Z. and Atalay, F. (2006). Effects of exopolysaccharide-producing probiotic strains on experimental colitis in rats. *Diseases of the Colon and Rectum* 49(2): 250–258.
- Shahbal, S., Hemme, D. and Desmazeaud, M. (1991). High cell wall-associated proteinase activity of some *Streptococcus thermophilus* strains (H-strains) correlated with a high acidification rate in milk. *Lait* 71: 351–357.
- Shankar, P.A. and Davies, F.L. (1978). Proteinase and peptidase activities of yogurt starter bacteria. XX Intern. Dairy Congr., Paris.
- Shermak, M.A., Saavedra, J.M., Jackson, T.L., Huang, S.S., Bayless, T.M. and Perman, J.A. (1995). Effect of yogurt on symptoms and kinetics of hydrogen production in lactose-malabsorbing children. *American Journal of Clinical Nutrition* 62: 1003–1006.
- Sieuwerts, S., Molenaar, D., van Hijum, S.A.F.T., Beerthuyzen, M., Stevens, M.J.A., Janssen, P.W.M., Ingham, C.J., de Bok, F.A.M., de Vos, W.M. and van Hylckama Vlieg, J.E.T. (2010). Mixed culture transcriptome analysis reveals molecular basis of mixed culture growth in *Streptococcus thermophilus* and *Lactobacillus bulgaricus*. *Applied and Environmental Microbiology* 76: 7775–7784.
- Sieuwerts, S., de Bok, F.A., Hugenholtz, J. and van Hylckama Vlieg, J.E. (2008). Unraveling microbial interactions in food fermentations: from classical to genomics approaches. *Applied and Environmental Microbiology* 74(16): 4997–5007.
- Sonestedt, E., Wirfält, E., Wallström, P., Gullberg, B., Orho-Melander, M. and Hedblad, B. (2011). Dairy products and its association with incidence of cardiovascular disease: the Malmö diet and cancer cohort. *European Journal of Epidemiology* 26: 609–618.
- Spinnler, H.E., Bouillanne, C., Desmazeaud, M.J. and Corrieu, G. (1987). Measurement of the partial-pressure of dissolved CO₂ for estimating the concentration of *Streptococcus thermophilus* in coculture with *Lactobacillus bulgaricus*. *Applied Microbiology and Biotechnology* 25: 464–470.
- Stingele, F., Neeser, J.R. and Mollet, B. (1996). Identification and characterization of the eps (Exopolysaccharide) gene cluster from *Streptococcus thermophilus* Sfi6. *Journal of Bacteriology* 178: 1680–1690.

- Suzuki, I., Kato, S., Kitada, T., Yano, N. and Morichi, T. (1986). Growth of *Lactobacillus bulgaricus* in milk. 1. Cell elongation and the role of formic acid in boiled milk. *Journal of Dairy Science* 69: 311–320.
- Sybesma, W., Starrenburg, M., Kleerebezem, M., Mierau, I., de Vos, W.M. and Hugenholtz, J. (2003). Increased production of folate by metabolic engineering of *Lactococcus lactis*. *Applied and Environmental Microbiology* 69: 3069–3076.
- Tamime, A.Y. and Robinson, R.K. (1999). *Yoghurt Science and technology*. Tamime and Robinson (eds.). Woodhead Publishing, Cambridge England.
- Terence, D.T. and Vaughan, L.C. (1984). Selection of galactose-fermenting *Streptococcus thermophilus* in lactose-limited chemostat cultures. *Applied and Environmental Microbiology* 48: 186–191.
- Thomas, M., Wrzosek, L., Ben-Yahia, L., Noordine, M.-L., Gitton, C., Chevret, D., Langella, P., Mayeur, C., Cherbuy, C. and Rul, F. (2011). Carbohydrate metabolism is essential for the colonization of *Streptococcus thermophilus* in the digestive tract of gnotobiotic rats. *PLoS one* 6(12).
- Tinson, W., Broome, M.C., Hillier, A.J. and Jago, G.R. (1982). Metabolism of *Streptococcus thermophilus*. 2. Production of CO₂ and NH₃ from urea. *Australian J Dairy Technol* 37: 14–16.
- Touhami, M., Boudraa, G., Mary, J.Y., Soltana, R. and Desjeux, J.F. (1992). Clinical consequences of replacing milk with yogurt in persistent infantile diarrhea. *Annales de Pédiatrie (Paris)* 39: 79–86.
- Trapp, C.L., Chang, C.C., Halpern, G.M., Keen, C.L. and Gershwin, M.E. (1993). The influence of chronic yogurt consumption on population of young and elderly adults. *International Journal of Immunotherapy* 9: 53–64.
- Tsilingiri, K. and Rescigno, M. (2013). Postbiotics: what else? *Beneficial Microbes* 4: 101–107.
- Turcic, M., Rasic, J. and Canic, V. (1969). Influence of *Str. thermophilus* and *Lb. bulgaricus* culture on volatile acids content in the flavour components of yoghurt. *Milchwissenschaft* 5: 277–280.
- Vaillancourt, K., LeMay, J.-D., Lamoureux, M., Frenette, M., Moineau, S. and Vadeboncoeur, C. (2004). Characterization of a galactokinase-positive recombinant strain of *Streptococcus thermophilus*. *Applied and Environmental Microbiology* 70: 4596–4603.
- Van de Guchte, M., Penaud, S., Grimaldi, C., Barbe, V., Bryson, K., Nicolas, P., Robert, C., Oztas, S., Mangenot, S., Couloux, A., Loux, V., Dervyn, R., Bossy, R., Bolotin, A., Batto, J.-M., Walunas, T., Gibrat, J.-F., Bessières, P., Weissenbach, J., Ehrlich, S.D. and Maguin, E. (2006). The complete genome sequence of *Lactobacillus bulgaricus* reveals extensive and ongoing reductive evolution. *Proceedings of the National Academy of Sciences USA* 103: 9274–9279.
- Van de Water, J., Keen, C.L. and Gershwin, M.E. (1999). The influence of chronic yogurt consumption on immunity. *Journal of Nutrition* 129(7 Suppl): 1492S–5S.
- Van den Bogaard, P.T.C., Hols, P., Kuipers, O.P., Kleerebezem, M. and de Vos, W.M. (2004). Sugar utilisation and conservation of the gal-lac gene cluster in *Streptococcus thermophilus*. *Systematic and Applied Microbiology* 27: 10–17.
- Vanindegem, F., Zamfir, M., Adrian, T. and De Vuyst, L. (2004). Fermentation conditions affecting the bacterial growth and exopolysaccharide production by *Streptococcus thermophilus* ST 111 in milk-based medium. *Journal of Applied Microbiology* 97: 1257–1273.
- Van't Veer, P., Dekker, J.M., Lamers, J.W.J., Kok, F.J., Schouten, E.G., Brants, H.A.M., Sturmans, F. and Hermus, R.J.J. (1989). Consumption of fermented milk products and breast cancer: a case-control study in the Netherlands. *Cancer Research* 49: 4020–4023.
- Vaughan, E.E., vandenBogaard, P.T.C., Catzeddu, P., Kuipers, O.P. and deVos, W.M. (2001). Activation of silent gal genes in the lac-gal regulon of *Streptococcus thermophilus*. *Journal of Bacteriology* 183: 1184–1194.
- Veiga, P., Pons, N., Agrawal, A., Oozeer, R., Guyonnet, D., Brazeilles, R., Faurie, J.M., van Hylckama Vlieg, J.E., Houghton, L.A., Whorwell, P.J., Ehrlich, S.D. and Kennedy, S.P.

- (2014). Changes of the human gut microbiome induced by a fermented milk product. *Scientific Reports* 4: 6328.
- Veringa, H.A., Galesloot, T.E. and Davelaar, H. (1968). Symbiosis in yoghurt (II). Isolation and identification of a growth factor for *Lactobacillus bulgaricus* produced by *Streptococcus thermophilus*. *Netherlands Milk and Dairy Journal* 22: 114–120.
- Wilt, T.J., Shaikat, A., Shamliyan, T., Taylor, B.C., MacDonald, R., Tacklind, J., Rutks, I., Schwarzenberg, S.J., Kane, R.L. and Levitt, M. (2010). Lactose intolerance and health. Evidence report/technology assessment (Full rep.) 192: 1–410.
- WHO-World Health Organization (1995). The treatment of diarrhoea. A manual for physicians and other senior health workers. WHO/CDR/95.3 10/95. Geneva: WHO.
- Wu, Q., Tun, H.M., Leung, F.C.C. and Shah, N.P. (2014). Genomic insights into high exopolysaccharide-producing dairy starter bacterium *Streptococcus thermophilus*. *Scientific Reports* 4(4974).
- Yamada, T., Takahashi-Abbe, S. and Abbe, K. (1985). Effects of oxygen on pyruvate formate-lyase *in situ* and sugar metabolism of *Streptococcus mutans* and *Streptococcus sanguis*. *Infection and Immunity* 47: 29–134.
- Yang, Y., Shevchenko, A., Knaust, A., Abuduresule, I., Li, W., Hu, X., Wang, C. and Shevchenko, A. (2014). Proteomics evidence for kefir dairy in Early Bronze Age China. *Journal of Archaeological Science* 45: 178–186.
- Zhang, Q., Yang, B., Brashears, M.M., Yu, Z., Zhao, M., Liu, N. and Li, Y. (2014). Influence of casein hydrolysates on exopolysaccharide synthesis by *Streptococcus thermophilus* and *Lactobacillus delbrueckii* ssp. *bulgaricus*. *Journal of Food Science and Agriculture* 94: 1366–1372.
- Zheng, H., Liu, E., Hao, P., Konno, T., Oda, M. and Ji, Z.S. (2012). *In silico* analysis of amino acid biosynthesis and proteolysis in *Lactobacillus delbrueckii* subsp. *bulgaricus* 2038 and the implications for bovine milk fermentation. *Biotechnology Letters* 34: 1545–1551.
- Zisu, B. and Shah, N.P. (2003). Effects of pH, Temperature, Supplementation with Whey Protein Concentrate, and Adjunct Cultures on the Production of Exopolysaccharides by *Streptococcus thermophilus* 1275. *Journal of Dairy Science* 86: 3405–3415.
- Zourari, A. and Desmazeaud, M.J. (1991). Caractérisation de bactéries lactiques thermophiles isolées de yaourts artisanaux grecs. I. Souches de *Lactobacillus delbrueckii* subsp. *bulgaricus* et cultures mixtes avec *Streptococcus salivarius* subsp. *thermophilus*. *Lait* 71: 463–482.
- Zourari, A., Accolas, J.P. and Desmazeaud, M.J. (1992). Metabolism and biochemical characteristics of yogurt bacteria. A review. *Lait* 72: 1–34.