Indian J Anim Health (2022), 61(2): 242- 249
DOI: https://doi.org/10.36062/ijah.2022.03922

Review Article

Recent advances in dairy starter cultures: A review

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Abstract

Starter cultures are considered as the heart of the fermented dairy products industry. Apart from the basic function of producing lactic acid, starter cultures also impart numerous technological and health-beneficial properties to fermented dairy products. In this review, recent research works modeled to improve the technological properties of dairy starter cultures, like acceleration of the cheese ripening process, customer-oriented flavour and texture development, phage resistance, and immuno-modulation for increased food safety, are outlined. Propagating pH-sensitive bacteriophages in fermented dairy products to limit excessive souring to extend the shelf-life of these products may be a wonderful hypothesis.

Key words: Exopolysaccharides, Flavour components, Genetic modification, Phage resistance, Starter cultures

Highlights

- Dairy starter cultures are primarily used to accelerate the fermentation process.
- Great scientific advances have been made in dairy starters in the recent past.
- Advances in bacteriophage control, organoleptic improvement, and manufacturing process have been highlighted.
- The potential role of fermented dairy foods in the modulation of immune function has been discussed.

INTRODUCTION

Cultured dairy products are driving the growth of dairy foods consumption around the world. Starters are of great industrial significance as they play a vital role in the manufacturing process, flavour, and texture development of fermented dairy foods and provide health benefits particularly in modulating immune function. Empirically, from relying on the 'back-slopping' technique for fermentation of beverages, vegetables, dairy, and meat products, application of starter cultures in fermented foods are nowadays 'knowledge-based' and molecular tools are being increasingly used for strain improvement. Advances in genetics and molecular biology have provided opportunities for genomic studies of industrially useful organisms and 'tailor-making' of cultures that aim at the rational improvement of industrially valuable strains.

Historically, the role of microorganisms in brewing fermentation was first reported by Louis Pasteur in 1877 (Pasteur, 1879). Starter culture may be defined as the strain of microorganisms with stable features to produce desirable characteristics in food under controlled conditions (Holzapfel, 2002). The first commercial yeast starter culture was introduced in 1893 in Denmark by Emil Christian Hansen (Holzapfel, 1997). Starter cultures are primarily used to accelerate the fermentation process. They concomitantly improve sensory properties, guarantee uniformity of product quality, significantly reduce the production period, and enhance the safety of the products. Dairy starter cultures are primarily actively growing cultures of lactic acid bacteria (LAB) and are the major bacteria used in milk fermentations worldwide. The commonly used bacterial dairy starter cultures belong to the

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genera: *Lactobacillus*, *Lactococcus*, *Bifidobacterium*, *Pediococcus*, *Leuconostoc*, *Propionibacterium* and *Streptococcus.* Yeast cultures of *Saccharomyces cerevisiae*, *Debaryomyces hansenii* species, and the fungal cultures of *Aspergillus*, *Penicillium* and *Rhizopus* also find specific applications in the dairy industry (Latha *et al*., 2015). Starter cultures may be applied singly, as mixed cultures with two or more strains or as monocultures containing the genetic resources of at least two desirable strains.

In addition to the controlled denaturation of proteins due to the production of lactic acid, LAB is also predominantly used in food fermentation for its mild proteolytic and lipolytic activities, ability to synthesize peptides, antimicrobial metabolites, aromatic compounds, and exopolysaccharides (EPS) (Gaenzle, 2015). EPS play a crucial role in improving the texture of food products.

Emphasis has been laid on improving the performance of starter cultures in key areas like cheese ripening and metabolic engineering, bacteriophage resistance, and the production of antimicrobial compounds. Hybrid clones or recombinant monocultures of antibiotic-resistant lactobacilli produced by the fusion of protoplasts have been reported to possess higher reproducibility, acid production capacity, ability to assimilate and ferment a greater number of carbon sources (Borpuzari and Murgov, 1996; Denkova and Murgov, 2001).

This review aims to describe some of the significant scientific advances made in dairy starters in the recent past, including genomic studies on dairy starter cultures, engineering of culture profiles, advances in bacteriophage control, and the potential role of fermented dairy foods in the modulation of immune function.

Ripening acceleration

The long maturation time of cheese adds a high cost to the product. Attempts have been made to reduce the ripening period by utilizing enzymes and elevated temperatures (Karaca and Guven, 2018; Ha, 2019) and by using starter strains with customized proteolytic enzyme systems. Since only small peptides are transferred into the cheese cell, induced lysis of casein by facilitating the release of peptidolytic enzymes into the cheese matrix accelerated the cheese ripening process (Crow *et al*., 1995). Over-expression of gene encoding peptidase activity in *Lc. lactis* subsp. *cremoris* NM1 positively impacted cheese flavour and specific free amino acids in cheese (Guldfeldt *et al*., 2001). For example, a genetically modified proteolytic system of lactococcal strains using *Bacillus subtilis* neutral proteinase gene (McGarry *et al*., 1994) or peptidase gene from the highly proteolytic *Lc. helveticus* (Joutsjoki *et al*., 2002) accelerated the rate of proteolysis in cheeses, thus shortening the ripening period. The cheese was manufactured with the bacteriocin-producing strain *Lc. lactis* ssp. *lactis* DPC3286 as an adjunct starter with *Lc. lactis* ssp. *cremoris* and exhibited increased lysis of starter cells which was in turn associated with higher concentrations of free amino acids, reduced bitterness, and higher grading scores (Morgan *et al*., 1997).

Bacteriophage resistance

Phage sensitivity of certain starter cultures is a serious issue in dairy fermentation that results in heavy production loss. Virulent phages of *Lc. lactis* spp. are the most frequently encountered phages in milk plants during cheese and dairy beverages production. Additionally, phages attacking *Streptococcus thermophilus* are often encountered in cheese and to a lesser degree in yoghurt manufacturing.

The first demonstration of plasmid-coded phage defense mechanisms in commercial cheese starter bacteria by conjugation was illustrated by Sanders *et al*. (1986) and thereafter by another researcher (Coakley *et al*., 1997). Several strains of *Lactococcus* exhibiting improved phage resistance are already in commercial use (Klaenhammer and Fitzgerald, 1994). Individual strains were designed to contain multiple defenses, each targeting different points in the phage lytic cycle, resulting in dramatically improved phage resistance properties of the host (Klaenhammer, 1989).

Lactobacilli and *Leuconostoc* spp. are less susceptible to phage attack. The mechanisms by which the LABs defend themselves against bacteriophages are inhibition of phage adsorption; blocking of phage DNA injection; restriction-modification systems; phage abortive infection systems; and the CRISPR/*cas* systems (clustered regularly interspaced short palindromic repeats). The knowledge about natural phage resistance mechanisms together with a set of genetic tools has helped to develop engineered defense systems conferring higher levels of resistance and/or broader phage specificity (Barrangou and Horvath, 2012; Szczepankowska *et al.*, 2013).

To enhance the fermentation performance of yoghurt in the presence of phages, a 3-component yogurt starter containing *Str. thermophilus* sensitive, *Str. thermophilus* insensitive and *L. bulgaricus* strains were designed by Ma *et al.* (2015).

Gas production and subsequent food spoilage, the appearance of fissures, cracks, or holes are undesirable consequences of the growth of saprophytic *E. coli* in cheese. The use of bacteriophages as biocontrol agents provided an effective tool to combat the early blowing of cheese without noticeably altering its microbiological or physicochemical parameters (Tabla *et al.*, 2022).

Flavour and texture development

Diacetyl imparts the buttery flavour and aroma to foods and is derived from the metabolism of citrate by LAB. With the knowledge of the enzymology and genetics of citrate metabolism, different methods have been developed to produce metabolically engineered *Lc. lactis* strains to augment diacetyl production (De Vos, 1996). Hugenholtz *et al.* (2000) reported on the production of diacetyl from glucose metabolism instead of citrate by *Lc. lactis*. Involving genome-scale flux models to simulate and analyze network capabilities and cell function in continuous cultures under aerobic or anaerobic conditions, Oliveira *et al.* (2005) successfully designed a prototype for increased production of diacetyl by *Lc. lactis* strains.

Metabolically engineered *Lc. lactis* produced high amounts of diacetyl (6.7 g/L) from a virtually free dairy waste-based substrate. The diacetyl could be easily concentrated and purified by vacuum distillation before use in foods or could be used as a precursor for making butter aroma compounds, *i.e.*, 2, 3-butanediol (Liu *et al.*, 2021).

Amino acids and small peptides, the proteolytic degradation products of casein, are essential for the metabolism of the fastidious lactococci and contribute to the development of flavour in fermented-milk products (Van Alen-Boerrigter *et al.*, 1991). Proteolysis of casein to small peptides and amino acids and lipolysis of milk fats to free fatty acids and other volatile compounds, such as methyl ketones, thioesters and lactones are the important biochemical reactions in flavour development in cheese. Enhanced production of aromatic compounds from amino acids, which are otherwise a rate-limiting factor, was made possible by encoding the gene for producing the enzyme involved in the stimulated conversion of amino acids to aroma compounds from a non-dairy *Lc. lactis* strain (Tanous *et al.*, 2005). Addition of low levels of highly proteolytic strain *Lb. helveticus* DPC4571 to a standard lactococcal starter system had a significant effect in altering the flavour profile of the final cheeses and lysis of *Lb. helveticus* resulted in increased production of flavour precursors and some volatile compounds of cheese (Hannon *et al.*, 2007).

LAB produces acetaldehyde, an important aromatic compound in dairy products, through several pathways. The most important pathway, however, is through the conversion of threonine into acetaldehyde and glycine, a reaction catalyzed by threonine aldolase. In *Str. thermophillus*, the enzyme with threonine aldolase activity is serine hydroxy-methyltransferase (SHMT) encoded by the *glyA* gene. Over-expression of *glyA* in *Str. thermophillus* strains resulted in the overproduction of acetaldehyde by 80-90% compared to parental strains (Chaves *et al.*, 2002). Another attempt to improve acetaldehyde production through metabolic engineering of *Lc. lactis* was reported by Bongers *et al.* (2005).

Diacetyl and acetoin, the key component in the aroma of fermented milk, are generally produced in low concentrations by starter cultures. Tian *et al.* (2022) found that recombinant culture of *Lacticaseibacillus casei* generated by modification of its multiple genes encoding enzymes for aroma production had a synergistic effect in the synthesis of the increased amount of diacetyl and acetoin during fermentation of milk.

Bacillus sp. DL01, which shows high acetoin production, was metabolically engineered for diacetyl production by manipulating factors that affected the diacetyl metabolic pathway (Hao *et al.*, 2017).

EPS have vast applications in the dairy, non-dairy, meat, and bakery industries. In the dairy industry, EPS are primarily used as thickeners and texturizers to increase the viscosity of the products. They also act as stabilizers by binding water, decreasing syneresis, and interacting with various milk constituents. EPS are excreted by *Lactobacillus* during their growth. They are natural, non-toxic, and bio-products with diverse chemical structures and biological activities. Around 165 Lactobacilli species have been identified as EPS-producers, including *Lb. plantarum*, *Lb. delbrueckii* subsp. *bulgaricus*, *Lb. casei*, *Lb. brevis*, *Lb. curvatus*, *Lb. helveticus*, *Lb. rhamnosus*, *Lb. acidophilus*, and *Lb. johnsonii*. Although *Lactobacillus* produces little of the EPS as compared to other bacteria, they have higher functional ability and resistance to the variable processing conditions (Bibi *et al.*, 2021). *Limosilactobacillus fermentum* ING8, a LAB strain isolated from *dahi*, is a multi-functional non-starter culture and has exhibited superior qualities in improving the technological properties *viz.*, EPS production, antimicrobial activity, and galactose utilization in different dairy products (Pakroo *et al.*, 2022).

Immune modulation

Probiotics are viable microorganisms, that while ingested in sufficient amounts, exert health benefits on the host" (FAO/WHO, 2002). Lactobacilli and Bifidobacteria are primarily used as probiotic cultures in fermented dairy products. Probiotics modulate the immune function mainly by modulating the production of cytokines and antimicrobial peptides to promote the health of consumers.

Contamination of commercial milk and milk products with heavy metals and mycotoxins is a serious issue. By acting as biosorbants, probiotics bind to heavy metals and toxins, and decrease their bioavailability and hazards in the human body. *Lb. bulgaricus*, Kefir grains, *Lb. acidophilus*, and *Lb. rhamnosus* have been used successfully in decreasing aflatoxin in milk and dairy products. Kefir grains are efficient removers of different heavy metals (Mirmahdi *et al.*, 2021).

Kefir and its probiotic contents modulate the immune system by suppressing viral infections. Kefir exerts antiviral action by the mechanisms of enhancing macrophage production, increasing phagocytosis, boosting production of a cluster of differentiation-positive CD4+, CD8+, immunoglobulin, B cells, T cells, neutrophils, as well as cytokines (Hamida *et al.*, 2021).

Probiotic efficacy and anticancer activities of *Lactiplantibacillus plantarum* ESSG1 (MZ683194.1) and *L. pentosus* ESSG2 (MZ683195.1) isolated from dairy products were confirmed by Abd Ellatif *et al.* (2022). *Lacticaseibacillus rhamnosus* could be used to develop recombinant strains to offer enhanced beneficial effects over other probiotics (Mathipa-Mdakane and Thantsha, 2022). *L. plantarum* LC38, a novel probiotic strain isolated from camel milk, was found to enhance the wound healing property in a diabetic rat model due to its antimicrobial properties (Chouikhi *et al.*, 2022). The probiotic-based oral vaccine has been developed by Pandya *et al.* (2021). Nisin, a bacteriocin produced by *Lc. lactis* is in use as a food-grade additive to cheese and other foods to control the growth of spoilage microorganisms (Klaenhammer, 1993). Bacteriocins produced by LAB inhibit the growth of dairy pathogens including

L. monocytogenes. Bacteriocin-producing genes of different LABs have been successfully transferred to dairy starter cultures enhancing their antimicrobial spectrum (Geisen and Holzapfel, 1996). Joerger and Klaenhammer (1990) transferred the gene for helveticin J, a bacteriocin from *Lb. helveticus* to *Lb. acidophilus* enabling the latter to produce helveticin J. The gene responsible for the production of lysozyme, an enzyme exhibiting lethal action against common dairy pathogen *L. monocygenes* from *Escherichia coli* was successfully transferred by Van de Guehte *et al*. (1992) to a strain of *Lc. lactis* rendering the dairy starter culture inhibitory to the contaminating *L. monocygenes*. Pisano *et al.* (2022) noted that *Lc. lactis* and *L. plantarum* strains as starter or adjunct cultures increased the safety of products against *L. monocytogenes* by producing organic acids and bacteriocin.

Bacteriocins act mainly against closely related species. They are reported to inhibit some strains in mixed cultures. By transfer of a resistance gene to sensitive cultures, resistance against the bacteriocin may be developed and could be used in a mixed culture (Von Wright *et al.*, 1990). Lacticin 3147, a bacteriocin is effective in many food systems for the control of *L. monocygenes* (O'Sullivan *et al.*, 2006).

Functional genomics in dairy starters

Dairy starter culture research is currently centering around functional genomics overlaid on traditional microbiology. The study on the intricate metabolic networks of industrial LAB strains will provide a repertoire of genetic markers for the 'data-based' selection of desirable LAB and the application of molecular tools for strain improvement. The first genome sequence of a lactic acid bacterium was that of *Lc. lactis* subsp. *lactis* (Bolotin *et al*., 2001). Genome sequencing of probiotic strains or 'classical' or traditional starter cultures have been of great interest to scientists as they assist in the elucidation and validation of health and other technological benefits claimed for these organisms. So far, a total of 25 LAB genomes have been sequenced and annotated (15 *Lactobacillus*, 3 *Lactococcus*, 3 *Streptococcus*, 2 *Leuconostoc*, 1 *Pediococcus* and 1 *Oenococcus*), while 67 projects are in progress (59 *Lactobacillus*, 3 *Lactococcus*, 3 *Leuconostoc*, 1 *Streptococcus*, 1 *Oenococcus*) (Mills *et al.*, 2010).

Extracellular cell wall proteinase enzyme (lactocepin) of *Lc. lactis* causes high levels of proteolysis and imparts bitterness to cheese. Broadbent *et al*. (2002) concluded that the bitterness defect in cheese could be altered through gene exchange or replacement in the starter culture by the construction of isogenic starter bacteria that resisted autolysis and differed only in lactocepin specificity.

Since the β-galactosidases produced by the starter cultures have low transgalactosylation activities resulting in galactose accumulation in dairy products that reduce the quality of fermented dairy products, Zhao *et al*. (2022) cloned a β-galactosidase gene encoded for high β-galactosidase hydrolysis activity from the strain *Str. thermophilus* SDMCC050237 to catalyze galactose into galactooligosaccharides (GOS) to improve the transgalactosylation activity of β-galactosidase for the manufacture of GOS-enriched yogurt. β-galactosidase converts lactose into glucose and galactose, and also catalyzes galactose to form GOS. Robitaille *et al*. (2007) developed a recombinant galactose-fermenting strain named MRAAC by introducing a plasmid carrying a functional *galK* gene from *Str. salivarius* into the non-galactose-producing *Str. thermophilus* MR-1C strain.

Conclusion and future directions

This review highlights the progress made in recent years in dairy starter cultures and discusses directions that will ultimately change the concept of dairy starters and interpretation of its performance. The intensive research carried out throughout the world, particularly in genomics and genetic engineering has brought about tremendous improvements in phage resistance, immune function, stabilization of important proteolytic activities and enzymatic properties of dairy starters, making it an industrially valuable knowledge-based culture. Integrated systems biology to combine the multiple perspectives of post-genomics technologies will elucidate the metabolic interactions among microorganisms. Future research would delve into the variation in cell physiology within the microbial populations as microenvironments or the so-called 'Nest' (Katsaras and Leistner, 1991) created due to spatial distribution within the cheese matrix could affect localized interactions of starters and non starter LABs. The use of pH-activated bacteriophages to restrict further souring of fermented dairy products like yoghurt beyond pH 4.4 may be a novel approach in extending the 'best before' end of such fermented dairy products.

Conflict of interest: Authors have no conflict of interest in this study.

Author's contribution: RRS: Acquisition of data and substantial contribution to the conception and design; RNB: Substantial contribution to the conception and design, interpretation of the results or drafting or critically revising the manuscript; TB: Substantial contribution to the conception and design.

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Received- 18.03.2022, Accepted- 19.11.2022, Published- 28.11.2022 (Online), 01.12.2022 (Print)