An Overview of Dairy Microflora

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Abstract

An assembly of bacterial and fungal communities in the milk and dairy products presents a complete picture of dairy born microflora. Fermentation and pasteurization processes are crucial for the maintenance of microflora. Chemical composition and initial colonization of bacteria and fungi define the mutualistic pattern of microbial communities. The abundance and variety of microbial communities in milk are highly variable and depend upon many factors ranging from the health of milking animals to the milking practices, storage, and transportation methods. Probiotics are beneficial microbes, specifically lactic acid bacteria such as *Lactobacilli* and *Bifidobacteria* are generally regarded as safe (GRAS) microorganisms that benefit the host physiology upon ingestion. Lactic acid bacteria are the predominant group in all dairy microbiota that display a diverse range of strains associated with the milk from different animals. Few dairy microbes behave as pathogens as well as the cause of food spoilage. Human diseases from milk-borne pathogens are usually due to raw milk or products made from raw milk. However, the enormous medicinal and health-promoting impact of microbes and their additives overcome the limited effects of few harmful bacteria in the dairy environment. In addition to the known advantages of dairy bacteria, the phenomenon of psychobiotics is introducing a new therapeutic channel for the treatment of many psychological disorders.

Keywords

Dairy microflora · Probiotics · Lactic acid bacteria · Nutraceutical · Psychobiotics

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4.1 Introduction

Dairy microflora refers to the assemblage of microorganisms present in milk and its associated products. Milk is an important food for human consumption and was considered as a drink of ancient times that aided in the survival of generations. For centuries it has served as a cure for a variety of diseases and as an instant source of energy (Shori 2012). Today, it is considered to host a complex microbial community with great diversity. The microbial quality of milk products is highly dependent on their initial microflora colonization. Each kind of milk and dairy products develops a specific microflora composition. The most common dairy associated microflora includes *Lactobacillus*, *Bifidobacterium*, *Enterococcus*, *Streptococcus*, *Pediococcus*, *Propionibacterium*, and *Leuconostoc* bacterial genera, and *Saccharomyces* and *Aspergillus* yeast genera (Abushelaibi et al. 2017; Amara and Shibl 2015; Ogier and Serror 2008).

Fermentation is one of the common and primitive methods for processing and preservation of the microbial community that has been used worldwide. This method conserves the food and makes sure that the food is safe for human consumption by boosting their desired microbial composition. As a source of probiotics, raw and fermented forms of milk are well known around the world. A combination of fresh and lyophilized, one or more pure microorganisms (starter cultures) are routinely used for the fermentation of dairy products (Ahmed and Kanwal 2004; Lourens-Hattingh and Viljoen 2001; Vinderola et al. 2000). Sugars are metabolized into lactic acid, which enables food preservation by providing an acidic environment that is hostile for spoilage microorganisms (Hati et al. 2013). The diversity of microorganisms is highly varied in raw and fermented milk, as well as in dairy products like yogurt, cheese, kefir, and dahi. The quality of dairy products entirely depends on the viable count of microbiota in fresh milk, breeding area, nutritive condition, breed type, age of the animal, stage of lactation, and milking practices (Khaskheli et al. 2005). Milk microbiota exploration relies on both culture-dependent and molecular culture-independent approaches, including sequencing of 16S rRNA clone libraries and metabolomics, based on 16S rRNA gene amplicon sequencing (Gill et al. 2006; Verdier-Metz et al. 2012).

4.2 Different Sources of Milk Microbes

Various bovine and non-bovine milk sources have been reported in the account of diverse microflora. Generally, all types of milk carry a variety of bacterial and fungal strains in its raw and fermented forms. However, complete specie level identification and accurate count of viable and non-viable microorganisms in pasteurized and fermented forms are not known yet. Modern high-throughput sequencing technologies (including second- and third-generation sequencing and combinations thereof) enabled the detection and inventory of animal-specific complex microbial communities. Milk microbiota is well documented in various hosts like cows (Addis et al. 2016; Falentin et al. 2016; Oikonomou et al. 2014), goats, sheep, camel,

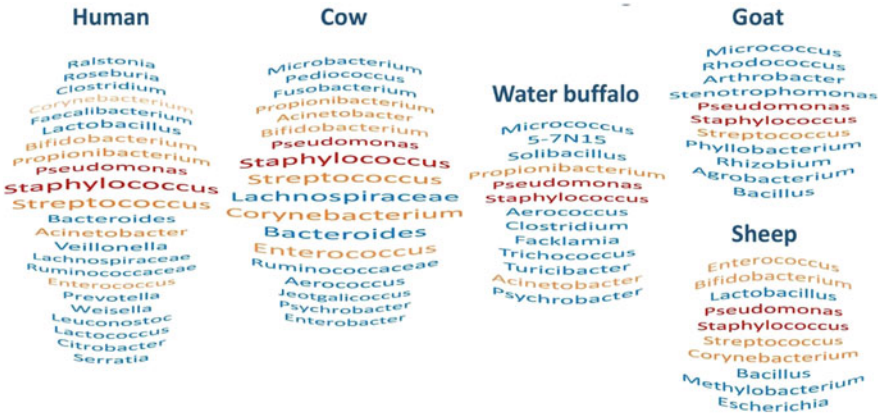

Fig. 4.1 Milk-associated microbiota in humans, cow, water buffalo, sheep, and goat. Major taxa, Red and orange taxa are shared between all human and animal species or present in three species out of five, respectively. For humans and bovines, taxa size reveals citation frequency

donkeys, buffalo, deer, reindeer, mice (Catozzi et al. 2017; De Los DoloresSoto et al. 2017; McInnis et al. 2015; Quigley et al. 2013; Treven et al. 2015), and human (Hunt et al. 2011; Jost and Lacroix 2013; Fitzstevens et al. 2017). Nevertheless, significant differences have been reported in the milk bacterial communities of different ruminants, such as water deer, reindeer, and goat, suggesting host-microbial adaptation, although the influence of environment and herd management should not be excluded. Recently, a comparison of bovine and human milk microbiota exhibited the clear metataxonomic picture and revealed the presence of common genera including *Bifidobacterium*, *Staphylococcus*, *Pseudomonas*, *Streptococcus*, *Propionibacterium*, *Corynebacterium*, *Bacteroides,* and *Enterococcus* which are among the most reported taxa in scientific reports related to bovine and human microbiota (Fig. 4.1) (Oikonomou et al. 2014).

4.2.1 Cow Milk

Culture-independent approaches described cow milk microbiota as one of the complex and diverse community comprised of 146 bacterial strains, with *Bacteroides*, *Bifidobacterium*, *Corynebacterium*, *Enterococcus*, *Propionibacterium*, *Pseudomonas*, *Staphylococcus,* and *Streptococcus* being the predominant taxa (Addis et al. 2016; Boix-Amorós et al. 2016; Cabrera-Rubio et al. 2012; Derakhshani and Naghizadeh 2018; Hoque et al. 2019; Jiménez et al. 2015; Murphy et al. 2017; Oikonomou et al. 2014; Urbaniak et al. 2016). Similar milk bacterial profiles were noticed through the shotgun metagenomic approach (Jiménez et al. 2015; Pärnänen et al. 2018) and described the presence of fungal, protozoal, and viral DNA. Colostrum microbiome depends on the lactation number and major taxonomic profile; and diversity of primiparous colostrum microbiome includes the presence of *Staphylococcus*, *Prevotella*, *Ruminococcaceae*, *Bacteroidales*, *Clostridiales,* and *Pseudomonas* (Lima et al. 2018).

4.2.2 Buffalo Milk

Differential microbial communities and diversity in buffalo milk include major taxa of *Micrococcus*, *Propionibacterium*, *Solibacillus*, *Staphylococcus*, *Aerococcus*, *Facklamia*, *Trichococcus*, *Turicibacter*, *Clostridium*, *Acinetobacter*, *Psychrobacter,* and *Pseudomonas* through Ion Torrent 16S rRNA gene sequencing (Catozzi et al. 2017).

4.2.3 Sheep Milk

Sheep milk is reported to have various genera of lactic acid bacteria. These genera are identified as *Bacillus*, *Enterococcus*, *Lactobacillus*, *Lactococcus*, and *Leuconostoc*. The species identified for these genera are *Bacillus shackletonii*, *E. casseliflavus*, *E. durans*, *E. faecium*, *Lactobacillus rhamnosus*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus casei*, *Lactobacillus delbrueckii*, *Lactococcus lactis* ssp. *cremoris*, *Lactococcus lactis* ssp. *lactis*, *Lactococcus lactis subsp. biovar diacetylactis,* and *Leuconostoc* spp. (Acurcio et al. 2014; Aziz et al. 2009; Medina et al. 2011; Patil et al. 2019).

4.2.4 Goat Milk

Lactic acid bacteria isolated from the goat milk belonged to the genera *Enterococcus*, *Lactobacillus*, *Lactococcus, Leuconostoc*, *Pediococcus,* and *Streptococcus*. Isolated species are identified as *Enterococcus faecium*, *Enterococcus durans*, *Enterococcus faecalis*, *Enterococcus hirae*, *Enterococcus avium*, *Lactobacillus acidophilus Lactobacillus delbrueckii subsp. bulgaricus*, *Lactobacillus fermentum*, *Lactobacillus lactis subsp. lactis Lactobacillus paracasei*, *Lactobacillus plantarum*, *Lactobacillus rhamnosus*, *Lactobacillus reutei*, *Lactobacillus casei*, *Lactobacillus bulgaricus*, *Lactobacillus brevis*, *Lactobacillus curvatus*, *Leuconostoc mesenteroides subsp. mesenteroides*, *Leuconostoc mesenteroides subsp. dextranicum*, *Lactococcus plantarum*, *Lactococcus lactis subsp. lactis*, *Lactococcus raffinolactis*, *Pediococcus pentosaceus, Streptococcus thermophiles*, *Streptococcus salivarius subsp. thermophillus* (Medina et al. 2011; Mittu and Girdhar 2015; Perin and Nero 2014; Pisano et al. 2019).

4.2.5 Camel Milk

Nowadays an increasing attention is being focused towards consumption of camel milk. Its composition is closer to human milk than cow's milk; therefore it is better for humans especially for infants and children. Camel milk is an enriched source of *Lactococcus*, *Lactobacillus*, *Enterococcus*, *Streptococcus*, *Weissella*, and *Pediococcus.* Isolated strains belonged to *Enterococcus durans*, *Enterococcus faecium*, *Enterococcus gallinarum*, *Lactobacillus brevis*, *Lactobacillus salivarius*, *Lactobacillus reuteri*, *Lactobacillus fermentum*, *Lactobacillus plantarum*, *Lactobacillus pentosus*, *Lactobacillus helveticus*, *Lactococcus garvieae*, *Lactococcus lactis*, *Leuconostoc pseudomesenteroides*, *Leuconostoc mesenteroides*, *Pediococcus pentosaceus*, *Pediococcus acidilactici*, *Weissella sp. t4r2c13*, *Weissella paramesenteroides*, *Weissella confusa*, *Streptococcus infantarius subsp. infantarius*, *Streptococcus equinus*, and *Str. thermophilus* (Abushelaibi et al. 2017; Amara and Shibl 2015; Bin Masalam et al. 2018; Edalati et al. 2019; Fguiri et al. 2015; Ogier and Serror 2008; Rahmeh et al. 2019).

4.3 Sources of Contaminant Microbes in Milk

The microbiological quality of dairy products reflects good hygienic practices during the milking process; raw milk contamination may occur in diseased or infected animals with environmental bacteria (Kongo et al. 2008). The detection of mesophilic aerobes and total coliforms is a clear indication of *E. coli* contamination; in addition to this the presence of *L. monocytogenes* and *Salmonella spp*. revealed poor microbiological quality of dairy products and cause interference with the native microbiota of milk. The predominant bacterial species isolated at the dairy farm comes from the water, feedstuffs, and milking equipment. In this context, *Bacillus licheniformis* and *Bacillus pallidus* act as entry points being in the form of highly heat-resistant spores in raw milk. The contamination risk of such aerobic spore-forming bacteria could lead to spoilage of milk and dairy products. The fecal material attached to the udder skin of milking animals is another source of contamination. Many species of *Lactobacillus* and *Enterococcus* are major fecal genera in the milk from rural and farm animals.

4.4 Indigenous Bacterial Community Composition

4.4.1 Raw Milk

The abundance and variety of microbial communities in raw milk varies and depends upon many factors ranging from the health of milking animal, to the milking practices, storage, and transportation methods (Kable et al. 2019; Skeie et al. 2019). The immediate cold storage of fresh milk reduces the bacterial growth and keeps milk in its native load of microflora (Li et al. 2018). The breeding practices, lactation period, and availability of feeding plants in specific geographic location of herd are important factors for the change of microbial community patterns in the milk (Kable et al. 2019; Li et al. 2018; Parente et al. 2020; Skeie et al. 2019).

Modern high-throughput metagenomic sequencing of milk is a robust tool for the identification and estimation of indigenous microbiota of milk (Ercolini 2013; Zhang et al. 2019). Recently, Li et al. (2016) reported *Proteobacteria* as predominant group in fresh buffalo milk; however the population of abundance of *Firmicutes* increased and *Proteobacteria* and *Bacteroidetes* decreased significantly during the 24 h of cold storage. Looking at the genera-level microbial population pattern, *Streptococcus*, *Lactococcus,* and *Pseudomonas* were found in the fresh milk, and after 24 h of refrigeration the abundance of *Lactococcus* and *Streptococcus* populations increased significantly ($P < 0.05$), with the *Lactococcus* population contributing up to 38.6% of the total microflora (Li et al. 2016). One of the noticeable aspects was the robust growth of *Pseudomonas* and *Acinetobacter* genera (62%) in 72 h of cold storage (Fig. 4.2; Li et al. 2016).

4.4.2 Pasteurized Milk

Due to risk of pathogen contamination in milk produced from healthy animals under sanitary milk conditions, pasteurization of milk prior to consumption destroys pathogens, and provides hygienic milk (Fusco et al. 2020; Melini et al. 2017). Occasionally, human illness has been linked to pasteurized milk products but these cases usually have been a result of contamination of the product after pasteurization or due to improper pasteurization.

Despite the pasteurization process, a diverse bacterial population is a key characteristic feature of milk. According to Li et al. (2016), *Paenibacillus* is a dominated taxon at genus level in the microbial population. Other predominant bacterial populations appeared after prolonged storage, were psychotropic in nature, and were mostly associated with the spoilage of dairy products (Li et al. 2016). However, pasteurization appeared sufficient for eliminating contaminants from the *Pseudomonas* and *Acinetobacter* genera. However, there is a crucial need for developing novel technologies for controlling the proliferation of *Paenibacillus* to extend the shelf life of pasteurized milk products (Doll et al. 2017; Li et al. 2016).

Pasteurized milk bacterial composition did not significantly change during a storage period of 7 days; however the population of *Lactococcus* increased, while *Streptococcus* reportedly decreased (Li et al. 2016). At phylum level, *Firmicutes* and *Proteobacteria* contributed to more than 90% of the microbial composition after 7 days of storage. However, after 14 days of storage period, there was a significant increase in the population of *Firmicutes*, with a decrease in the population of *Proteobacteria* (Li et al. 2016). The analysis of the pasteurized milk after 21 days of storage showed that the *Firmicutes* increased and contributed to 90% of the total composition, along with *Paenibacillus* which increased to 80% in the bacterial population (Fig. 4.3; Li et al. 2016).

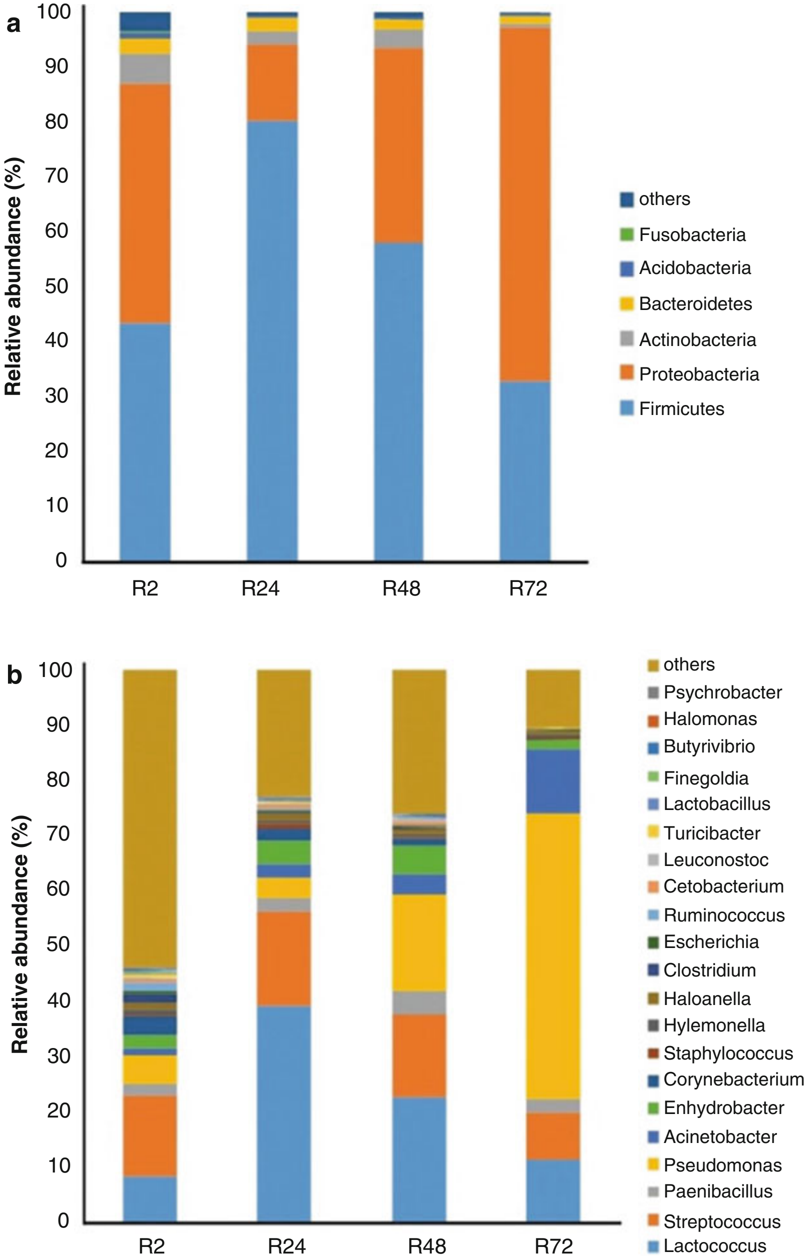

Fig. 4.2 Composition of the indigenous microflora, at the phyla (**a**) and genus (**b**) levels, in raw milk samples stored under refrigerated temperatures. Data represent the mean percentage from the metagenomics analysis of three separate raw milk samples. R_2 = raw milk samples stored for 2 h, R_{24} = raw milk samples stored for 24 h, R_{48} = raw milk samples stored for 48 h, R_{72} = raw milk samples stored for 72 h (Li et al. 2016)

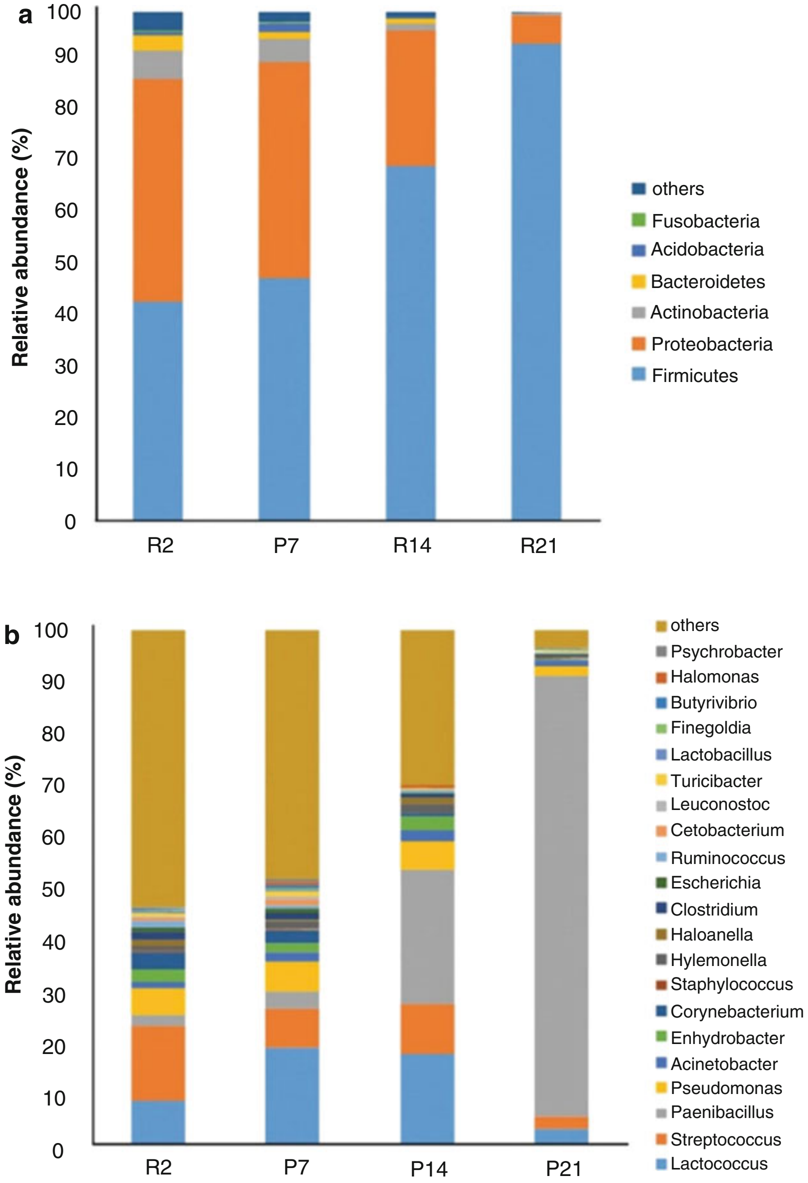

Fig. 4.3 Composition of the indigenous microflora, at both the phyla (**a**) and genus (**b**) levels, in pasteurized milk stored at refrigerated temperature. Data represent the mean percentages from the metagenomic analysis of 3 separate raw milk samples. R_2 = raw milk samples stored for 2 h, P_7 = pasteurized milk samples stored for 7 days, P_{14} = pasteurized milk samples stored for 14 days, P_{21} = pasteurized milk samples stored for 21 days (Li et al. 2016)

4.4.3 Fermented Milk

Fermented milk and its associated products are the richest and traditional source of probiotic microorganisms (Bernardeau et al. 2006). Naturally fermented milk has a variable microbial diversity in each of the resultant products, which contributes to their taste and texture (Zhong et al. 2016). Fermentation results in the functionally active microbial population to increase the bioavailability of nutrients for the consumers, while degrading toxic components to enhance the safety and bio-preservation of the final product (Tamang et al. 2016a). Low pH, fermented environment is an ideal medium to flourish beneficial microbial population (Savadogo et al. 2006; Sun et al. 2020). Fermented milk associated lactic acid bacteria (LAB) include *Enterococcus*, *Lactobacillus*, *Lactococcus*, *Leuconostoc*, *Pediococcus*, *Weissella*, *Bifidobacterium*, etc. these species of these genera are widely present in all types of milk (Axelsson et al. 2012; Tamang et al. 2016b).

Gao et al. (2017) reported *Lactococcus* as most predominant and *Lactobacillus* as subdominant genera in the milk samples collected in different times of year. Other genera found are *Leuconostoc*, *Streptococcus*, *Enterococcus*, *Chryseobacterium*, *Acetobacter*, *Weissella*, *Dysgonomonas*, *Macrococcus*, *Xenophilus*, *Pseudoclavibacter*, and *Corynebacterium* in variable proportions. Among fungal genera, *Pichia*, *Kluyveromyces*, and *Geotrichum* are found predominantly in the milk through the year. However, *Naumovozyma* and *Hanseniaspora* are subdominant genera (Fig. 4.4; Gao et al. 2017).

4.5 Types of Microbes

4.5.1 Beneficial Microbes

Beneficial bacteria are well known as "Probiotics" (usually lactic acid bacteria such as *Lactobacilli* and *Bifidobacteria*) that benefit the host physiology upon ingestion. Food and Agriculture Organization (FAO) and World Health Organization (WHO) defined probiotics as "Live microorganisms which when administered in adequate amount confers a health benefit on the host". They have become very popular over the past two decades due to their countless benefits to human health and for this reason they have been incorporated in many food-related products, mainly fermented products. Probiotic strains are marketed in the form of capsules, powder, or fermented products. The global market of probiotics is rapidly increasing annually due to consumers' interest in optimizing their health with functional foods (Di Cerbo and Palmieri 2015).

Lactic acid bacteria are generally regarded as safe (GRAS) microorganisms and are gram positive, facultative aerobes or anaerobes with bacilli, coccobacilli, or cocci morphology. These are non-respiratory, catalase-negative, acid-tolerant, and non-spore-forming bacteria, grouped on the basis of physiological, morphological, and metabolic constellation. These bacteria are normally associated with human and animal healthy mucosal surfaces and are a part of various animal and plant niches.

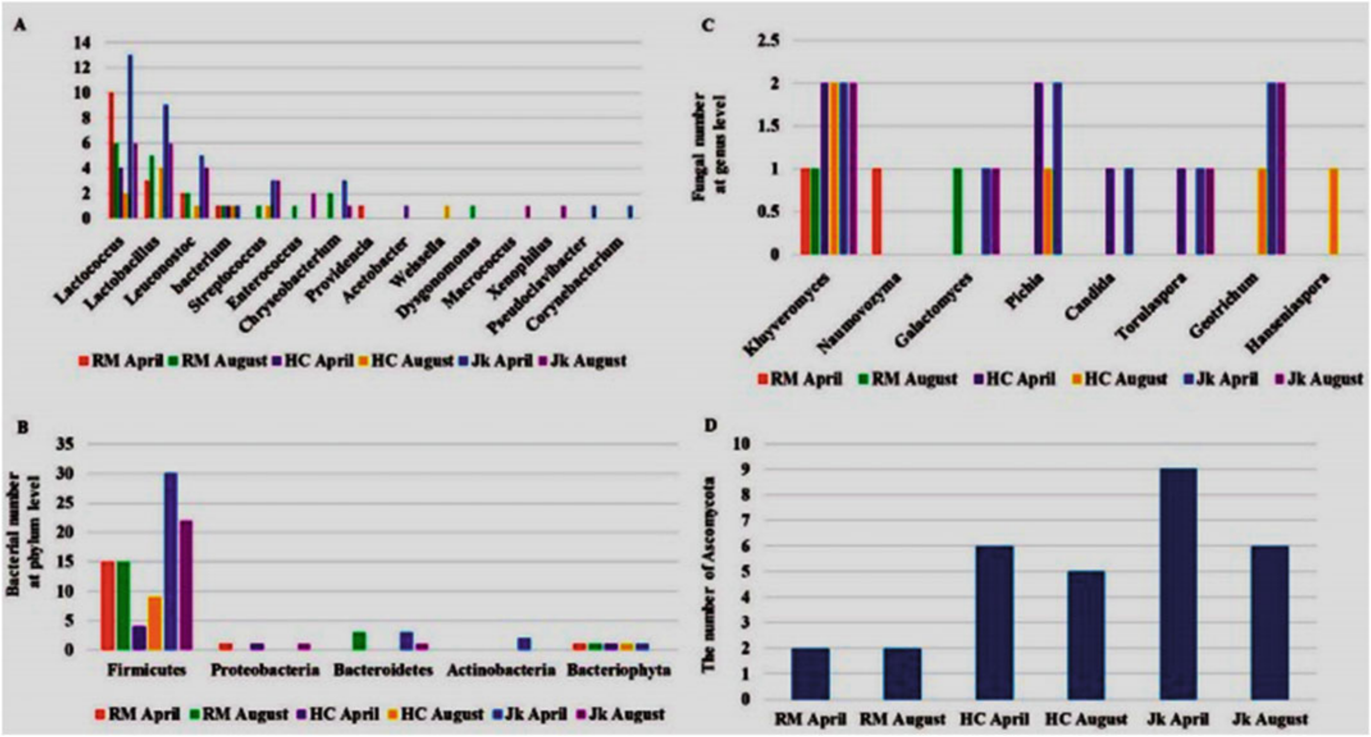

Fig. 4.4 Composition of the indigenous microflora, at the bacterial genus (**a**) and phyla (**b**) levels, and fungal genus (**c**) and Ascomycota (**d**) levels in raw and fermented milk samples. Data represents the number from the metagenomics analysis of two raw milk samples, and four fermented milk samples. RM April = raw milk samples collected in April, RM August = raw milk samples collected in August, HC April = Hurood Cheese samples collected in April, HC August = Hurood Cheese samples collected in August, Jk April = Jeuke samples collected in April, and Jk August = Jeuke samples collected in August (Gao et al. 2017)

Historically, the core genera of lactic acid bacteria include *Pediococcus*, *Lactobacillus*, *Streptococcus,* and *Leuconostoc*; however, nowadays there are 20 taxonomic revised genera. The significant LAB genera from food technology point of view are *Lactococcus*, *Leuconostoc*, *Lactobacillus*, *Enterococcus*, *Pediococcus*, *Aerococcus*, *Carnobacterium*, *Tetragenococcus*, *Vagococcus*, *Oenococcus,* and *Weissella* (Makarova et al. 2006).

Fermented milk associated LAB play a crucial role in the production of fermented beverages and other dairy products. They are strictly fermentative and produce lactic acid as a major product during the course of sugar fermentation. They are classified into two major groups based upon their fermentation potential, e.g., homofermentative or heterofermentative. Homofermentative LAB produces twice the energy from glucose fermentation as compared to heterofermentative. Homofermentation occurs through Embden Meyerhof Parna's pathway, whereas heterofermentation occurs either through hexose monophosphate or pentose phosphate pathway. The end product in the former case is mainly lactic acid, while in the latter ethanol/acetic acid and CO_2 are also significantly produced (Bassyouni et al. 2012; Çetin 2011; Rattanachaikunsopon and Phumkhachorn 2010).

A higher intake of fermented dairy products would reduce the risk of immune and metabolic disorders that will reduce the risk of obesity. Metabolizable nutrients and beneficial microorganism are incorporated due to the intestinal microbiota flourishing with the consumption of fermented dairy products. Yogurt is one of the dairy products that is well known for its numerous health benefits due to the probiotics. The intestinal health is maintained with the restoration of healthy balance between the good and bad bacteria from the probiotic intake. Moreover, it enhances the humoral and cellular immunity (Borchers et al. 2009). Despite general gut microenvironment, every individual's gut has a unique pattern of microbial community, and thus the response towards the use of probiotics is different.

Flu-like symptoms and upper respiratory infections are decreased with consumption of probiotics, as there is an immunity boost with the production of IgA antibodies, T lymphocytes, and natural killer cells. Crohn's disease, colorectal cancer, celiac disease, ulcerative colitis, and irritable bowel are some of the diseases that are improved with the use of yogurt. The severity of diarrhea is reduced with the use of probiotics, as it is among the side effects of consuming antibiotics. Therefore, doctors have suggested the use of yogurt for patients taking an antibiotic course to prevent the risk of antibiotic associated diarrhea. A study showed how certain strains of good bacteria present in the probiotics will help reduce the time of infectious diarrhea (Kechagia et al. 2013).

Another interesting research shows how the probiotics impact the mental health, as there is link between the brain and gut called the gut-brain axis (Mayer et al. 2014). Yogurt has proven to help reduce anxiety and stress which further improves the mental health of the individual. The *Bifidobacterium* and *Lactobacillus* strains for 1–2 months have been proven to positively affect the memory, obsessive compulsive disorder, autism, depression, and much more. Probiotic supplements introduced in the diet for 8 weeks decreased 40 patient's depression levels along with C-reactive protein that causes inflammation.

Probiotics have been declared to be healthy for all those suffering from chronic heart illnesses, such as angina, cardiovascular disease (CVD), heart attack, etc. due to their potential to reduce pressure and cholesterol by lowering the low-density lipoproteins (LDL). Moreover, probiotic microbes help with digestion, as the cholesterol is broken down into bile, which adds digestion. The benefit of having probiotics is the prevention of the reabsorption of the broken-down cholesterol in the blood. Studies suggest the reduction of allergies and eczema in children and infants with the consumption of probiotics in the form of milk or yogurt.

The health-promoting properties of conjugated linoleic acid (CLA) include anticarcinogenic, antiatherogenic, anti-inflammatory, and antidiabetic activity, as well as the ability to reduce body fat (Sosa-Castañeda et al. 2015). Although it is a native component of milk, the amount consumed in foods is far from that required in order to obtain desired beneficial effects. Thus, increasing the CLA content in dairy foods through milk fermentation with specific LAB offers a promising alternative. An effective way to increase CLA uptake in humans is to increase its level in dairy products by using strains with high production potential.

4.5.2 Pathogenic Microbes

Mammary glands of milking animal are natural reservoirs of microbes. Many of these bacteria are not harmful to humans, but some may be harmful to humans even though the animals are not affected and appear healthy. As listed in Table 4.1, the bacteria present in dairy products may cause disease or spoilage. Human diseases from milk-borne pathogens are usually due to the consumption of raw milk or products made from raw milk such as fresh cheeses. Till now, major dairy microorganisms are predominately associated with *Brucella* spp., *Campylobacter jejuni*, *Coxiella burnetii*, *Salmonella enterica*, *Listeria monocytogenes*, *Mycobacterium bovis*, *Mycobacterium paratuberculosis*, *Yersinia enterocolitica*, and *Escherichia coli* O157:H7 (Table 4.1).

4.5.2.1 *Brucella* spp.

Brucella species (spp.) are found in many animal species including cattle, sheep, and goats. *Brucella* spp. are destroyed by pasteurization. *Brucella* spp. cause illness with symptoms that are flu-like and include fever, sweats, headaches, back pain, and physical weakness. In some cases, long-lasting symptoms of fever, joint pain, and fatigue may occur.

4.5.2.2 *Campylobacter jejuni*

Campylobacter jejuni is found in the intestinal tract, udder, and feces of cattle, in poultry and wild birds, and in contaminated water sources. *C jejuni* is destroyed by pasteurization. *C. jejuni* is one of the most common bacterial causes of diarrheal illness. *C jejuni* generally causes illness 2–5 days after exposure, and illness typically lasts 5–10 days. Symptoms of campylobacteriosis include diarrhea, bloody diarrhea, abdominal pain, cramping, nausea, vomiting, and fever. Patients with

Table 4.1 Dairy pathogenic bacteria and associated diseases

Organism	Source of microorganism	Disease condition	Reference
Campylobacter jejuni	Intestinal tract and feces	Gastroenteritis	Facciolà et al. (2017)
Coxiella burnetii	Infected cattle, sheep, and goats	Q fever	
Escherichia coli O157:H7	Intestinal tract, and feces	Gastroenteritis, Hemolytic uremic syndrome (HUS)	
Listeria monocytogenes	Water, soil, and environment	Listeriosis	Radoshevich and Cossart (2018)
Mycobacterium bovis or tuberculosis	Infected animals	Tuberculosis	Lan et al. (2016)
Mycobacterium paratuberculosis	Infected animals	Johne's (ruminants)	Whittington et al. (2019)
Salmonella spp.	Feces, and environment	Gastroenteritis, Typhoid fever	
Yersinia enterocolitica	Environment, water, and infected animals	Gastroenteritis	Sabina et al. (2011)

Campylobacteriosis usually recover without specific treatment other than fluid and electrolyte replacement. In some persons with a compromised immune system, *C. jejuni* infection can lead to the more serious diseases like Guillan-Barré syndrome and Reiter syndrome. Guillan-Barré syndrome is a disorder that results in temporary neuromuscular paralysis, although 20% of those infected may have long-term disability and it may cause death. Reiter syndrome is a reactive arthritis that may affect multiple joints, particularly the knee joint. The prevalence of *C jejuni* is very widespread. It has been reported in bulk tank raw milk samples in Illinois, Michigan, Minnesota, Ohio, Pennsylvania, South Dakota, Tennessee, Virginia, and Wisconsin, suggesting that the organism is ubiquitous. In these studies, *C jejuni* was found in 0.4–12.3% of the bulk tank milk samples (Facciolà et al. 2017; Jayarao et al. 2006).

4.5.2.3 *Coxiella burnetii*

Coxiella burnetii is a pathogen shed in the milk, urine, and feces of cattle, goats, and sheep. *C. burnetii* is considered to be the most heat-resistant, non-spore-forming pathogen commonly found in milk, and the established conditions for milk pasteurization are specifically designed to destroy this organism. *C. burnetii* causes Q fever, an illness characterized by a sudden onset of high fever, severe headache, nausea, vomiting, diarrhea, abdominal pain, chest pain, chills, sweats, sore throat, non-productive cough, and general malaise. Fever can last for 1–2 weeks. Most patients recover without any treatment, although *C. burnetii* may result in death. The prevalence of *Coxiella burnetii* was >94% in raw milk samples from the North-eastern, Midwestern, and Western regions of the USA tested between 2001 and 2003 (Kim et al. 2005).

4.5.2.4 *Escherichia coli* O157:H7

Escherichia coli O157:H7 is one strain in a large family of bacteria. Strains of *E. coli* are considered fecal coliforms. Most strains of *E coli* do not cause illness and live in the intestinal tracts of healthy humans and animals. *E. coli* O157:H7 is found in the intestinal tract and feces of cattle and destroyed by pasteurization. *E. coli* O157:H7 produces toxins that cause illness in humans. Symptoms of illness include bloody diarrhea and abdominal cramps. In some cases, particularly in young children, *E. coli* O157:H7 infection causes hemolytic uremic syndrome, which destroys red blood cells and causes kidney damage or failure, and in some cases death. The prevalence of *E. coli* O157:H7 and Shiga-toxin producing *E. coli* have been reported for bulk tank raw milk samples in Minnesota, Pennsylvania, South Dakota, Wisconsin, and Ontario. *E. coli* O157:H7 was found in 0.87–10% of the bulk tank milk samples tested (Jayarao et al. 2001, 2006).

4.5.2.5 *Listeria monocytogenes*

Listeria monocytogenes is found in soil and water and has been isolated from a large number of environmental sources. It is destroyed by pasteurization, but if food products are contaminated after pasteurization, *it* can grow at refrigerator temperatures. Illness can occur as sporadic events or larger outbreaks. *L. monocytogenes* typically causes illness in pregnant adults, newborns, the elderly, and patients with compromised immune systems, but healthy adults and children may also become infected. Symptoms of Listeriosis include flu-like symptoms, fever, muscle aches, stiff neck, headache, septicemia, meningitis, miscarriage, stillbirth, premature delivery, abortion, or death. The prevalence of *L. monocytogenes* has been reported for bulk tank raw milk samples in individual states (or grouped by region) for California, Colorado, Florida, Idaho, Illinois, Indiana, Iowa, Kentucky, Massachusetts, Michigan, Minnesota, Missouri, Nebraska, New Mexico, New York, Ohio, Pennsylvania, South Dakota, Tennessee, Texas, Washington, Wisconsin, Vermont, Virginia, and in Alberta and Ontario, Canada. *Listeria monocytogenes* was found in up to 12% of the bulk tank milk samples tested (Jayarao et al. 2001, 2006; Van Kessel et al. 2004) illustrating the widespread presence of *L. monocytogenes* in unpasteurized milk.

4.5.2.6 *Mycobacterium bovis* and *Mycobacterium tuberculosis*

Mycobacterium bovis and *Mycobacterium tuberculosis* are found in infected cattle worldwide. Both of these organisms are destroyed by pasteurization. *Mycobacterium bovis* and *Mycobacterium tuberculosis* cause tuberculosis, a lung disease. Tuberculosis in the USA is not very common today, although historically milk was a common source of tuberculosis. Tuberculosis is a concern in many parts of the world. *Mycobacterium paratuberculosis* causes Johne's disease in cattle. It has been suggested that *M. paratuberculosis* may be associated with Crohn's disease, an intestinal disorder, in humans, but this has not been confirmed (Peden 2000; Whittington et al. 2019).

4.5.2.7 *Salmonella* spp.

Salmonella species (spp.) contain several strains that cause illness in humans; the most common are the serotypes Enteriditis and Typhimurium. *Salmonella* has been found in the intestinal tracts of all warm-blooded animals including humans. *Salmonella* is destroyed by pasteurization. *Salmonella* spp. causes illness that can develop 12–72 h after exposure, and can last 4–7 days. Symptoms of Salmonellosis include diarrhea, abdominal cramps, and fever. Most people recover without treatment other than fluid and electrolyte replacement. Some cases may be severe and require hospitalization. A small number of people may develop Reiter syndrome, which is a reactive arthritis that may affect multiple joints, particularly the knee joint. The prevalence of *Salmonella* spp. has been reported for bulk tank milk samples in individual states (or grouped by region) for California, Colorado, Florida, Idaho, Illinois, Indiana, Iowa, Kentucky, Michigan, Minnesota, Missouri, New Mexico, New York, Ohio, Pennsylvania, South Dakota, Tennessee, Texas, Washington, Wisconsin, Vermont, Virginia, and Ontario, Canada. *Salmonella* spp. were found in 0.17–8.9% of the bulk tank milk samples tested (Jayarao et al. 2001, 2006; Van Kessel et al. 2004), indicating the widespread presence of *Salmonella* in unpasteurized milk.

4.5.2.8 *Yersinia enterocolitica*

Yersinia enterocolitica is found in the intestinal tract of farm animals, especially pigs, and in the environment. *Y. enterocolitica* is destroyed by pasteurization, but if food products are contaminated after pasteurization, *Y. enterocolitica* can grow at refrigerator temperature. *Yersinia enterocolitica* causes illness with symptoms of fever, abdominal pain, and diarrhea. The prevalence of *Yersinia enterocolitica* has been reported for bulk tank milk samples in Michigan, Minnesota, Pennsylvania, South Dakota, Tennessee, Wisconsin, Virginia, and Ontario, Canada. *Yersinia enterocolitica* was found in 1.2–18% of the bulk tank milk samples tested (Jayarao et al. 2001, 2006; Sabina et al. 2011).

4.5.2.9 Other Pathogens

Coliforms are a large group of bacteria that are found in the intestines of warm-blooded animals. Most coliforms are not pathogenic, but their presence indicates contamination, usually from fecal sources. Coliforms are destroyed by pasteurization. The prevalence of coliforms was detected in 62–95% of the raw bulk tank milk tested in regions that included California, Colorado, Florida, Idaho, Illinois, Indiana, Iowa, Kentucky, Michigan, Minnesota, Missouri, New Mexico, New York, Ohio, Pennsylvania, South Dakota, Tennessee, Texas, Washington, Wisconsin, Vermont, and Virginia (Jayarao et al. 2001, 2006; Van Kessel et al. 2004).

Psychotropic bacteria are capable of growing at 44.6 °F (7 °C) or less. This group of microbes is a concern in dairy products because they grow at refrigerator temperature and cause spoilage, often resulting in off-flavors. The most common psychrotrophs are in the genus *Pseudomonas*. These organisms are killed by pasteurization, but may occur in milk from contamination after pasteurization. Some bacterial pathogens are psychrotrophic, including *Listeria monocytogenes*, *Yersinia* *enterocolitica*, some *E. coli* strains, and some *Bacillus* strains (Radoshevich and Cossart 2018; Sabina et al. 2011).

4.6 Microbial Additives

Milk itself is a natural source for a variety of bacteria; the group of lactic acid bacteria is one of the prime sources of microbial additives. Many health-promoting effects are achieved from bioactive molecules produced by dairy fermented products. In contrast to the conventional concept of probiotic (ingestion of alive bacteria for the production of metabolites within human gut), a biologically functional food concept is based on the endogenous production of healthy metabolites in the fermented products, as a result of the metabolic response of bacterial machinery. The main biologically active molecules produced by LAB during dairy fermentation are vitamins, gamma-aminobutyric acid, bioactive peptides, bacteriocins, enzymes, conjugated linoleic acid, and exopolysaccharides.

4.6.1 Bioactive peptides

In the process of milk fermentation, lactic acid bacteria digest many proteins into short peptides through proteolytic activity. These peptides are biologically functional and exhibit antioxidative, antimicrobial, antihypertensive, immunomodulatory, and antithrombotic properties (Nongonierma and FitzGerald 2015). One of the most important bioactive peptides is Angiotensin-I-converting enzyme (ACE) inhibitory peptides. ACE inhibitory peptides display strong antihypertensive features and have been reported from a number of dairies (Fitzgerald and Murray 2006; Pritchard et al. 2010). Initially, ACE-inhibitory peptides, Ile-Pro-Pro (IPP), and Val-Pro-Pro (VPP) were extracted from milk fermented by *L. helveticus* (Slattery et al. 2010). Later on, other lactic acid bacteria including *L. rhamnosus*, *L. plantarum*, *L. delbrueckii*, *L. acidophilus*, *Lactococcus lactis*, *and S. thermophilus were reported as* dairy starter cultures in the industry as a source of inhibitory peptides of ACE (Hafeez et al. 2014). β-casein (SLVYPFPGPI) is another bioactive peptide produced by *L. delbrueckii* in fermented milk (Qian et al. 2011). Similarly, two short peptides are produced by the hydrolysis of α-S2 casein during the process of fermentation; both peptides are antimicrobial and display protective function against many human pathogens including *Saccharomyces thermophilus*, *E. coli*, *Helicobacter pylori*, *Staphylococcus aureus*, *Streptococcus pyogenes,* and *Listeria monocytogenes* (Nagpal et al. 2011). Lactoferrin is another source of antimicrobial peptides (Zivkovic et al. 2013). Peptic digestion of lactoferrin produces short peptides that displayed antimicrobial activity against a broad range of bacteria including *E. coli*, *Listeria*, *Salmonella*, *Campylobacter*, and many fungal strains, however, non-toxic to *Bifidobacterium* (Quintieri et al. 2013; Shah 2007).

4.6.2 Bacteriocins

Bacteriocins are major ribosomal antimicrobial peptides known to inhibit adhesion and invasions of pathogens through direct microbial interaction or by altering the exterior environment leading to slow to no growth of microbes (Hernández-Ledesma et al. 2014). Different types of ribosomal short peptides and their respective immunity proteins are produced by many lactic acid bacteria, which provide a broad range of antimicrobial activity against major human pathogens. Thus, bacteriocin producers are a potential alternative to pharmaceutically synthesized antibiotics and offer a means of controlling pathogen-induced inflammation (Cotter et al. 2013). Many lactic acid bacteria are generally regarded as safe (GRAS) for human consumption. These are the ideal source of bacteriocin production on a commercial scale (Nes et al. 2007). Because of the strong antimicrobial characteristics of bacteriocin, the producing strains also use as natural food-preservatives.

Nisin is the most used for food preservation due to its antimicrobial effect against spoilage and disease-associated bacteria like *Listeria* and clostridia spores. Plantaricin C is another broad-spectrum peptide produced by *L. plantarum* and documented as an immunomodulator for dendritic cells (Meijerink et al. 2010). Briefly, the use of bacteriocins directly or bacteriocin-producing bacteria as a starter culture for the generation of bacteriocins through fermentation became an efficient health-promoting strategy. Similarly, the use of lacticin-producing strain of *Lactococcus lactis* greatly inhibits the growth of *Listeria monocytogenes* in Cheddar cheese (Chen and Hoover 2003). Many other lactic acid bacteria like *L. acidophilus*, *Pediococcus acidilactici*, and *Leuconostoc mesenteroides* known for their specific bacteriocins can be added as an adjunct in many food fermentations processes as food preservatives (Anjum et al. 2014). Besides the production of antimicrobial peptides, these bacteria pose many other advantages to enhance flavor, texture, and nutritional value of the product (Gaggia et al. 2011; Jiang et al. 2012; Grosu-Tudor et al. 2013; Mitra et al. 2010; Khan et al. 2010; Tamang et al. 2009).

4.6.3 Enzymes

Many *Lactobacillus*, *Lactococcus*, and *Streptococci* species can ferment milk by producing hydrolytic enzymes. The proteolytic machinery of lactic acid bacteria (LAB) comprises membrane-bound aminopeptidases, endopeptidases, and proteinases for the production of hydrolysates. Fermentation-associated microbes depend on the degradation of milk proteins to get free amino acid residues and short peptides required for their growth. Yogurt and other conventional fermented dairy products associated with bacteria reduce lactose intolerance and improve lactose digestion by degrading lactose through the activity of microbial β-galactosidase (De Vrese et al. 2001; Patel et al. 2013).

4.6.4 Vitamins

Although milk contains many vitamins, however, in the fermented milk the vitamin producer lactic acid bacteria enhance the nutritional value of the product. Many species of *Lactobacillus* and *Bifidobacterium* genera secrete vitamin B complex (B1, B2, B7, B9, B12) during the fermentation process. Dietary depletion of vitamin B1 (thiamine) and vitamin B2 (riboflavin) can dysregulate glucose metabolism in the brain and lead to both skin and liver diseases, respectively (Russo et al. 2014). Some *Propionibacteria* and lactic acid bacteria can produce cobalamin, folic acid, and biotin, such as *L. casei* richly produce thiamine and riboflavin in fermented milk (Hugenholtz et al. 2002; Drywień et al. 2015).

Vitamin B7 (Biotin) deficiency can be genetic or dietary that affects the skin and hair health. Starter culture of lactic acid bacteria, e.g., *L. helveticus* and Propionibacteria, ferment and produce biotin-enriched milk products (Patel et al. 2013). The deficiency of vitamin B9 (Folate) is linked to neural tube impairment and cardiac issues. Limited strains of lactic acid bacteria including *Streptococcus thermophilus* CRL803/CRL415, *L. amylovorus*, and *L. bulgaricus* are designated as vital for dairy folate enrichment (Laiño et al. 2014). Among *Bifidobacteria, B. catenulatum* is known as rich folate producer.

Plants, animals, and fungi are unable to produce, thus bacteria are the exclusive source of vitamin B12 (cobalamin) (LeBlanc et al. 2011). It has been demonstrated that vitamin B12 cobalamin can be synthesized by some bacteria such as *L. reuteri*, *Propionibacterium freudenreichii*, and *B. animalis* (Gu et al. 2015; Moslemi et al. 2016; Patel et al. 2013; Van Wyk et al. 2011). *Propionibacterium freudenreichii* is able to secrete vitamin B12 and the pseudovitamin B12 isoforms during the milk fermentation process. Pseudovitamin B12 converts into vitamin B12 to enhance the bioavailability of cobalamin (Deptula et al. 2017).

Vitamin K is essential for arterial de-calcification to reduce the risk of cardiovascular disorders. Its deficiency can cause medical ailments such as osteoporosis and hemorrhage (LeBlanc et al. 2011). Vitamin K in nature exists in the forms of phylloquinone (vitamin K1) and menaquinone (vitamin K2). Menaquinone is microbial vitamin synthesized by *Lactococcus lactis*, *a common starter culture for the* industrial production of sour cream, cheese, kefir, and buttermilk (Walther et al. 2013).

4.6.5 Gamma-Aminobutyric Acid

Gamma-aminobutyric acid (GABA) is one of the exclusive inhibitory neurotransmitters (INT) of the central nervous system (CNS). Glutamate decarboxylase (GAD) catalyzes glutamate in the process of α-decarboxylation and synthesizes GABA (Tajabadi et al. 2015). Interestingly, *Bacteroides* genus is the largest GABA producer group; for example, *Bacteroides fragilis* produces GABA, polysaccharide A, and sphingolipids; the latter two are evident for the health of immune and gut systems (Tan et al. 2019; Troy and Kasper 2010). In addition to

Bacteroides, several lactic acid bacteria have been reported as the source of GABA producers including *Lactococcus lactis*, *Lactobacilli* (*L. paracasei*, *L. brevis*, *L. delbrueckii*, *L. plantarum*, *L. helveticus*, *L. buchneri*), *Streptococcus thermophilus*, and *Bifidobacterium* spp. (Barrett et al. 2012; Li and Cao 2010) which are most promising candidates.

Few strains, *S. salivarius* fmb5, *L. casei* Shirota, and *L. plantarum* NDC75017, were selected for commercial production of GABA-enriched fermented milk drink (Chen et al. 2016; Inoue et al. 2003; Shan et al. 2015). Similarly, yogurt and cheese enriched with GABA were produced by using the strain *S. thermophiles* APC151, *L. brevis* OPY-1, and *Lactococcus lactis* (Linares et al. 2016; Park and Oh 2007; Pouliot-Mathieu et al. 2013).

4.6.6 Conjugated Linoleic Acid

Polyunsaturated fatty acids (PUFA) are important metabolites of lactic acid and bifidobacteria bacteria such as conjugated linoleic acid (CLA) produced by conversion of linoleic acid. Many LAB and bifidobacterial strains like *L. casei*, *L. plantarum*, *Lactococcus lactis*, *L. rhamnosus*, *L. acidophilus*, *B. bifidum*, and *B. animalis* were reported to produce CLA in dairy products (Florence et al. 2009; Sosa-Castañeda et al. 2015; Van Nieuwenhove et al. 2007; Yang et al. 2015). These strains also used to add extra CLA contents in cheese and yogurt as adjunct cultures (Van Nieuwenhove et al. 2007).

4.6.7 Exopolysaccharides

Exopolysaccharides (EPS) are complex carbohydrates produced by a group of lactic acid bacteria, Propionibacteria, and bifidobacteria in the form of secretions during the fermentation process of dairy products and support the immune system by promoting host beneficial microflora (Salazar et al. 2016). Lactic acid bacteria including *L. delbrueckii*, *L. mucosae*, *Lactobacillus kefiranofaciens*, *Lactococcus lactis*, *and S. thermophilus* are predominant EPS-producing species in the yogurt and cheese and boost immune-stimulatory effects and reduce cholesterol levels (Darilmaz and Gumustekin 2012; Makino et al. 2016; Ryan et al. 2015). Specifically, *Lactobacillus kefiranofaciens* produce EPS metabolites, which dramatically inhibit the invasion of pathogens like *Listeria monocytogenes* and *Salmonella enteritidis* in the enterocytes (Jeong et al. 2017; Medrano et al. 2008). Antimicrobial effects of these metabolites may extend to other microbial species in the gut microflora.

In addition to health-promoting effects, EPS greatly enhance the quality, sensory and rheological features of dairy products. For example, *Bifidobacterium longum* and *S. thermophiles* are well known for immune-modulatory effects and high EPS production that directly reduces syneresis and improves the texture and viscosity of fermented ice-cream and yogurt (Dertli et al. 2016; Han et al. 2017; Hidalgo-Cantabrana et al. 2012; Prasanna et al. 2013).

4.6.8 Other Bio-Functional Molecules

Carbohydrate-fermenting microbes also secrete many neuroactive molecules including Clostridia metabolites, short-chain fatty acids, histamine, and diacylglycerol kinase (Karl et al. 2018; Shaw 2017). Mycelial fungi *Aspergillus, Actinomucor*, *Monascus*, *Amylomyces*, *Mucor*, *Rhizopus,* and *Neurospora* also produce various carbohydrate enzymes including ß-galactosidase, α-amylase, pectinase, maltase, cellulase, amyloglucosidase, hemi-cellulase as well as lipase and proteases.

4.7 Industrial Importance of Dairy Microbes

The dairy starter culture is used on a large scale in the food industries for the manufacturing of butter, cheese, yogurt, kefir, sour cream, and other fermented milk products. The principle purpose of the starter culture is to convert lactose and other sugars present in milk to lactic acid. The industrially important lactic acid bacteria are used as a starter culture for the preparation of many important food products and they impart various sensory characteristics to them, i.e., aroma, texture, viscosity, and flavor; henceforth, an increase in the use of LAB probiotics has been observed in the recent years. Dairy industry has become an integral part of food industries worldwide. Henceforth, the demand for starter culture is growing by leaps and bounds over the past few years. Lactic acid bacteria have also been reported to play a crucial role in the cheese ripening and giving it perfect consistency, flavor, and aroma (Hannon et al. 2003). Apart from this, many antimicrobial short peptides, exopolysaccharides, and enzymes are associated with dairy microbes to enhance nutritional value and shelf life of product.

The growth of the dairy starter culture market is driven by the growth of dairy industry. The overall increase in the production of dairy products and growing demand for dairy-based products is expected to boost the demand for the dairy starter culture globally.

4.8 Nutraceutical Properties of Milk Microbiota

Milk proteins exhibit a wide range of nutraceuticals and biological properties. Most of the dairy proteins are specific in biological functions and display many health-promoting effects. These short peptides are inactive within the endogenously secreting proteins and can be cleaved by proteolytic activity of gastrointestinal enzymes upon ingestion of milk or fermentation process. Proteins are the essential components of dairy products that have a variety of applications in several food industries.

4.8.1 Antihypertensive

Although many fermented food products exhibit medicinal characteristics, however, fermented dairy products are exceptional in the nutraceutical contents. Regular consumption of fermented dairy products displayed anticholesterol and antihypertensive properties, thus reducing the risk of cardiovascular diseases. In addition to milk proteins, fermented milk-associated probiotic bacteria secrete some proteins and metabolites and exert an overall positive impact on the health of the consumer. Kefir and Calpis contain many short peptides that are responsible for hypotensive effects. Some lactic acid bacteria functionally antihypertensive such as *L. rhamnosus*, *L. plantarum*, *L. delbrueckii* ssp. *bulgaricus*, *Lactococcus Lactis*, *L. acidophilus*, *and S. thermophilus in fermented milk are the commercial source of* ACE inhibitory peptides (Hafeez et al. 2014), and thus greatly reduces elevated blood pressure (Shah 2015).

4.8.2 Anticarcinogenic

Many dairy raw and fermentation-associated bacteria like *L. acidophilus* inhibit the conversion of paracarcinogenic molecules into carcinogenic forms by reducing specific enzymes including azoreductase ß-glucuronidase, and nitroreductase in human, hence, trigger and boost body immunity. In this context, South Asian fermented milk product *dahi* (yogurt) is the most known anticarcinogenic dairy product. Daily use of yogurt can reduce the risk of cervical, bladder, and colon cancer (Mohania et al. 2014).

4.8.3 Gastrointestinal Support

Many fermented dairy lactic acid bacteria significantly reduce a load of gastrointestinal diseases (Verna and Lucak 2010). Intake of *Lactobacillus* species in the food improves the symptoms of ulcerative colitis, paucities, and inflammatory bowel disease (Orel and Trop 2014). Similarly, *L. rhamnosus* specifically treat severe diarrheal issue (Szajewska et al. 2007). Moreover, probiotics in fermented dairy products manifest immunomodulatory effects and thus inhibit the growth of pathogens in the gastrointestinal tract (Balamurugan et al. 2003).

4.8.4 Anti-allergic Effects

Lactobacillus kefiranofaciens has an anti-allergic effect. In the process of fermentation, cleavage, and degradation of casein proteins of allergenic reactivity thus increases tolerance (Alessandri et al. 2012). Several species of *Lactobacillus* captured attention because of their ability to produce interleukins and interferons, and thus significantly reduce allergic reactions due to food or dermatitis. Yogurt is a rich probiotic supplement that increases glucose tolerance and reduces oxidative stress, hyperglycemia, dyslipidemia, hyperinsulinemia, indicating a lower risk of diabetes (Yadav et al. 2007).

4.8.5 Alleviation of Lactose Intolerance

Lactose intolerance both in children and in adults arises because of the unavailability of ß-D-galactosidase (Shah 2015). Lactic acid bacteria including *L. delbrueckii* and *S. thermophilus* strains are capable to secrete high contents of ß-D-galactosidase which improve the symptoms of lactose malabsorption in lactose intolerant people. Consumption of fresh yogurt (with live yogurt cultures) has demonstrated better lactose digestion and absorption than with the consumption of a pasteurized product. *Kefir* can minimize the symptoms of lactose intolerance by providing an extra source of β-galactosidase (Hertzler and Clancy 2003**)**.

4.8.6 Brain Gut Axis Aid

Many mental conditions including psychiatric, neurodevelopmental and neurodegenerative disorders can be potentially treated with the psychobiotic microbes. These bacteria include many species of *Lactobacillus*, *Lactococcus*, *Bifidobacterium*, *Streptococcus* and few species of *Bacillus* and *Clostridium* genera. Appropriate dose management of these microbes display psychotropic potential by the production of neuroactive molecules, such as neurotransmitters (GABA, serotonin, norepinephrine, acetylcholine, glutamate), neuropeptides (neuropeptide Y, glucagon-like peptide-1 and 2, Tyr-Tyr peptide), and other molecules like cholecystokinin and substance P for the regulation of brain-associated protein like brain-derived neurotrophic factor (BDNF). The regulation of neuronal proteins is important to modulate specific behavior types. Psychobiotics employ antidepressant, antianxiety, and antidepressant properties, and improve sleep quality and energy metabolism of brain through enteric neural network, systemic, humoral, and metabolic mechanisms in the body and establish a brain gut axis. The bacteria-brain communication is important in the modulation of behaviors related to the central nervous system (Hao et al. 2019).

4.9 Dairy Psychobiotics

Lactobacillus and *Bifidobacterium* have reportedly shown potential psychobiotic activity when present in higher numbers in the human gut microbiome. Dairy products which undergo fermentation have proven to be a chief reliable source of *Lactobacillus* species. Species of *Lactobacillus* are reported to produce a variety of neurotransmitters, and their precursors *in vitro*. The gut microflora plays an important role in the regulation of bioavailability of the precursor molecules for neurotransmitters. In the brain, dopamine is converted to norepinephrine through an enzyme known as dopamine-β-hydroxylase. The inhibitors of this enzyme 4-hydroxyphenylacetate, and 4-cresol, are metabolites produced by *Clostridia*, a class of *Firmicutes*. Similarly, the microbes that ferment carbohydrates produce a short-chain fatty acid, known as butyrate that has been reported to impact the intestinal entero-chromaffin cells by stimulating them to synthesize serotonin (5-HT). As shown in Table 4.2, these precursor molecules for neurotransmitters and other metabolites produced by the probiotic microbes are neuroactive molecules, and have an influence on the modulation of enteric nervous system signaling, which in turn impacts the gut-brain axis (Yong et al. 2020).

4.9.1 *Lactobacillus rhamnosus*

Lactobacillus rhamnosus has been a commercially available probiotic for quite some time. It has been reported that *L. rhamnosus* is able to metabolize glutamate and gamma amino-butyric acid (GABA), which are the excitatory and inhibitory neurotransmitters, respectively. *L. rhamnosus* in vitro has reportedly utilized microbial enzymes glutamate decarboxylase to produce GABA and glutaminase to produce glutamate. Studies on mice models have shown that an intervention of *L. rhamnosus* in the diet resulted in alleviation of anxious and depressive behaviors. The alteration was brought about in the expression of mRNA of the receptors of GABA. However, the reduced anxious and depressive behavior of the mice was also dependent on the neural signaling from the intact vagus nerve. GABA produced by the gut microbiota is reported to utilize the H^+/GABA symporter to cross the intestinal barrier *in vitro*. The enteric neurons and the vagus afferents have a large number of GABA receptors and transporters, since it is a chief inhibitory neurotransmitter. These GABA receptors and transporters are possibly utilized by GABA molecules which are produced by microbes, such as *L. rhamnosus* (Bravo et al. 2011; Nielsen et al. 2012; Lin 2013; Yong et al. 2020).

4.9.2 *Lactobacillus casei*

Lactobacillus casei has a potential for maintaining gut health, and is known for its industrial value as a starter culture for fermentation. A dietary intervention of milk containing *L. casei* resulted in a reportedly uplifted mood in individuals. In the analysis of saliva collected from individuals who reported to be stressed, it was found that cortisol levels were high. Consequently, the high cortisol levels resulted in abdominal disturbances and flu symptoms. However, in the clinical trials, an intervention with *L. casei* reportedly alleviated the abdominal and flu symptoms, and reduced the stress frequency by lowering the cortisol levels. Similar to *L. rhamnosus*, *L. casei* was also able to produce GABA, which is involved in inhibition mechanisms. The presence of *L. casei* in a probiotic comprising a mixture of similar species resulted in a reduction in the depression levels of individuals diagnosed with

Table 4.2 The neurotransmitters produced by probiotics and their regulatory functions

Neurotransmitter	Regulatory functions	Probiotics	References
Gamma-aminobutyric acid (GABA)	• Hippocampal neurogenesis • HPA axis regulation • Mood	*L. brevis* *L. rhamnosus* *L. reuteri* *L. paracasei* *L. plantarum* *L. bulgaricus* *L. helveticus* *L. casei*	Barrett et al. (2012), Oleskin et al. (2014)
Serotonin (5-HT)	• Impulsivity • Aggression • Appetite • Circadian rhythm • Learning • HPA axis regulation • Mood	*L. plantarum* *L. helveticus*	Oleskin et al. (2014)
Dopamine (DA)	• Motivation • Concentration • Psychomotor speed • Ability to experience pleasure • Mood	*L. plantarum* *L. helveticus* *L. casei* *L. bulgaricus*	Oleskin et al. (2014)
Norepinephrine (NE)	• Aggression • Cognitive function • Sleep • Sympathetic activity • HPA axis regulation • Mood	*L. helveticus* *L. casei* *L. bulgaricus*	Oleskin et al. (2014)
Glutamate (Glu)	• Gastrointestinal reflexes • Intestinal motility • HPA axis regulation • Mood	*L. rhamnosus* *L. reuteri* *L. plantarum* *L. paracasei* *L. helveticus* *L. casei* *L. bulgaricus*	Oleskin et al. (2014)
Histamine	• Motivation • Learning • Memory • Appetite • Sleep • Sympathetic activity • Mood	*L. plantarum* *L. reuteri*	
Acetylcholine (ACh)	• Cognition • Synaptic plasticity • Analgesia • Sleep • HPA axis regulation • Mood	*L. plantarum*	

clinical depression, and those exhibiting depressive symptoms. The production of microbial GABA by *L. casei* shows that there is a possibility to have similar mechanisms, and the resultant antidepressant effect like *L. rhamnosus* (Kato-Kataoka et al. 2016; Oleskin et al. 2014; Takada et al. 2016; Yong et al. 2020).

4.9.3 *Lactobacillus brevis*

Lactobacillus brevis has a possible overlap in the underlying mechanisms for GABA production, with *L. rhamnosus* and *L. casei*, though reportedly the central GABAergic system remains uninfluenced by its presence. *L. brevis* utilizes the microbial glutamate decarboxylase to produce GABA. An increase in the total GABA content was observed in a quantitative analysis of milk fermented with a starter culture of *L. brevis*. A study on rat models for depression found that *L. brevis* exhibited antidepressive potential, much like fluoxetine, after a dietary intervention of milk fermented with *L. brevis*. Since GABA is the primary inhibitory neurotransmitter, it plays an important role in sleep quality and REM cycle, and hence its imbalance may result in sleep disorders. Sleep disorders such as insomnia are mostly treated by an increased dosage of GABA through diet, or by treatment with pharmacological benzodiazepine which targets GABA receptors. In mice models, the presence of *L. brevis* in the diet has reportedly improved the quality of sleep; therefore it shows great potential to be a therapeutic intervention for treatment of insomnia in people suffering from major depressive disorder (Ko et al. 2013; Miyazaki et al. 2014; Yamatsu et al. 2015; Yong et al. 2020).

4.9.4 *Lactobacillus reuteri*

Lactobacillus reuteri is a probiotic that enhances the immune system. *L. reuteri* is reported to have anti-inflammatory effects on the human body. Hydrogen peroxide is a chief metabolite produced by *L. reuteri*, that inhibits the activity of indoleamine 2,3 dioxygenase through peroxidase-mediated catalyzed reactions. Indoleamine 2,3 dioxygenase is reported to impact levels of kynurenine, and the microbial hydrogen peroxide can possibly cross the intestinal epithelial lining, and reduce the activity of indoleamine 2,3 dioxygenase. Hence, the suppressed activity of this key enzyme lowers the kynurenine levels. *L. reuteri* utilizes microbial histidine decarboxylase to produce histamine from the metabolism of dietary L-histidine. Diacylglycerol kinase is also a microbial enzyme produced by *L. reuteri*, which metabolizes diacylglycerol to phosphatidic acid which plays a role in the microbial histamine anti-inflammatory activity. Both the microbial histamine and the enzyme diacylglycerol kinase produced by *L. reuteri* have been reported to interact with the histamine receptors and enhance the immune response by reducing the inflammatory cytokines in the gastrointestinal tract (Jang et al. 2019; Réus et al. 2015; Yong et al. 2020).

4.9.5 *Lactobacillus plantarum*

Lactobacillus plantarum has been reported to utilize fatty acid synthase II-thioesterase to synthesize butyrate following a butyrogenic pathway mediated by glutamine. Studies on mammals have reported that a dietary intervention of *L. plantarum* has antidepressive effects. It has also been reported that there was an overall increase in levels of butyrate, as *L. plantarum* not only produces butyrate as a metabolite, it also favors the colonization of *Bacteroidetes, Lactobacillus*, and *Roseburia* which are also butyrate-producing bacteria. Supplements containing *L. plantarum* have exhibited the enhancement of hippocampal brain-derived neurotrophic factor. Similarly, analysis of butyrate levels from the cecum showed an elevation after the administration of *L. plantarum* (Botta et al. 2017; Dhaliwal et al. 2018; Yong et al. 2020).

4.9.6 *Lactobacillus gasseri*

Lactobacillus gasseri is known for its anti-inflammatory effect on the immune system. Heat-killed or live form of *L. gasseri*, both have the ability to alter the levels of gut microbiome by favoring the colonization of few microbes over others in the gastrointestinal tract. A study reported that consumption of milk containing probiotics including *L. gasseri* showed an altered gut microflora composition in stressed individuals. *L. gasseri* is reported to produce gassericins which have antibacterial properties against possible pathogens present in the gastrointestinal tract. An introduction of live *L. gasseri* resulted in reduced growth of inflammatory bacterial populations such as *Enterobacteriaceae*, *Clostridium cluster IV group*, and *Veillonella*, along with altered levels of short-chain fatty acids. The heat-killed form of *L. gasseri* reportedly increased the population of *Dorea longicatena*, while decreasing *Bacteroides vulgatus*. *L. gasseri* when administered in heat-killed form across multiple studies showed that it does not have a unique microbial target, but alters the gut microflora composition towards a favorable anti-inflammatory environment (Nishida et al. 2017; Sawada et al. 2017; Yong et al. 2020).

4.9.7 *Lactobacillus helveticus*

Lactobacillus helveticus is a probiotic that imparts multiple health benefits to the human body. *L. helveticus* has been reported to increase immunity by protection against pathogenic bacterial colonization, along with prevention of diseases of the gastrointestinal tract. In patients diagnosed with clinical depression and symptoms related to depression, a probiotic intervention was introduced which included *L. helveticus* and *Bifidobacterium longum*, and a positive result was observed as depressive symptoms were reduced. In a study involving cognitively impaired rodent models, it was reported that an intervention of *L. helveticus* enhanced cognitive performance and memory. Similarly, *L. helveticus* introduced as a dietary intervention improved cognition abilities such as attention, memory, and learning as reported by studies on animal models and human participants (Liang et al. 2015; Oleskin et al. 2014; Yong et al. 2020).

4.9.8 *Lactobacillus paracasei*

Lactobacillus paracasei belongs to the *Lactobacillus casei* group which also includes *L. rhamnosus* and *L. casei*. The *Lactobacillus casei* group is the most used *Lactobacillus* species, and is used as a potential therapeutic agent for health, along with being of industrial and commercial use. Lactocepin is a protein that is produced by *L. paracasei*, it is a serine protease, and hence is sensitive to high temperatures. However, studies have demonstrated that whether alive or heat-killed, *L. paracasei* exhibits antidepressive and mood uplifting mechanisms. Reportedly while an intervention of heat-killed *L. paracasei* resulted in elevated levels of dopamine in the brain, introduction of live *L. paracasei* increased the levels of serotonin. In a study on mice models, where depression was induced by corticosterone, oral administration of both forms of *L. paracasei* demonstrated potential for antidepressive agents in par with fluoxetine. Similarly, in a study done on healthy individuals in stressful times, a dietary intervention of *L. paracasei* in its heat-killed form kept the mood stable and prevented it from deteriorating (Chunchai et al. 2018; Réus et al. 2015; Wei et al. 2019; Yong et al. 2020).

4.9.9 *Lactobacillus kefiranofaciens*

Lactobacillus kefiranofaciens is reported to have a variety of physiological alterations as a result of its administration. In a study on chronically stressed depressive mice models, the oral administration of *L. kefiranofaciens* showed a marked improvement in their behavior: alleviated depressive and stress-related mood. *L. kefiranofaciens* is reported to affect the Tryptophan/Kynurenine metabolic pathway by increasing the levels of tryptophan in circulation in the body, and hence reducing the Kynurenine/Tryptophan ratio. The presence of *L. kefiranofaciens* also favors the abundance of beneficial gut microbiome such as *Akkermansia*, *Bifidobacteriaceae,* and *Lachnospiraceae*, while reducing the abundance of *Proteobacteria* in the gastrointestinal tract. *L. kefiranofaciens* impacts the immune system by increasing the level of splenic IL-10, and decreasing the levels of splenic IL-6 and IFN-γ levels. The exopolysaccharide is being considered the potential focal point for future researches, as it seems to play a role in the *L. kefirofaciens*' ability to mediate the hypothalamus-pituitary-axis, the immune system, the tryptophan/ kynurenine metabolic pathway, and the colonization of gut microbiome (Jeong et al. 2017; Sun et al. 2020; Yong et al. 2020).

4.9.10 *Bifidobacterium breve*

Bifidobacterium breve is a probiotic widely known for its antidepressant potential. There has been no widely reported success in understanding and clarifying the exact mechanism of action of *B. breve*. However, a metabolite produced by *B. breve*, benzoic acid, was reported in a study to play a role in the antidepressive mechanism. *B. breve* introduced to schizophrenic patients showed reduced depressive symptoms, and hence is prescribed as an antidepressive agent. It was also reported that *B. breve* uplifted mood, and enhanced cognition in cognitively impaired elderly individuals (Okubo et al. 2019; Yong et al. 2020).

4.9.11 *Clostridium butyricum*

Clostridium butyricum belongs to *Clostridia* which are a class of bacteria responsible for fermenting free sugars and carbohydrates. *C. butyricum*, as the name suggests, produces a metabolite known as butyrate as a result of carbohydrate fermentation. Similar to *L. paracasei* and *B. infantis*, *C. butyricum* has a potential to upregulate the central BDNF-5HT system through a mechanism involving its metabolite, butyrate. This microbial butyrate-mediated upregulation results in reduced depressive symptoms. Despite being a potential antidepressant agent, not all strains of *C. butyricum* are safe for consumption, as few are reportedly pathogenic and can cause gastrointestinal complications (Anderberg et al. 2016; Cassir et al. 2016; Yong et al. 2020).

4.10 Conclusions

Conclusively, total dairy microflora presents a complete profile of differential bacterial and fungal communities that predominately depends on the chemical composition of milk. Lactic acid bacteria are the most versatile group in all dairy microbiota that display a variety of strains associated with the milk of different animals. The health-promoting advantages of microbes and their additives are overwhelming the few effects of few harmful bacteria in the dairy environment. Despite many benefits of dairy associated bacteria, the emergence of psychobiotics is directing a new avenue towards personalized treatment of many psychological disorders and enhancing the need to explore new microbes with therapeutic potential (Table 4.2).

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