Chapter 4
Probiotics: Origin, Products, and Regulations in India

Amrita Narula

Abstract The concept of probiotics is well known from the time of Greeks and Romans. The term 'Probiotics' is defined as the substances produced by microorganisms that help stimulate the secretion of another. Though the definition has been redefined by many, the most recent and acceptable definition is by FAO/WHO (2001) and has defined it as: 'Live microorganisms that when being administered in appropriate dose, confer the benefit of health to the receiver'. Probiotics are usually found in dairy and non-dairy products, infant formula, dietary supplements, and energy drinks. They are generally recommended for consumption after the antibiotic therapy and help to manifest a positive balance of valuable microbes in the intestine. The most often used probiotic species belongs to *Lactobacillus* and *Bifidobacterium*, apart from these some of the yeast *Saccharomyces cerevisiae* and some *Bacillus* and *E. coli* species are also used as they too demonstrated the probiotic properties. To be a probiotic, the strain needs to fulfil certain specific criteria (GRAS, nontoxic, stable, etc.) and their mechanism of probiosis includes manipulating gut microbial communities, immunomodulation, suppressing pathogens, stimulating epithelial cell proliferation and differentiation; and fortification of the intestinal barrier. The use of probiotics can restore the replenished good bacteria and overcome the adverse effect of chronic diseases. Yakult, Danone, Nestle, Amul, and Mother Dairy are the common probiotic brands in India which have made their remark of recognition in this industry along with many others (some minor brands) are too heading towards better quality pre and probiotic products. The laws governing probiotics are ambiguous due to the categorization of probiotics in functional food or drugs, therefore are regulated differently in countries as per their intended use. Regulations for the probiotic production and release in India have been framed by regulatory bodies of ICMR, DBT, and FSSAI. The outlook of researchers is looking out for commercialization of Indian probiotic strains and a new technique that holds promises to help prolong the shelf-life of probiotic products. This will create more acceptability in consumers and increase the probiotic market.

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4.1 History of Probiotics

Scientists are studying the flora of the human intestine from long and generally bacteria have always been kindred with the disease and have made the human face much grief. Hence the concept of saddling bacteria for health benefits has a poetic ring to it (Joshi and Pandharbale 2015).

Ellie Metchnikoff has been accredited with the idea of working with food-friendly microbes without knowing the actual hero in the background was Stamen Grigorov. Grigorov was a Bulgarian physician and in 1905 he identified the starter culture (*Lactobacillus*) used in fermented Bulgarian dairy products. He got popularized as he published his work and was then invited to work in the Pasteur Institute of Paris. By the age of 27, he was able to accidentally retrieve that consumption of yoghurt is the secret behind the long life of the Bulgarian people. With this discovery, he was offered a post to work with the Pasteur Institute. But to live up to the promise that he had made to serve his people, he refused the offer and returned to Trun, Bulgaria. Therefore, the institute later authorized Metchnikoff to work on this subject. Later Metchnikoff and his assistants Coendi and Mikelson named the bacteria as *Lactobacillus bulgaricum* in recognition of Grigorov.

In 1917 German Professor, Alfred Nissle, discovered the non-pathogenic *Escherichia coli* Nissle strain during the outbreak of dysentery (shigellosis), using the faeces of two non-affected soldiers at the time of World War I. It was also discovered that *E. coli* Nissle strain 1917 played an important role in the food and medical industries before the antibiotics were discovered. His studies also revealed that probiotics not only could help treat the infectious diseases but also could be used in the medication of other ailments especially related to the GI tract (Sonnenborn and Schulze 2009).

Henry Tissier (working in Pasteur Institute) isolated the *Bifidobacterium* strain from a breast-fed infant and named the bacterium as *Bacillus bifidus communis* in 1889. He claimed that this bacteria helps displace the proteolytic bacteria causing diarrhoea and therefore can be prescribed to the infants suffering from the same. This discovery led to the conceptualization 'specific bacteria play role in maintaining health' (Soccol et al. 2010).

Isaac Carosso, a physician, treated numerous patients with gastrointestinal disorders by recommending yoghurt which helped in recovering the intestinal health. Following the conventional methods, he started producing the yoghurt, for that he procured the purified bacterial cultures from the Pasteur's institute. Thereafter the World War I, he commercialized the yoghurt production entitled 'Danino'—an outlet named after his son (Fuller 1995). Carosso then migrated to the USA from Paris, due to the onset of World War II, and in 1942, he launched 'Dannon Milk Products' which became the first American yoghurt plant.

After World War I, two Armenians named Sarkis and Rose Colombosian had emigrated to the USA and were collaterally working on yoghurt production. They sold their homemade product under the brand named 'Madzoon' meaning yoghurt in Armenian. Madzoon could not arouse the people's interest so to enhance their sales they replaced 'Madzoon' with 'Yogurt' and in 1929 and with their hard work they led to the establishment of their company 'Colombo and Sons Creamery'—became the USA's first yoghurt brand labelled as 'Colombo Yogurt'. Later in 1993 'Colombo Yogurt' was then sold to General Mills (Ozen and Dinleyici 2015).

Meanwhile in the 1930s in the far east Dr. Minoru Shirota isolated *Lactobacillus casei* strain *Shirota* in the Microbiological Laboratory of Kyoto University, Japan. The strain had the property of tolerance towards bile and gastric juices and therefore it could travel easily to the lower intestine, hence with this probiotic bacteria, Dr. Shirota developed the diary product 'Yakult' (Yakult 2014) hypothesizing that its day to day consumption might boost enteric health and extend the lifespan.

It was a turning point and from then on, people have been all about eating probiotics—good microbes—to benefit their health.

4.2 What Are Probiotics?

Probiotics derived from 'pro bios' the Greek term meaning 'for life'. The history of probiotics is well associated with the emergence of man; fermented milk and cheese, the concept popular among the Greeks and Romans. Fermentation was not just tasty; it was also known to be healthy and people were consuming fermented foods: beer, wine, yoghurt, cheese, kefir, etc.

Probiotic now not a new term, was first introduced by Lilly and Stillwell (Fuller 1989) in 1965 (antonym of the term 'antibiotics') to describe the substances produced by a microorganism that helps stimulate the secretion of another (Soccol et al. 2010). Later different interpretations for probiotics were given by the researchers considering their functioning and their health benefits for humans (Anandharaj 2020).

In 1974, Parker defined 'probiotic' as 'substances and microorganisms which contribute to intestinal microbial balance', whereas Fuller (1989) modified it to as 'viable microbial dietary supplement that beneficially affects the host through its effects in the intestinal tract'. de Vrese et al. (2001) in collaboration with the ILSI (International Life Sciences Institute) of Europe defined this term as 'a viable microbial food supplement which beneficially influences the health of the host' (Salminen et al. 1998). Lately in 2001 FAO/WHO defined probiotics as: 'Live microorganisms that when being administered in appropriate dose, confer benefit of health to the receiver'.

According to the current concurrences correlated to defining probiotics, the out-turn of probiotics is not pondered to be only restricted to microflora mediated, but, other types of mechanisms are getting investigated and familiarized too. This

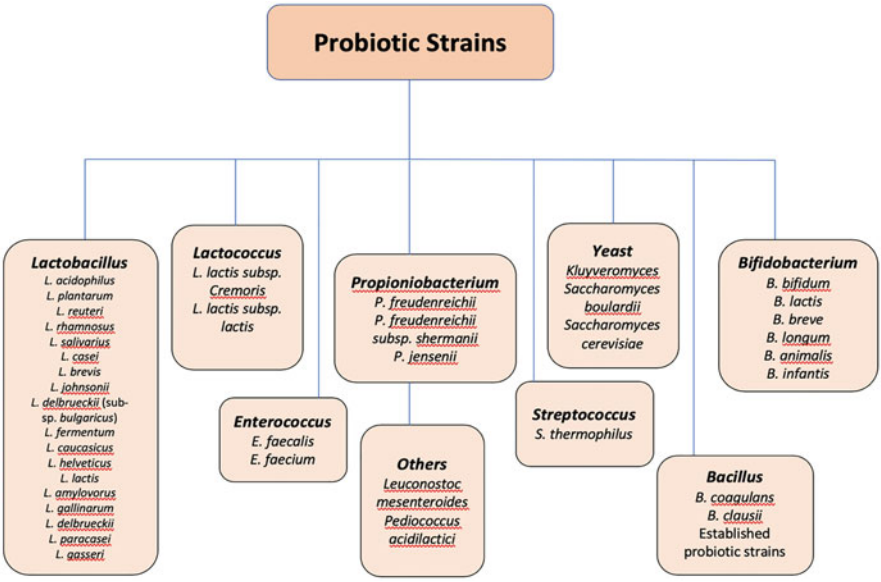

Fig. 4.1 Probiotic strains used by industries

revelation on probiotics encouraged innovation in this field and opened the doors for a wider range of probiotic possibilities (Sanders et al. 2019).

In normal human intestines where 10^{10}–10^{12} live microorganisms per gram in the human colon have been reported (Collins and Reid 2016), and around 400 variable bacterial species coexist, making it a more nexus ecosystem. The colon only is approximate to contain above 70% of all the microorganisms in the human body. Generally, the microflora of the gut is persistent but numerous factors including age, environment, diet, stress, and medication can affect the ratio (Anandhraj 2020). The frequently used species in probiotics production belong to bacterial species of *Lactobacillus* and *Bifidobacterium* and some of *E. coli* and *Bacillus* species are recently included, apart from these some of the yeast includes *Saccharomyces cerevisiae, Saccharomyces boulardii, Kluyveromyces* are also used, as they too demonstrated the probiotic properties (Fig. 4.1).

Probiotics are naturally found in dairy and even in non-dairy products, infant formula, and dietary supplements. They are recommended for consumption after the antibiotic treatment (taken for some ailment). This generally eradicates the inhabited good microbial flora of the digestive tract in addition to the targeted harmful microbes. Therefore, probiotic products enriched with beneficial microbes is recommended for regular consumption, manifesting the positive balance of valuable microbes in the intestine.

4.3 Criteria's to Be a Probiotic

During recent years, almost every fermented food has been considered to possess the probiotic properties, but not all such products are probiotics. Despite different definitions given for probiotics, there have to be certain fixed criteria's to consider the microbial suspension as a probiotic. These include:

- Should be nontoxic.
- Should be genetically stable.
- Should be a lactic acid producer.
- Should possess antimicrobial activity.
- Should possess lower generation time.
- Should possess forbearance to food additives.
- Should possess stability in the food matrix.
- Should be able to avoid the effect of peristalsis.
- Should be safe for the host/non-pathogenic (GRAS).
- Should be able to evaluate its resistance to antibiotics.
- Should avoid inhibition of adhesion of pathogenic bacteria.
- Should have the power to adhere to epithelial cells and tissue.
- Should be able to produce antibacterial substances (bacteriocin).
- Should have resistance towards gastric acids and pancreatic secretions.
- Should be able to enhance the eradication rate and reduce the adverse effect when given in combination with the antibiotics.

  (Pandey et al. 2015; Anandharaj 2020).

Although to fulfil all the criteria is difficult but certain properties are mandatory to be a probiotic.

4.4 Concept of Prebiotics and Synbiotics

4.4.1 Prebiotics

The notion of Prebiotics was first defined in 1995 by Glenn Gibson and Marcel Roberfroid. According to them, prebiotics is useful in manoeuvring the microorganisms in the host to ameliorate quantifiable health outcomes. It was reframed by Gibson in 2004 as: 'A prebiotic is a selectively fermented ingredient that allows specific changes, both in composition and/or activity in the gastrointestinal microflora that confers benefits upon host wellbeing and health' (Gibson et al. 2004). 'Probiotics are live microbial feed supplements whereas prebiotics is fibre or dietary carbohydrates'. Prebiotic examples include β-fructans, lactulose, inulin, and GOS that have selective metabolism in the colon and help to escalate the numerical amount of probiotic producing bacteria like LAB (Broekaert and Walker 2006).

Prebiotics may serve as a substitute for probiotics or as ancillary support for them. However different prebiotics will help stimulate the growth of variable native enteric bacteria. Prebiotics has a lower risk of degradation and problems like allergic reactions or intolerance than probiotics due to their fibre constitution. Other beneficial effects of prebiotics include enhanced resistance to invading pathogens, improved bowel movement, lipid reduction, reduced risk of colon cancer, improved calcium, and iron utilization (Bosscher et al. 2003; Ferguson and Philpott 2007; Bruzzese et al. 2009).

4.4.2 Synbiotics

Gibson and Roberfroid inaugurated the term synbiotic in 1995 and was reserved for products where the prebiotic compound(s) selectively favour the growth of the probiotic organism(s) (Cencic and Chingwaru 2010). The concept of synbiotics came into existence to overcome the toil of probiotics, as they are efficient implants in the colon and contribute to maintaining the intestinal homeostasis (Peña 2007).

The probiotic strains used in synbiotic formulations include *Bifidobacteria spp, Lactobacilli, B. coagulans, S. boulardii,* etc., whereas the prebiotics used majorly comprised of xyloseoligosaccharide (XOS), fructooligosaccharide (FOS), GOS, inulin, and even prebiotics from natural sources like yacon roots and chicory, etc., could be incorporated (Pandey et al. 2015). They have many health benefits like cholesterol reduction, antimutagenic effect, anti-hypertension, antibiotic-induced diarrhoea, boosting immunity, overcoming allergy, *Helicobacter pylori* infection, irritable and inflammatory bowel syndrome (Gupta et al. 2014).

4.5 Mechanism of Action of Probiotics

The process by which the probiotics deploy their biological effects is still poorly understood. Certain non-specific terminologies like competitive exclusion or colon resistance development are generally used to explain their mode of execution (Elo et al. 1991).

The concept of competitive elimination or exclusion first emerged in the early 1970s (Nurmi et al. 1992). Oelschlaeger (2010) reported three variable modes of probiotic working stating that they:

1. perhaps modulate the host's innate or acquired immune system.
2. directly affect neighbouring microbes, might be commensals or pathogenic ones.
3. could affect the microbial (like toxins) or host products (e.g. bile salts and food ingredients).

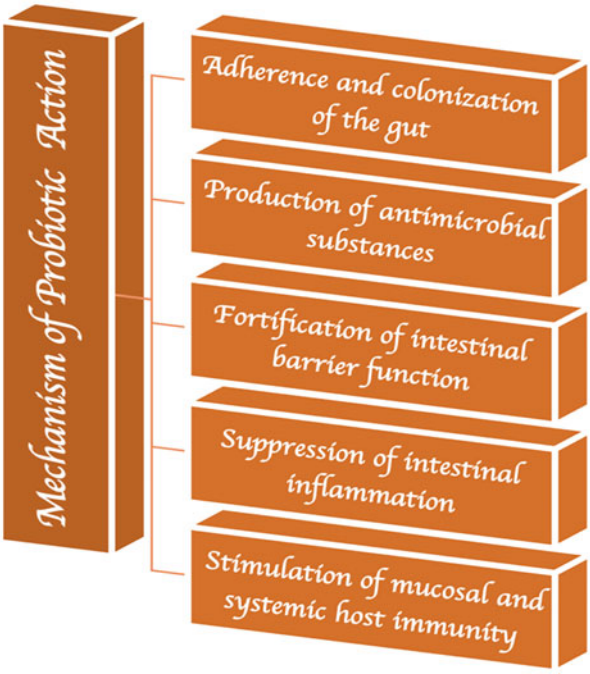

Fig. 4.2 Mechanism of probiosis in human beings

Individually or combination of such properties in a certain specific probiotic strain could determine its action and serve as a product towards the prevention and/or treatment of a certain disease (Soccol et al. 2010).

The studies have been conducted using different tools and techniques including culturing or sequencing on diversity, composition, and function of the microbial gut flora, and hence the variability in the probiotics mode of operation has been suggested through these variable experimental models. However, the exact mechanisms remain unanswered. Though in 2004 Sartor in his research study has illustrated multiple mechanisms of probiosis, including manipulating gut flora, suppressing pathogen, immune response modulation, inducing epithelial cell proliferation and differentiation, and fortification of gastroenteric hindrances (Fig. 4.2) (Thomas and Versalovic 2010). He has stated some general rules as:

4.6 Adherence and Colonization of the Gut

Competition for space does exist among the native and foreign bacteria resulting in knock-back of exogenous pathogens. Certain microbes like *Lactobacilli* or *Bifidobacteria* have the potential to adhere to the mucosal membrane (Ohashi and

Ushid 2009). This enhances the probiotics intestinal endurance and limits the access of pathogens to the epithelium (Ouwehand et al. 2001; Boudeau et al. 2003).

The Glycocalyx is the outermost layer of the cells that are concocted with glycolipids and glycoproteins, plays a crucial role in protecting the epithelial cells of the intestine from mechanical injury, and also helps obstruct the invading bacteria, thereby protecting the host from contamination (Bron et al. 2012). Also during the intestinal inflammation, mucins or glycosylated proteins act as ligands for membrane receptors leading to dysbiosis (Larsson et al. 2011; Sommer et al. 2014). Commonly used probiotic species of *Lactobacillus* and *Bifidobacterium* share some common surface molecules, having a significant role in the interconnection with the mucus components (Lebeer et al. 2010). The surface molecules may include mucin-binding proteins (Mubs), surface layer associated proteins (SLAPs), and the most commonly known lipoteichoic acid (LTA). The initial adhesin is generally non-specific, driven by hydrophobic interactions, once bonded to specific cell wall components like proteinases, adherence becomes irreversible. This helps amplify hydrophobicity and consequently adhesion in some lactic acid bacteria (Radziwill-Bienkowska et al. 2017; Zhang et al. 2015; Muñoz-Provencio et al. 2012).

For example, such adherence is seen between mucins as well as the C-terminal Leu-Pro-any-Thr-Gly motif (LPxTG) of the peptidoglycan layer of the cell wall because these mucus-binding proteins contain domains of Mub and/or MucBP (MUCin-Binding Protein), which can develop this bond. Though MucBP/Mub domains are exclusively discovered in human gut isolated LAB (van Tassell and Miller 2011; Monteagudo-Mera et al. 2019; Boekhorst et al. 2006) they are even observed in the pathogenic bacteria like *Listeria monocytogenes* (Popowska et al. 2017).

Like proteins, bacterial fimbriae or pili can also promote adhesion. Such patterns have been widely characterized in case of both Gram-negative (Type IV pili) and Gram-positive bacteria. For instance, *Bifidobacterium* possesses such type of pili (Piepenbrink and Sundberg 2016; O'Connell Motherway et al. 2011) and more specific example of SpaCBA pili have been observed in some species of Lactobacillus (*Lactobacillus rhamnosus* LGG) (Toh et al. 2013; Reunanen et al. 2012). These structures could possibly be a trump card in colonizing mucosal tissues superficially (Monteagudo-Mera et al. 2019; Hospenthal et al. 2017).

A few other peripheral proteins like surface layer proteins (SLPs) and fibronectin-binding proteins (FBPs) have also been found in contributing to the phenomena of bacterial adherence to the intestinal mucosal sheath. FBPs have been recognized extracellularly in the intestine, in an insoluble form among both Gram-negative and Gram-positive bacteria. These proteins assist in intensifying the process of adhesion which is beneficial for the probiotic bacteria and excludes pathogenic strains (Monteagudo-Mera et al. 2019; Hymes et al. 2016; Lehri et al. 2015). SLP's are extracellular too but on contrary to FBPs have para-crystalline proteins covering the entire bacterial cell surface. These SLP's perform variable functions like generating virulence in pathogenic bacteria or constructing structural components, among these adhesion promoters aid in probiotics functioning. These also act as

immunomodulators and assist in probiotic bacterial interaction with host's intestinal receptors (Konstantinov et al. 2008).

Such adhesion mechanisms have been studied by various researchers and have produced fine results.

4.7 Suppressing Growth of Pathogenic Bacteria Using Antimicrobial Substances

Antimicrobial agents or Antagonistic compounds are chemical in nature, used to demolish microbes (especially pathogenic) or to prevent their burgeon. Among the broad antimicrobial spectrum properties, this ability is of utmost importance for probiotics functionality (Fijan 2016). Probiotics are more responsive and metabolically active in (in vivo) intestinal environment (Walter et al. 2003; Bron et al. 2004) hence to restrain the epithelial invasion by the pathogens they either instigate cells of the host to produce peptides or directly liberate peptides causing interference in pathogenic activities (Gogineni et al. 2013).

Certain antimicrobial peptides like defensins (hBD protein, elafin, and SLPI), cathelicidins, hydrogen peroxide, lysozyme, nitric oxide, secretory phospholipase A2, and short-chain fatty acids (SCFA), for instance, acetic and lactic acids, expressed constitutively by the Paneth cells (specialized secretory cells of small intestine located in the intestinal crypts of Lieberkuhn). These peptides exhibit antimicrobial activity towards an array of microbes (Kelsall 2008; Furrie et al. 2005) by reducing the lumen acidity (Penner et al. 2005) and help diversify the richness of beneficial gut flora (O'Hara and Shanahan 2007).

The antimicrobial peptides act in the following manner, SCFA hampers the outer membrane of bacteria (Gram-negative) (Alakomi et al. 2000) whereas bacteriocins help create pores disrupting cells (Liévin-Le Moal and Servin 2006) and Microcins along with the structural synthesizing enzymes (of DNA/RNA) attacks the inner membrane (Duquesne et al. 2007).

4.8 Fortification of Intestinal Barrier Function

Intestinal epithelial cells have a role in both as a barrier and immunomodulator in the gut, as epithelial and immune cells can interact and influence each other. Microbe as a whole with its structural components or metabolites produced can stimulate the epithelial cell signalling pathways (Madsen 2012). Some of the probiotics have been advised in preserving epithelial barrier function, safeguard and reformation of the damaged mucosal sheath, incited by various factors including enteric pathogens, drugs, food antigens, or pro-inflammatory cytokines (Resta-Lenert and Barrett 2006; Rosenfeldt et al. 2004; Montalto et al. 2004; Resta-Lenert and Barrett 2003).

Probiotics help serve to combative effects which are mediated by successive mechanisms (Madsen 2012):

1. mucus secretion by goblet cells (Chichlowski et al. 2007),
2. maintaining cytoskeletal and tight junction proteins by phosphorylation (Brown 2011),
3. refurbishing chloride secretion,
4. enhancing trans-epithelial resistance (O'Hara and Shanahan 2007).

4.9 Suppression of Intestinal Inflammation

Researchers have presented sufficient scientific evidence supporting the role of probiotics in mucosal inflammation, particularly by restraining or restoring 'leaky' epithelial barriers (Leisched 2014). The anti-inflaming property of probiotics negates the source of pro-inflammatory stimuli and is used as therapeutic against chronic diseases like Gastroenteritis, Inflammatory bowel syndrome, Lactose Intolerance, UTI's, etc.

Combining comprehensively researched probiotic strains can assist to control and restore inflammation directly and indirectly by various modes such as:

1. arresting probable key stimulant of acute inflammation, including LPS (Claros et al. 2013),
2. simultaneously modulating multiple signalling pathways (Bermudez-Brito et al. 2012; Thomas and Versalovic 2010),
3. yielding short-chain fatty acids with anti-inflaming properties (e.g. butyrate),
4. synthesis of antimicrobial peptides (Leisched 2014),
5. synthesis of heat shock proteins (Ohland and Mac Naughton 2010; Rao and Samak 2013),
6. increased expression of mucins (Ohland and Mac Naughton 2010; Rao and Samak 2013),
7. release of metabolites and bioactive molecules (Ohland and Mac Naughton 2010; Rao and Samak 2013),
8. suppression of oxidative stress (Ohland and Mac Naughton 2010; Rao and Samak 2013),
9. interference with inflammatory pathways (Ohland and Mac Naughton 2010; Rao and Samak 2013),
10. augment levels of IgA (Ohland and Mac Naughton 2010; Rao and Samak 2013),
11. acting as a ligand for Toll-Like Receptors (TLR) influencing key pro-inflammatory pathways (Thomas and Versalovic 2010; Bermudez-Brito et al. 2012),
12. Influence development, maturation, and differentiation of dendritic and T-cells (Bermudez-Brito et al. 2012; Thomas and Versalovic 2010).
13. Influence synthesis of the important regulatory cytokines like IL-10 and TGF-β (Smits et al. 2005; Hseih et al. 2012).

4.10 Stimulation of Mucosal and Systemic Host Immunity

The researchers have demonstrated that on Oral administration of a fragment of probiotic bacteria only, a complex network of signals gets initiated inside the Interstitial Epithelial Cells (IECs). The commensal bacteria through pattern recognition receptors leads to (1) immune engagement and demonstrable systemic immunologic changes (McCarthy et al. 2003) associated with the tissue of GALT in the lamina propria like mucosal; (2) immune development; (3) to maintain and repair gut (Rakoff-Nahoum et al. 2004; Fukata et al. 2005); and (4) activating mainly the innate response and the cytokines released by T-cells (Galdeano and Perdigón 2004). Even the immune sensory cells (i.e. dendritic cells, M cells, and enterocytes) in the alimentary canal constantly respond to intestinal bacteria (O'Hara and Shanahan 2007).

Transmitting the antigenic information to the underlying cells is a crucial process towards immune fate: leading to activation versus suppression/tolerance. Three such mechanisms are involved which help process the antigenic material and lay before the underlying immune cells. These aforesaid mechanisms are further controlled by distinct antigen-presenting cells (APCs) (Hardy et al. 2013).

Consuming probiotic strains '*Bifidobacterium lactis* Bb-12, *Lactobacillus* GG (Rautava et al. 2006), and *Saccharomyces boulardii'* (Rodrigues et al. 2000) alleviates the production of IgA and its secretion via cytokine environs causes an alteration in the gut mucosa. These bacteria manifest epithelial cell expression of interleukins IL-6, IL-10 as well as TGFβ (transforming growth factor-β) and help favour IgA production through the medium of antibody class-switching, B-cell maturation phenomena (Shang et al. 2008; He et al. 2007). Finally augmenting polymeric Ig receptors expression into the gut lumen (Reséndiz-Albor et al. 2010).

4.11 Health Benefits by Probiotics

The intestinal tract harbours a complex and dynamic microbial ecosystem, capable of producing elevated concentrations of chemicals for detection and signalling particles—molecules affecting cells in the entire body. The bacteria lying in the gut produces some influential proteins which can affect the chemical and signalling molecules of the intestine either positively or negatively (Yan et al. 2007). If the ratio of good-to-bad bacteria shows disparity, initiates the activity of many of these detectors probably in negative ways, triggering a host of diseases, not just those associated with the gut but even in other body areas too (Furness et al. 1999). Fortunately, the use of probiotics can restore the replenished good bacteria and reverses the signalling which can lead to chronic diseases (Kotzamanidis et al. 2010; Ley 2010; Vyas and Ranganathan 2012; Mortaz et al. 2013). The summary for such diseases along with the probiotic use has been stated below (Table 4.1):

Table 4.1 Use of probiotics for treatment of various diseases

Sr. No	Disease	Cause	Clinical Symptoms	Probiotic Microbes Used in treatment	References
1	Chronic Diarrhoea	Small bowel bacterial over-growth	Loose or watery stools that persist for weeks, abdominal cramps, bloating, nausea	*Lactobacillus acidophilus* and *Lactobacillus casei* *Saccharomyces boulardii*	Gaon et al. (2002), Xiao et al. (2003), Le Luyer et al. (2010)
2	Inflammatory bowel disease (IBD)	Use of antibiotics caused inflamed mucosal tissue decreasing the count of lactobacilli	Diarrhoea, abdominal pain and cramping, fever, fatigue, blood in your stool, anorexia, and weight loss	VSL#3 *Bifidobacterium* strains, four lactobacilli strains, and one Streptococcus strain)	Favier et al. (1997), Gionchetti et al. (2000)
3	Irritable bowel syndrome (IBS)	Weak intestinal muscle contractions, poor coordinated signals between brain and intestines, inflammation in intestine, severe infection, and change in the gut microflora	Gas, cramps, abdominal pain and swelling, and constipation or diarrhoea, or even both	*Propionibacterium freudenreichii* ssp. *shermanii* JS, *L. rhamnosus* LC705, *Bifidobacterium breve* Bb99, and GG *Lactobacillus plantarum* significantly lowered flatulence	Kajander et al. (2005), Nobaek et al. (2000)
4	Lactose intolerance (LI)	Small intestine gets deficient of lactose causing indigestion of milk sugar, also leads to calcium deficiency causing osteoporosis	Borborygmic, abdominal pain and distension, flatulence, and diarrhoea (between 30–-120 minutes of lactose ingestion)	*Lactobacillus acidophilus* W22, *Lactobacillus acidophilus* W70 *Lactobacillus salivarius* W24 *Streptococcus thermophilus* W69 *Bifidobacterium lactis* W52 *B. animalis* *Streptococcus thermophilus, Lactobacillus reuteri, B. longum*, *Lactobacillus bulgaricus*, *Lactobacillus rhamnosus*, *Lactobacillus acidophilus*	Besseling-van der Vaart, (2016), Monteagudo-Mera et al. (2019), Le Luyer et al. (2010), de Vrese et al. (2001), He et al. (2008), Rampengan et al. (2010), Ojetti et al. (2010), Parra and Martınez (2007), Vesa et al. (1996), Agustina et al. (2007)

5	Atopic dermatitis (cow's milk allergy)	Lactobacilli and Bifidobacteria is significantly reduced	Eczematous skin lesions, increased serum IgE levels, or family history. Environmental factors: Microbes, irritants, and extremes of temperature, psychological stress, and food allergens	*L. rhamnosus* GG *L. reuteri* and *L. rhamnosus* GG *L. paracasei* and *L. rhamnosus* GG	Viljanen et al. (2005), Rosenfeldt et al. (2003), Myllyluoma et al. (2005)
6	Urinary tract infections (UTI)	Bacterial infection in kidneys, bladder, and urethra, generally occurs in young and pregnant women	Inflammation and irritation, painful and frequent urination, urinary incontinence, bad-smelling urine, haematuria, mild fever, pain or pressure in lower abdominal, and dysuria	*L. Rhamnosus and L. fermentes* *E. coli Lactobacillus fermentum RC-14 and Lactobacillus rhamnosus GR-1* *Lactobacillus rhamnosus (1 x 109 CFU per 1 billion) and a Lactobacillus reuteri* *L. Acidophilus 01; Lactobacillus salivarius UCM572, and L. plantarum CLC17*	Reid et al. (2001), Morelli et al. (2004), Darouiche et al. (2001), Hull et al. (2000), Reid et al. (2001), Anukam et al. (2006), de Llano et al. (2017)
7	Crohn's disease	Inflammation of digestive tract (small intestine and colon), significant reduction in faecal bifidobacteria	Enduring diarrhoea, often turns to dysentery, weight reduction, fever, abdominal pain, tenderness, and hematochezia.	*Lactobacillus rhamnosus* GG	Favier et al. (1997)
8	Hepatic encephalopathy (HE)/ cirrhosis	Dreaded (chronic) complication of liver disease, cannot remove toxins and hence decline in brain function	Disoriented, personality changes, lack of focus, confusion, amnesia, anxiety, seizures, fatigue, and shaky hands.	*Clostridium* cluster I and *Bifidobacterium* Lactobacillus acidophilus *Enterococcus faecium S68/lactolus*	Xia et al. (2018), Ziada et al. (2013), Loguercio et al. (1995)

(continued)

Table 4.1 (continued)

Sr. No	Disease	Cause	Clinical Symptoms	Probiotic Microbes Used in treatment	References
9	Acute pancreatitis (AP)	Acute abdomen inflammation of pancreatic and peri-pancreatic tissues	Gall stones, sudden immune system attack, pancreatic or gall bladder damage due to surgery/injury; excessive fat (triglycerides) in blood; alcohol abuse, cystic fibrosis, etc.	*Streptococcus Thermophilus, Lactobacillus acidophilus, and Bifidobacterium lactis*	Muftuoglu et al. (2006)
10	Dental caries/ periodontal diseases	Results from a homeostatic imbalance between the host and microbiota causing plaque formation or plaque attacks	Toothache, tooth sensitivity; tooth cavity; fluorosis staining	*Lactobacilli* spp. and *bifidobacteria* spp. *Streptococcus dentisani Lactobacillus rhamnosus* GG, *Lactobacillus reuteri,* and *Bifidobacterium Streptococcus thermophilus L. Paracasei SD1*	Twetman et al. (2009), Keller et al. (2011), Hasslof et al. (2010), Lopez-Lopez et al. (2017), Näse et al. (2001), Caglar et al. (2005), Cotter and Hill (2003), Arioli et al. (2010), Wattanarat et al. (2015)
11	Anaemia	Caused by blood loss, decreased or faulty RBC production or destruction of RBCs	Dizziness, fast or unusual heart pulsation, body pain, joints pain, headache, difficulty in breathing, pale skin, fatigue, cold hands and feet, growth maturation problems for children and teens	*Lactobacillus plantarum* 299v *Streptococcus thermophilus*, *L. acidophilus*, *Lactobacillus bulgaricus*, *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Bifidobacterium longum*, and *Bifidobacterium breve* *B. lactis* W52, *Bifidobacterium bifidum* W23, *Lactobacillus acidophilus* W37, *B. lactis* W51, *L. casei*W56, *L. brevis* W63, *Lactococcus lactis* W19, *L. salivarius* W24, and *Lc. lactis* W58	Korčok et al. (2018), Shariaty et al. (2017), Skrypnik et al. (2019)

12	Diabetes	Metabolic syndrome causing increased blood sugar level. Type I: Autoimmune disorder Type II: Genetic and lifestyle disorder	Increased hunger and thirst, weight reduction, dysuria, blurry vision, extreme exhaustion, wound/sore healing delayed, decreased eroticism (especially in men), ED and poor muscle strength whereas women have UTI, yeast infection, dry and itchy skin	*Lactobacillus plantarum* DSM 15313 and L gasseri BNR17 *L. rhamnosus* GG *Lactobacillus acidophilus* and *L. casei*	Andersson et al. (2010), Yun et al. (2009), Tabuchi et al. (2003), Yadav et al. (2007), Yadav et al. (2006)
13	Obesity	Consuming more calories than burn causes excessive amount of body fat deposition, no physical exercise, medication or it may be genetic, behavioural, metabolic, and hormonal influences on body weight, pregnancy, PCOs, hypothyroidism	Body mass index (BMI) is 30 or higher	*L. gasseri, Lactobacillus (L. casei strain Shirota (LAB13), L. plantarum, and L. rhamnosus, among others) and Bifidobacterium (mainly B. longum, B. infantis, and B. breve B3)* *Lactobacillus curvatus HY7601 and Lactobacillus plantarumKY1032* *Lactobacillus paracasei CNCM I-4270 and Lactobacillus rhamnosus CNCM I-3690* *Bifidobacterium* spp. (*B. longum* SPM 1205, *B. pseudocatenulatum* SPM 1204, and *B. longum* SPM 1207 or *B. adolescentis* *Pediococcus pentosaceus* LP28 *Bacteroides uniformis* CECT 7771 *Akkermansia muciniphila*	Ejtahed et al. (2019), Barengolts (2016), Chen et al. (2012), Yoo et al. (2013), Wang et al. (2015), An et al. (2011), Chen et al. (2012), Zhao et al. (2012), Gauffin et al. (2012), Everard et al. (2013)

(continued)

Table 4.1 (continued)

Sr. No	Disease	Cause	Clinical Symptoms	Probiotic Microbes Used in treatment	References
14	Cardiovascular diseases	High blood pressure, diabetes, smoking, high cholesterol, laziness, obesity, inherited	Chest pain, tightness, and chest discomfort (angina), difficulty in breathing; loss of sensation, weakness in your legs or arms due to narrowed blood vessels; pain in the neck, jaw, throat, belly, or back.	*Lactobacillus, Lactococcus, and Bifidobacterium* *L. fermentum* NCIMB 5221 and NCIMB 2797 *L. reuteri* NCIMB 30242	Ishimwe et al. (2015), Kumari et al. (2011), Tomaro-Duchesneau et al. (2015), Ryan et al. (2015)
15	Cancer issues	Uncontrolled cell growth, mutations, error in DNA repair	Lethargy, thickening under the skin, unintended weight loss or gain, delayed sore healing, dyspepsia, croakiness, constant trouble in breathing or coughing, skin discolouration (yellowing, darkening, or redness), changes in existing moles, incontinence bowel or bladder habits, extreme muscle or joint pain, inexplainable fevers or night sweats and bleeding, dysphagia	*Lactobacillus acidophilus*, and *L. casei*; *L. rhamnosus* GG and *L. casei* *L. rhamnosus* GG and *L. paracasei*IMPC2.1 *L. casei* ATCC 39392 and *L. acidophilus* ATCC 4356 *L. Plantarum* *L. johnsonii* BCRC17010 *Pichia kudriavzevii* AS-12 *Saccharomyces cerevisiae* *Pediococcus pentosaceus* FP3	Baldwin et al. (2010), Escamilla et al. (2012), Orlando and Refolo (2012), Soltan Dallal et al. (2015), An and Ha (2016), Chen et al. (2017), Saber et al. (2017), Sambrani et al. (2019), Thirabunyanon and Hongwittayakorn (2013)
16	Atopic dermatitis (AD/eczema)	May be related to gene variation or environmental factors, irritants, and allergens	Dry skin, itching predominantly at night, red or grey patches on hands, wrist feet, neck, bends of elbow, chest, eyelids, ankle, and knees especially in infants, face, scalp, or swollen skin may leak if scratched excessively	*Bifidobacterium longum* BB536 and *Bifidobacterium breve* M-16 V *Lactobacillus fermentum*, *Lactobacillus salivarius* *Lactobacillus reuteri* DSM 122460; *Lactobacillus rhamnosus* 19,070–2	Enomoto et al. (2014), Huang et al. (2017), Jacobsen et al. (1999), Rosenfeldt et al. (2003)

17	Arthritis	Reduction in cartilage tissue, infection or injury in joints rheumatoid arthritis (RA) is autoimmune disorder-attacks synovium.	Joint pain, stiffness, swelling, redness around joint; in case of RA it causes tiredness, loss of appetite, lower RBC, and fever at times.	*Bifidobacterium bifidum, Lactobacillus casei,* and *Lactobacillus acidophilus Lactobacillus casei*	Zamani et al. (2016), Wescombe et al. (2009)
18	Gastritis	*Helicobacter pylori* infection, regular use of pain killers, excessive alcohol consumption	Nausea, abdominal pain and bloating, recurrent upset stomach, vomiting, dyspepsia, heartburn in stomach usually after meals, hi-cough, vomiting, anorexia, black and tarry stools	*Lactobacillus reuteri* "Folk yogurt", containing yeast and lactobacilli	Mukai et al. (2002), Oh et al. (2002)
19	Chronic fatigue syndrome (CFS)	Viral attack, weak immune system, stress, and hormonal imbalances	Chronic insomnia, other sleep disorders, loss of memory, reduced concentration, orthostatic intolerance, muscle pain, sore throat, multi-joint pain, and swollen lymph nodes	*Lactobacillus casei strain Shirota* (*LcS*)	Rao and Samak (2013)

4.12 Probiotic Scenario in India

'Probiotics'—the term has created a buzz as it has entered the Indian food market since 2007. Though this merchandise in India is diminutive (only 1%) in comparison with the Western countries, at the moment it is all set to shoot up. The world's largest cattle population exists in India hence the largest producer of milk. Therefore, India is progressing to be a future prime probiotic market and can play a crucial role in the probiotic revolution as it is the rapidly expanding arena among the functional foods. Its annual growth rate of 13.56% was observed in 2019 and is expected to reach a market size of US$961.856 million in 2025 (Research and Market Reports, June 2020). Yakult, Danone, Nestle, Amul, and Mother Dairy are the common probiotic brands in India which have made their remark of recognition in this industry. Minor brands like Carbamide Forte, Wow Probiotics, Nature's Velvet, BoldFit, and many others are too heading towards better quality pre and probiotic products.

These well-known probiotic industries presently are using the outsourced strains, i.e. microbes of foreign origin. Scientists believe that the intestinal environment is home for gut flora as the members of a specific community have originated (from different food habits) and henceforth well accommodated, giving tough competition to the evolved probiotic bacteria. Though they have proven results adapting to the Indian gut easily since, isolated from a similar gut environment. But the probiotics in either form have to be taken daily as they can only transiently colonize the gut and presumed to be washed out anyway. Not all the scientists and researchers would agree, as there is no proof, this statement is merely based on the existing knowledge.

On that account, scientists of different Indian universities like NDRI (Karnal), Christian Medical College (CMC) in Vellore (Tamil Nadu), Anand Agricultural University (Gujarat), and some others are working on the optimization and production of Indian probiotic strains. For decades, Virender K Batish (Emeritus scientist) and his colleague Sunita Grover (Principal scientist) from NDRI (Karnal) have been working in this field and have generated a repository collection of 120 types of bacteria. They have planned to market *Lactobacillus fermentum*-1 (Lf-1) and *Lactobacillus plantarum*-91 (Lp-91) in near future for colitis and cholesterol reduction, respectively. These strains have shown motivating results in animal trials and studies are continuing on humans. They are even working on probiotics to overcome India's burgeoning obesity epidemic.

Not only in NDRI but other institutes like in Anand Agricultural University, Gujarat, the head of the dairy microbiology department, J B Prajapati, is working on species of Lactobacilli for the past 25 years. His team has standardized and very well incorporated these beneficial probiotic bacteria (MTCC 5463- L. helveticus, MTCC 5462- L. rhamnosus) into curd, buttermilk, and lassi (sweet buttermilk). The role of these microbes is now even tested for improving immunity especially in people between the age of 65 and 75 years. B.S. Ramakrishna (HOD Gastroenterology, CMC) is also working on the Lactobacillus genus but has studied various bacteria isolated from Indian dairy animals. His work is in the nascent stage, will take around

the next 5–10 years to reach out to the market. These researchers are facing certain bottlenecks mainly funds for biosafety trials and tie-up with a commercial entity.

Companies in India have launched a range of probiotic products, Amul has introduced the concept of ice-creams and lassi enriched with probiotic. B-Activ Probiotic Curd, b-Activ Dahi, b-Activ Probiotic Lassi, and Nutrifit (Strawberry and Mango) are the Mother Dairy's range of probiotic products. Nestle launched Nesvita-India's first probiotic Dahi. Yakult, Danone Group's probiotic drink is prepared using Lactobacillus, some sugar, and fermented milk. The probiotic drug market is also emerging with companies like Ranbaxy (Binifit), Dr. Reddy's Laboratories, comprising four sub-brands: Unichem, Zydus Cadila, Glaxo SmithKline, and JB Chem. Major pharmaceutical companies have come in-action and attempting to formulate newer supplements aiming specific needs like immunodeficiency and gastrointestinal problems. These products are listed in Table 4.2.

4.13 Regulatory Guidelines for Probiotics in India

Industrialization based on probiotics is enhancing in India as well as in other countries, but the status for the release of any probiotic product is still ambiguous. Probiotics nowadays are being produced under variable categories of food products (functional foods), nutraceuticals, health supplements, or energy drinks (examples as stated above in Table 4.2). This being the case, are regulated diversely in countries and as per their desired use. In India, products enriched with pre and probiotics are in huge demand due to their unusual health care benefits and some claims to cure certain diseases (but not all of them are certified). Though, in India, they are recommended once in a while by doctors as part of medicament, not as a drug substitute. Henceforth, these claims by manufacturers and the absence of particular regulations have made the regulating bodies in various countries to elucidate parameters and guidelines. These should be on par with drugs to regulate their safety, efficacy, claims, and quality (Gokhale and Nadkarni 2007).

Initially, with the advent of probiotics in India, there were no specific regulations. So for evaluating the safety and to avoid popularization of probiotic products with false claims, the Indian Council of Medical Research (ICMR) in association with the Department of Biotechnology (DBT) constituted a task group, framing the regulatory guidelines for probiotic production in India (Arora and Baldi 2015).

4.14 The ICMR-DBT Guidelines Are Stated Under the Following Sub-Requirements as

(a) *Identification of Genus, Species, and Strain for Probiotic Use*:

Table 4.2 A list of commercial probiotics

Sr. No.	Probiotic Company	Incorporated strains	Consumable Amount	Product claims	No of strains used	Contains
Probiotic capsules for men and women						
1	Cabamide forte	L. Plantarum, L. acidophilus, L. rhamnosus, L. gasseri, L. fermentum, L. casei, L. reuteri, L. paracasei, B. lactis, B. infantum, B. infantis, B. bifidum, B. longum, B. breve, S. thermophilus, and S. boulardii	30 billion CFU/capsule	Post-workout supplement, digestion and immunity booster	16	0.20 g carbohydrates, 0.59 g fat, 0.03 g protein, and 6.82Kcal of energy
2	Wow probiotics	L. Plantarum, L. casei, L. rhamnosus, L. reuteri, L. salivarius, L. fermentum, L. paracasei, L. gasseri, B. lactis, B. infantis, L. acidophilus, B. bifidum, B. breve, and S. thermophilus	20 billion CFU/capsule	Improves immunity, effective for digestion, constipation and maximizes nutrient absorption.	14	2000Kcal
3	Dr. formulated probiotic for men	L. Plantarum, L. rhamnosus, L. gasseri, L. fermentum, L. casei, L. paracasei, L. brevis, L. bulgaricus, L. salivarius, B. lactis, B. infantis, L. acidophilus, B. bifidum, B. breve, and B. longum	50 billion CFU/capsule	Supports colon health, improve the digestive and immune system, and designed for men's daily gastrointestinal problems	15	

4	Now foods probiotic	L. Plantarum, L. rhamnosus, L. salivarius, L. casei, L. paracasei, B. breve, B. lactis, L. acidophilus, B. longum, and S. thermophilus	25 billion CFU/capsule	Boost your immunity, digestive system, and gut health, supports breakdown, delivery, and utilization of nutrients obtained from diet	10	
5	Cabamide forte probiotic supplement	Saccharomyces boulardii, L. acidophilus, L. rhamnosus, and B. longum	2.75 billion CFU/capsule	Relives from unwanted gas and acidic pain, improve your immunity system, digestion power, and gut health	4	4.28 kcal, 0.15 g carbohydrate, 0.02 g protein, and 0.38 g fats
6	Inlife pre and probiotic supplement	Saccharomyces boulardii, L. rhamnosus, B. bifidus, B. longum, and L. acidophilus	2.75 billion CFU/capsule	Keeps you away from digestion and gas-related issues	5	0.545 kcal, 0.062 g carbohydrate, 0.0355 g protein, and 0 g fats
7	Simply herbal probiotic	L. Plantarum, L. fermentum, L. acidophilus, L. rhamnosus L. casei, L. reuteri, L. salivarius, L. paracasei, L. gasseri, B. breve, B. infantis, B. lactis, B. bifidum, and S. thermophilus	25 billion CFU/capsule	Easier digestion, stronger immunity and fuller nutrition, this formula can reach the large intestine making it 20% more effective	14	
8	Complete probiotics by Purayati	B. bifidum, L. rhamnosus B. longum, L. acidophilus, and Saccharomyces boulardii		Friendly bacteria maintains intestinal microflora and play major role in metabolizing vitamins and collect energy from undigested carbohydrates	5	0.36 kcal, 90 mg carbohydrate, 0 g protein, and 0 g fats
9	Daily probiotic by my protein	Lactobacillus salivarius, Bifidobacterium bifidum, Lactobacillus acidophilus,		Supports digestive system and builds muscle when	10	

(continued)

Table 4.2 (continued)

Sr. No.	Probiotic Company	Incorporated strains	Consumable Amount	Product claims	No of strains used	Contains
		Lactobacillus plantarum, Lactobacillus casei, Lactobacillus rhamnosus, Bifidobacterium breve, Bifidobacterium longum, Lactobacillus bulgaricus, and Lactobacillus lactis		taken in addition to protein sources		
10	Nature's velvet probiotic	Bacillus coagulans				
11	Hawaiian herbal probiotic plus powder	Bifidobacterium lactis, Bifidobacterium longum, Lactobacillus paracasei, lactobacillus plantarum, and Lactobacillus acidophilus	Not FDA approved	Along with an immunity booster, useful in numerous health issues including Crohn's disease, diarrhoea, inflammatory or irritable bowel syndrome, peptic ulcers, necrotizing enterocolitis (generally in premature babies), urinary tract infections, respiratory infections, milk intolerance, eczema, hypercholesteremia, prevents helicobacter pylori infections	5	
12	Women's probiotic	Lactobacillus rhamnosus LR-32, Lactobacillus acidophilus LA-14, Bifidobacterium bifidum BB-06, Lactobacillus casei LC-11, Lactobacillus	5 billion CFU/capsule			

		plantarum LP-115, Lactobacillus salivarius LS-33, Lactobacillus paracasei LPC-37, Bifidobacterium lactis BL-04				
13	Flora^{+} probiotic	Bifidobacterium lactis BL-04, Lactobacillus rhamnosus LR-32	4.5 B/CFU and 1.8 B/CFU, respectively/capsule	Contributes to natural healthy gut flora, restores and maintain digestive, respiratory, and immune health, supports brain gut axis	2	
14	Kapiva probiotic with Amla gummies	Lactowise (Bacillus organisms/Galactomanan)	3 billion CFU/Gummie	Combined with ripe amlas it provides a natural solution for strong gut health, in a convenient gummy form. These break down the bile in the gut and reduce the level of bad cholesterol in the gut		23.20 kcal, 5.80 g carbohydrate, 0 g protein, 4.10 g sugars, amla 200 mg, 0 g fats, and Lactowise 30 mg
15	Boldfit probiotics supplement	L. Acidophilus, L. casei, L. rhamnosus, L. gasseri, L. plantarum, L. fermentum, L. reuteri, B. lactis, B. infantum, B. infantis, B. bifidum, B. longum, B. breve, L. paracasei, S. thermophilus, and S. boulardii	30 billion CFU/capsule	Balances optimal digestive health leads to healthy and light gut, improves immunity, and supports energy level and heart health	16	6.82 kcal, 0.20 g carbohydrate, 0.03 g protein, and 0.59 g fats
16	Herbora probiotics for children	Bifidobacterium infantis, Bifidobacterium animalis ssp. lactis, Lactobacillus casei, Lactobacillus acidophilus, Lactobacillus reuteri	7 x 109 CFU /g, 7 x 109 CFU /g, 7 x 109 CFU /g, 7 x 109 CFU /g, 7 x 109 CFU /g, respectively	Preventive treatment for infections and loss of intestinal flora, after an infectious process, diarrhoea, gas, digestive discomfort, etc., including colitis of the baby	5	

(continued)

Table 4.2 (continued)

Sr. No.	Probiotic Company	Incorporated strains	Consumable Amount	Product claims	No of strains used	Contains
17	Complete pre and probiotic by Olympian lab Inc.	Bifidobacterium lactis HA-194, L. rhamnosus HA-111, L. plantarum HA-119, L. acidophilus HA-122, Bifidobacterium longum HA-135	25 billion CFU/capsule	The live bacteria of probiotic with the energy source of prebiotic—Helps to maintain optimal digestive growth	5	
18	Healthy hey nutrition probiotic	Lactobacillus sporogenes (Bacillus coagulans)	20 billion CFU/capsule	Temperature stabilized capsules for digestion and immune health. Delayed release capsule, hence protects it from stomach acid. Helpful in constipation, diarrhoea, and overall health	1	
19	Health XP pre and probiotic	Lactobacillus sporogenes	20 billion CFU/capsule	Boosts immunity and fights fatigue, provides relief from gas pain, acidity, stress, and strain of antibiotics by promoting digestion	1	0.84 kcal, 0.21 g carbohydrate, 0 g protein, and 0 g fats
20	Probiotic immune by zenith nutrition	L. Acidophilus, B. bifidum, L. rhamnosus, and B. longum	2 billion CFU/capsule	Helps maintain intestinal flora, dietary supplement	4	
21	Acidophilus probiotic by Nature's bounty	Lactobacillus acidophilus	100 million CFU/capsule	Stomach friendly, supports overall well being	1	
22	BigLac	Bifidobacterium Bifidum, Lactobacillus acidophilus,	–	Diarrhoea due to excessive antibiotics consumption	4	

		Saccharomyces Boulardii, and Streptococcus Thermophilus.				
23	New chapter probiotic AllFlora	Bifidobacterium bifidum, Lactobacillus plantarum LP01 Bifidobacterium breve BR03, Lactobacillus rhamnosus and Lactobacillus acidophilus, Saccharomyces boulardii	10 billion CFU/capsule	Boosts immune defences and promotes digestive health including bowel regularity, bloating, diarrhoea, gas, and constipation, helps to reduce problematic yeast like Candida while replenishing healthy gut bacteria	6	
24	Meadberry probiotic	L. Plantarum, L. reuteri, L. rhamnosus L. casei, L. salivarius, L. paracasei, L. gasseri, L. acidophilus, L. fermentum, B. breve, B. infantis, B. lactis, B. bifidum, and S. thermophilus	20 billion CFU/capsule	Dietary supplement for moderate working men and women	14	2.0 kcal, 0.122 g carbohydrate, 0.086 g protein, and 0 g fats
25	GNC probiotic complex	L. Acidophilus (CUL-21), B. animalis subsp. lactis (CUL-34), B. bifidum (CUL-20), L. acidophilus (CUL-60)	25 billion CFU/capsule	Provides digestive and immune support	4	
Probiotic drinks for men and women						
1	Yakult	Lactobacillus casei strain Shirota (LcS)	6.5 billion CFU/serving	Prevents digestive disorders such as constipation, diarrhoea, boosts immunity and reduces infection.		50 cal/bottle, 12 g carbohydrate, 1 g protein, and 0 g fats
2	GoodBelly	L. Plantarum (LP299V)	12 billion CFU/serving	Delicious probiotic drink in different flavours, suitable for		

(continued)

Table 4.2 (continued)

Sr. No.	Probiotic Company	Incorporated strains	Consumable Amount	Product claims	No of strains used	Contains
				expecting mothers and improves digestive health.		
3	Beyond berry		38 CFU/serving	Excessive inflammation, helps protect cells from oxygen damage, improves potential to respond to stress, supports your adrenal glands, enhances energy, protects against radical damage, brings mental clarity and focus, cellular degeneration, and ageing, strengthens your immune system, rich in antioxidants prevents free radical damage		Low calorie
4	DanActive by Danon	Lactobacillus casei Immunitas® (L. casei DN-114001)	10 billion CFU/serving	Provides required nutrients like calcium, survives and remains active in intestine		
5	Pre probiotic enhancer		2.5 billion CFU/serving	Variety of flavours, healthy boost to your digestion at any time of the day		Zero calorie drink
6	Kyo Dophilus probiotics plus fibre	B. longum, L. gasseri, and B. bifidum	1 billion CFU/serving	Fibre-rich and improves the functioning of the digestive system, it enhances immunity and promotes good health		15 calories, 3 g carbohydrate, 3 g dietary fibre

7	PHD 2Go probiotic drink		20 billion CFU/serving	Helps to detox your digestive system, strengthens immunity, improves overall health	6	
8	CoCo biotic by body ecology	Lactobacillus delbrueckii and Lactobacillus acidophilus	4 billion CFU/serving	Improves digestion, reduces sugar cravings, energy booster and improves liver cleansing		10 calories, 3 g carbohydrate, 2 g sugar, 10 mg sodium, and 22 mg potassium
Probiotics for children						
1	Children's probiotic	Lactobacillus bulgaricus LB-87, Lactobacillus casei LC-11, Lactobacillus acidophilus LA-14, Lactobacillus salivarius LS-33, Streptococcus thermophilus ST-21, Bifidobacterium bifidum BB-06, Lactobacillus paracasei LPC-37, Bifidobacterium longum BL-05, Lactobacillus brevis LBR-35, Lactobacillus gasseri LG-36, Bifidobacterium breve BB-03, Lactobacillus plantarum LP-115, Bifidobacterium lactis BL-04, Lactobacillus rhamnosus LR-32	3 billion CFU/capsule	Neutralize the harmful bacteria that would otherwise cause occasional constipation, gas, and bloating	14	
2	BioGaia	Lactobacillus reuteri DSM 17938	100 million/5 drops	Provides colic relief that reduces excessive crying, helps build stronger immune system	1	

(continued)

Table 4.2 (continued)

Sr. No.	Probiotic Company	Incorporated strains	Consumable Amount	Product claims	No of strains used	Contains
3	Dr. formulated probiotics	Bifidobacterium lactis, Lactobacillus gasseri, Bifidobacterium bifidum, Lactobacillus plantarum, Lactobacillus Casei, Bifidobacterium breve, Lactobacillus brevis, Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus salivarius, Lactobacillus bulgaricus, Lactobacillus paracasei, Bifidobacterium infantis, Bifidobacterium longum	5 billion CFU/capsule	Promotes immune system and digestive health	14	5 calories, 1 g carbohydrate, >1 g sugar
4	Billion cheers probiotic immunity Junior's drink	Lactobacillus rhamnosus, Bifidobacterium lactis and Lactobacillus acidophilus	5 billion CFU/serving	Probiotic drink for kids 5^{+}	3	156 kcal, 0.9674 g carbohydrate
5	Good day chocolate probiotic	Bacillus coagulans MTCC 5856	1 billion CFU/serving	Promotes healthy digestion and keeps thing moving and growing		15 calories, 3 g carbohydrate, 2 g sugar, < 2 g fat, < 1 mg protein and 2 mg sodium
6	Cipla active kids Unobiotics junior	Lactobacillus rhamnosus GG	30 billion CFU/serving	Delivers 5 times more probiotic activity than traditional uncoated freeze-dried form, maintains the health and integrity of the intestinal cells		4.024 kcal, 75 g carbohydrate, 0.024 g protein

7	ProbiTec	Lactobacillus reuteri FloraActive®; Lactobacillus rhamnosus FloraActive®	250 million CFU/serving	Boosts immune system and contributes to optimal development of teeth and bones	2	
8	Neo' peques probiotic	Saccharomyces boulardii, Bifidobacterium infantis SP37, Lactobacillus acidophilus LA3, Lactobacillus rhamnosus SP1, Bifidobacterium lactis W18, Lactobacillus casei BGP93	–	Enables an optimal balance of gut microflora in infants and young children in diarrhoea	6	
9	Culturelle probiotics kids	Lactobacillus GG		Helps to relieve from the tummy troubles of children	1	
10	GNC milestone kids probiotic		12.5 billion CFU/serving	Supports digestive, immune, and bone health		
11	Jarro-Dophilus Baby's probiotic	B. infantis M-63, L. rhamnosus R0011, L. casei R0215, B. longum BB536, B. breve M-16 V	3 billion CFU/serving	*B. infantis* capable of using unique sugars in breast milk to gain full benefits, rest support immunity and digestive health	5	
12	Hyperbiotics pro-kids	Lactobacillus acidophilus, Lactobacillus plantarum, B. infantis, and B. lactis	3 billion CFU/serving	Can survive stomach acid, helps to absorb nutrients	4	

The use of specific strain plays an important role in probiotic products, as their effects are dependent primarily on it. Therefore, strain identity is important and directly linked to specific health effects. Standard protocols and techniques, namely 'DNA fingerprinting, viz. Pulsed Field Gel Electrophoresis (PFGE) and ribotyping; 16S rRNA sequencing and PCR' help identify phenotypic as well as genotypic traits. The identified traits and the nomenclature should be confirmed through the scientifically validated 'International Committee on Systematics of Prokaryotes (ICPS)' (available at http://www.the-icsp.org/). These identified strains must be accumulated in internationally acclaimed repositories/culture collection centres for probiotic use. Indian repositories include: Microbial Type Culture Collection (MTCC), Chandigarh; Microbial Culture Collection (MCC), Pune; National Fungal Culture Collection of India, Pune; National Collection of Industrial Microorganisms, Pune; agriculturally important National Bureau of Microorganisms, and National Collection of Dairy Cultures, Karnal, etc. MTCC and MCC are IDA (International Depository Authority) recognized (Sharma and Shouche 2014; Source: http://www.wfcc.info/ccinfo/collection/col_by_country/i/91).

(b) *Screening of potential probiotic strains*:

For screening the putative probiotic strains, following in vitro tests are a must.

1. Withstand gastric acidity.
2. Show resistance to bile acid.
3. Antimicrobial activity towards potentially pathogenic bacteria (acid and bacteriocin production).
4. Ability to curtail pathogen adhesion to surfaces.
5. Bile salt hydrolase activity.

These are performed with specific standard methodology and are subjected to pre-clinical validation.

(c) *Safety studies in animal models* (*In Vivo*):

All the potential probiotic strains* are assessed for acute, subacute, and chronic toxicity of ingestion of exceedingly large amounts of probiotics.

(* not necessary for acclaimed strains)

(d) *Efficacy Studies in animal models* (*In Vivo*):

To justify the in vitro effects of probiotic strains, efficacy must be checked in animal models, before human trials.

(e) *Evaluation for human use*:

The probiotic strain used, must be GRAS approved and needs to be assured and characterized by the following tests:

1. Determining antibiotic resistance patterns, strain should not pose significant risk concerning transferring antibiotic resistance.
2. Evaluation of inadmissible side effects.
3. If the strain used in probiotic use belongs to species of well-known mammalian toxin producer/haemolytic potential, must be tested for both toxic and haemolytic activities consequently.

(f) *Evaluation of efficacy studies in humans*:

The results of efficacy studies should be proven with similar benefits in human trials*, including parameters like:

Statistical and clinically significant improvement in conditions, symptoms, quality of life, reducing the risk of reoccurrence of disease or faster recovery.

(*Phase-3 studies must be continued only if the probiotic claims for any specific health benefit)

If the probiotic in use has documented safe piece of evidence outside India, the data could be reviewed and sufficient enough to allow marketing within the country. While these studies are taken into account, the efficacy of abroad reports should be tested on Indian subjects.

(g) *Effective dose determination*:

The minimal effective dose along with the viable count of the strain used in terms of CFU/ml/day along with the targeted population must be indicated clearly.

(h) *Requirements for Labelling*:

The general labelling guidelines under food law have to be followed. Along with these, the display of the following information is a must:

1. Genus, species, and strain designation must be stated following the standard international nomenclature.
2. The minimum viable count of each probiotic strain should be specified both at the level at which efficacy is claimed and at the end of the shelf-life.
3. Health claim(s) should be stated clearly (only if approved based on evidences).
4. The suggested serving size to deliver the minimum effective quantity of the probiotic related to the health claim.
5. Proper storage conditions must be mentioned.

(i) *Manufacturing and Handling Practices to be followed*:

Good Manufacturing Practices should be obeyed while probiotic foods are manufactured. These practices should stick to the recommendations of the Codex General Principles of Food Hygiene and Guidelines for Application of Hazard Analysis and Critical Control Point (HACCP). These practices will ensure public protection from fraud and false manufacturing practices (Arora et al. 2013). Figure 4.3 represented the ICMR Guided Regulations for Probiotic Evaluation and Release.

ICMR also envisaged the formation of a special regulatory body 'Foods Safety and Standards Authority of India (FSSAI)' along with other sub-ordinate bodies to monitor all food relevant issues. Currently in India foods and drugs are regulated under the Prevention of Food Adulteration Act (PFA) and the Food and Drug Administration (FDA), respectively (Arora and Baldi, 2015). The guidelines in India released by the Foods Safety and Standards Authority of India (FSSAI) 2016, formed under the Food Safety and Standards Act, 2006 are as follows:

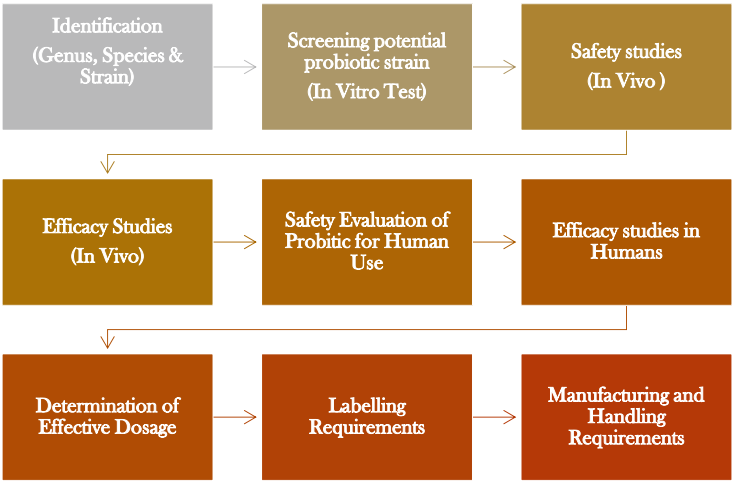

Fig. 4.3 ICMR guided regulations for probiotic evaluation and release

4.15 FSSAI General Guidelines Applicable to All Food Products Under Different Categories

1. The syrups, capsules, and tablets shall meet up to the general quality requirements and standards as specified in Indian Pharmacopoeia, British Pharmacopoeia, or the United States Pharmacopoeia.
2. The food business operator may use the approved colours and additives sanctioned in *Schedule VF*, further may use natural or synthetic flavours, which have to be following FSSAI Regulations 2011. The addition of flavours must be declared on the label of the packaging.
3. The amount of nutrients incorporated into the articles of food shall not outreach the approved daily limit as specified by ICMR.
4. If the food product claims to be a health supplement, the nutrient content recommended daily for an individual shall not be less than 15% and should be greater than 30% only if the nutrient claim is higher.
5. The standard nutrients added in the food article must deliver the desired level of energy, proteins, vitamins and minerals, and other essential nutrients required for the respective age group, gender, and physiological stage following the guidelines made by ICMR.
6. The purity of the ingredients used must be covered under regulations notified by the food authorities.
7. In case such standards are not specified, the purity criteria generally accepted by pharmacopoeias, namely, Indian Pharmacopoeia, Ayurvedic Pharmacopoeia of India, relevant Bureau of Indian Standards Specifications, Quality Standards of Indian Medicinal Plants, Indian Council of Medical Research, British Pharmacopoeia, United States Pharmacopoeia, Food Chemical Codex, Joint Food, and

Agriculture Organization, or World Health Organization Expert Committee on Food Additives or CODEX Alimentarius may be adopted by food Business operators.

8. The tolerance limit for variation in the case of the food articles shall not be more than (−) 10% from the declared value of the nutrients or nutritional ingredients on the label.

4.16 FSSAI Guidelines Specifically Applicable to Food Products with Added Probiotic Ingredients

1. The main ingredient of the probiotic food has to be the culture of live microorganisms, the culture used may be a single strain or combination of microbes.
2. The approved strains only can be added in the probiotic products (specified in *Schedule VII*), or those microbes approved from time to time by the authority.
3. It must confer specified health benefits to the consumer.
4. It may contain added prebiotics as per FSSAI regulations.
5. The microbes must be depicted on the labelling display panel of the product.
6. These microbes must be non-GMOs.
7. The viable count of the added microbes must be $\geq 10^8$ CFU in the recommended serving size per day.
8. Probiotic food product shall not claim or mention (in labelling or even in the advertisement) to have any property of preventing, healing, or treating human disease.
9. The food authority can allow the company to mention a particular statement regarding any health claim, only if supported with scientific evidence.
10. The packaging of the probiotic product must include the following:
    a. 'PROBIOTIC FOOD' must be mentioned clearly on the label
    b. Genus and species including strain designation or culture collection number as per MTCC (if applicable) in the list of ingredients.
    c. Serving size (recommended), duration of use, storage conditions, and 'best by' date after the container is opened.
    d. Viable count at the end of the shelf-life of the probiotic strain should be stated.
    e. 'NOT FOR MEDICINAL USE'—advisory warning must be written prominently
    f. Any other warning or precaution to be taken while consuming, known side effects, contraindications, and product-drug interactions, as applicable.
11. Only additives specified in *Schedule VA* to *Schedule VF* can be used in probiotic preparations (FSSAI Regulations 2016).

4.17 Future Direction

Commercial availability of probiotics is a diverse range including capsules, dried powders, sprays, dietary supplements in the form of energy drinks, fortified yoghurt, probiotic enriched curd, lassi, and even ice creams. These are enriched with microbes especially Lactic Acid Bacteria (LAB) which actually could not survive for longer, may not even reach live into the gut of humans. Hence, diminishing the benefits. So, DBT Biotech Consortium is looking out for commercialization of a new technique that holds promises to help prolong the serviceable life of probiotic products. Their concept says encapsulation of probiotic strains with food grade edible strips or coatings of biopolymers (made of milk protein and plant-based waxy substances) can keep the probiotic bacteria active for 1 month, stored at 4°C. They have validated their results by building an in house lab set up, generated proofs. This concept has given promising results and now offering a license to suitable industries for commercialization. This technology has the huge market potential both in India as well as outside and can reach USD 69.3 billion markets for probiotics by 2023 reported by Dr. Bilqeesha Bhat (Jan 30, 2020; Source: https://vigyanprasar.gov.in/isw/Technology-to-increase-shelf-life-of-probiotic-products.html).

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