Chapter 6
Probiotic Fermented Foods and Health Promotion

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6.1 Introduction

Fermentation is one of the oldest biotechnological processes for the development and production of desirable food products with improved organoleptic properties, increased palatability and shelf-life of the product (Ray and Joshi 2014). Food fermentation leads to inhibition of pathogenic or spoilage organisms by intermediate product developed during fermentation process, thus improving the shelf-life of fresh food product. The process of lacto fermentation occurs in food through natural bacteria or yeasts leading to production of lactic acid. Meanwhile, in the course of lactic acid fermentation, several metabolites such as such as lactic acid, carbon dioxide, ethanol, hydrogen peroxide, acetic acid, antimicrobial peptides (bacteriocin) gets produced from LAB, causing synergistically suppression as well as growth of spoilage and pathogenic microorganisms (Di Cagno et al. 2013). Furthermore along with preservation, fermentation also offers various characteristics such as flavor, texture, aroma, and nutritional enrichment into food (Ray and Joshi 2014). Bread is one of the classical examples of this innovative technique, where the principle objective of dough fermentation was to produce the distinctive organoleptic

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properties and textures in bread (Terefe 2016). Hundreds of dissimilar fermented foods are not known outside the instinctive area in which they have been fermented, produced and developed since long time ago. In addition, a huge list of fermented products are available showing that, how the diversity derives from the heterogeneity of traditional fermented food around the world based on cultural preferences, geographical areas as well as application of staple food products. Besides the huge list of fermented foods, these are some of the most common one such as beer, wine, cider, cheese, yoghurt, soya-based fermented food, beans, fish, meat and probiotics (Bell et al. 2017).

Currently, probiotics has been seen as one of the nutraceutical therapeutic approaches for the prevention and management of several chronic diseases including digestive and immune health. In addition, probiotics are also recommended as effective therapeutic interventions by health professionals including nutritionists and dieticians. Tissier was the first scientist, who identify gut microbiota from healthy breast-fed infants dominated by rods with a bifid shape bacteria (bifidobacteria), which were absent in infant formula-fed suffering from diarrhea, and led the idea how bifidobacteria played an important role in maintaining health (Kechagia et al. 2013). In 1965, Lilly and Stillwell was the first who introduced the term "probiotics" and described it as microbial derived factors that stimulate the growth of other organisms. Furthermore, Roy Fuller in 1989, stressed on the necessity of probiotics and presented the notion that probiotics have a beneficial effect on the host (Guarner et al. 2012). Initially probiotics were used for the improvement of human as well as animal health by virtue of intestinal microbiota modulation. Currently, several strains of probiotics likewise *Bifidobacteria* and *Lactobacilli* are available for human consumption for the treatment of gastrointestinal (GI) infections. Some of the positive effects of probiotic consumption include improvement of intestinal health by the regulation of microbiota, synthesizing and enhancing the bioavailability of nutrients, reducing symptoms of lactose intolerance, stimulation and development of the immune system and reducing the possibility of other ailments (Nagpal et al. 2012). Probiotics are described as 'live microorganisms' administered in acceptable amount conferring health benefits to the host' (FAO/WHO 2002). Additionally, probiotics have also been described as live microbial feed supplements that positively affect the host by improving its GI microbial balance, or in other words it can also be described as live microbial cultures ingested for health benefits beyond providing basic nutritional value (Nagpal et al. 2012; Agerholm-Larsen et al. 2000; Adnan et al. 2017; Alshammari et al. 2019). To understand the food fermentation, we have put forward some basic definitions such as probiotics, prebiotics, synbiotics and fermentation. **Probiotics;** Live microorganisms, which confers health benefits on the host GI tract when ingested in adequate amounts. **Prebiotics;** Fermented ingredients in particular, resulting into a specific change in the composition or activity of the intestinal microbiota, leading the benefits upon host health. **Synbiotics**; Any product which contains both probiotics and prebiotics strains are described as synbiotic products. **Fermentation;** A process by which a microorganism transforms food into other desirable food products, usually through the production of lactic acid, ethanol, and other metabolic end-product (Guarner et al. 2012). In recent times, traditional fermented foods have drawn the attention of the scientific communities mainly because of its several health benefits including the probiotic organism with its health promoting effects. The market for fermented food products are growing continuously and it requires further implementation and diversification of available products. In this chapter, we bring comprehensive details of fermented food, specifically probiotics and its health benefits including mechanism of action, safety and efficacy.

6.2 Food Fermentation and Lactic Acid Bacteria (LAB)

Fermented products and their microbial and functional characteristics have been widely studied (Rhee et al. 2011). It contain microorganisms, which is generally regarded as safe (GRAS) with several characteristics of producing beneficial metabolites such as ethanol, carbon dioxide, organic acids, fatty acids and bacteriocins (Mathur et al. 2020). Moreover, fermentation of food substrate usually involves application of microorganism like LAB and yeast (Mathur et al. 2020). LAB is a non-pathogenic, Gram positive, fermentative bacteria that are linked with the production of lactic acid from carbohydrates, making them useful for food fermentation. LAB fermentative ability is been well-known for providing enrichment of nutrients, improvement in organoleptic properties, improvement in food safety as well as provides health benefits to the host. Foods fermented along with LAB, plays a significant part in serving the world's population (Rakhmanova et al. 2018). Therefore, to serve the world population, several genus of LAB have been identified for food fermentation as well as for probiotic preparation purposes such as *Lactobacillus, Lactococcus* and *Streptococcus*. Specifically, selected species are *Lactobacillus acidophilus, Lactobacillus lactis, Lactobacillus bulgaricus, Lactobacillus helveticus, Lactobacillus casei, Lactobacillus plantarum, Streptococcus thermophilus, Lactobacillus salivarius, Enterococcus faecalis*, *Bifidobacterium* spp. (Sugiharto 2016).

Apart from dairy fermented foods, fermented vegetables, cereals and meat also contains LAB, which indicates its potential industrial application in food preservation as well as in dairy fermentation (yoghurt, butter milk, cheese and kefir). Based on metabolism of glucose, LAB is classified as homo-fermentative (Embden-Meyerhof-Parnas pathway) and hetero-fermentative bacteria (pentose monophosphate pathway) leading to production of lactic acid and carbon dioxide, while pentose monophosphate pathway produces lactic acid, acetic acid, ethanol and carbon dioxide. In addition, LAB also helps to improve the quality and shelf- life of fermented food by producing several secondary metabolites such as bacteriocins, exopolysaccharides and enzymes (De Melo Pereira et al. 2020; Ibrahim et al. 2018). Therefore, LAB is considered as a very important microorganism for preserving as well as producing a wide range of fermented foods such as cucumbers (pickles), fermented milks (yogurts and cheeses), protein-rich vegetables, protein meat substitutes (*tempe*), pastes produced by fermentation of cereals and legumes (Japanese *miso*, Chinese soy sauce), fermented cereal-fish-shrimp mixtures (Philippine *balao balao* and *burong dalag*), fermented cereal yogurt (Nigerian *ogi*, Kenyan *uji*), fermented meats (e.g., salami) and fermented milk-wheat mixtures (Egyptian *kishk*, Greek *trahanas*) (Steinkraus 1992). LAB contains a substantial amount of human gut flora which has been seen to possess the positive effect on intestinal tract (Gawai and Prajapati 2017). In addition, fermentation derived from LAB is considered to produce by-products with several bioactivity or health promoting effects such as anti-allergic, antioxidant, anti-obesity, immunomodulatory, anti-anxiety, as well as increases the bioavailability of minerals or vitamins (Mathur et al. 2020; Rakhmanova et al. 2018; Ashraf et al. 2021).

6.3 Selection of Probiotics and Starter Culture in Food Fermentation

Currently, large-scale fermentations with several advancements have emerged as the need of the hour, as well as selection of microorganism/starter culture for production of different food products has always been challenging. Therefore several microorganisms has been used based upon the food product fermentation such as *Lactobacillus* species in fermented milks, vegetables, and meats, *Saccharomyces cerevisiae* for alcoholic and beverage industry, as well as molds in the production of soy-based products such as tempeh, miso and shoyu. These microbial strains are used for fermentation processes and hence called as starter cultures (De Melo Pereira et al. 2020). Therefore, starter cultures are defined as any microbial culture which helps to initiate and promote the process of fermentation in food products. On the other hand, starters could also be utilized for standardization of fermented product, as well as it also reduces the food ripening/maturation time. Since, food safety of fermented food may get exposed to microbiological contaminations likewise food-borne pathogens (*Listeria* spp., *Salmonella* spp., etc) (Laranjo et al. 2019). Safety of fermented food products may be exposed by microbiological, namely food-borne pathogens (*Salmonella spp., Clostridium perfringens, Staphylococcus aureus, Listeria* spp., etc) (Laranjo et al. 2019).

The selection of right starter culture for food fermentation is very important to ensure the overall process of fermentation, improving the food safety, stability as well as organoleptic properties of the end product. Several fermented dairy products are produced with the help of LAB like curd, cheese, fermented milk, and these products are consumed around the world. Before a probiotic is used in the interest of human health, there are several criteria's that must be fulfilled to get the desired fermentation properties, hence that it can be produced and added to the food products without losing its survival and function, or creating an unpleasant taste; it must survive when passing through the GI tract, and must reach live to the site and should be able to function in the intestinal environment (Adnan and Pramaningtyas 2020; Saad et al. 2013). Several characteristics should be taken into consideration while

Fig. 6.1 Several factors associated for the selection of safe and appropriate probiotic

choosing a safe and appropriate probiotic as shown in Fig. 6.1 i.e., (Ray and Joshi 2014) safe strains, species and genera of probiotics (Di Cagno et al. 2013) viability and bioactivity during the process and storage (Terefe 2016) GI survival and resistance to gastric acid and bile acids (Bell et al. 2017) stimulating the selection of beneficial bacteria and suppressing harmful bacteria (through the production of antimicrobial compounds and competitive elimination) (Kechagia et al. 2013) antagonistic activity against pathogens such as *Clostridium difficile*, *Salmonella*, *Helicobacter pylori* and *Listeria monocytogenes* (Guarner et al. 2012) adhesion to the intestinal epithelium (Nagpal et al. 2012) anti-carcinogenic properties and anti-mutagenic (Agerholm-Larsen et al. 2000) modification and improvement of the immune system (Peivasteh Roudsari et al. 2019). In addition, there are various other factors that should be considered for the selection of starter culture for any food fermentation processes.

6.4 Probiotic and Its Mechanism of Action

The current definition of probiotics by Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) is "live microorganisms which when administered in adequate amounts confer a health benefits to the host". The word probiotic is been derived from Greek meaning "for life." Hence, probiotic is considered very useful for several therapeutic purposes, due to its ability to adhere to the intestinal mucosa, ability to colonize the intestinal tract, bile salt and gastric acid stability (Khalighi et al. 2016). Additionally, probiotic *Lactobacillus paracasei* A221 has been reported to improve the bioavailability and functionality of kaempferol glucoside in kale by its glucosidase activity (Shimojo et al. 2018). Bergillos-Meca reported that, bacterial strain *Lactobacillus fermentum* D3 has the ability to increase the bioavailability of Zn, Ca and P in *in-vitro* fermented goat milk (Bergillos-Meca et al. 2013). Furthermore, several studies also pointed out the probiotic therapeutic effects; however its mode of action is still poorly understood. In this section we have elaborated the possible mechanism of action of probiotics.

6.4.1 Mechanism of Action

The exact mechanisms of action (MOA) by which probiotics show its beneficial effect have not been well described. However, there are various proposed mechanisms that explain its favorable effects as shown in Fig. 6.2. The probiotic organism influences the host cell in many ways. Different strains of probiotic effect in various ways like by impact on intestinal luminal environment, mucosal immune system, epithelial and mucosal barrier function. Probiotic additionally affect directly or indirectly on the host cells or food components. Furthermore, efficacy of probiotics depends on its metabolic properties of the specific strains and the molecular structure (DNA or peptidoglycan) present on the surface of the microorganism. It also affects the monocytes/macrophages, dendritic cells, epithelial cells, T cells and B cells of the host cell (Nagpal et al. 2012; Cencic and Chingwaru 2010). In other words, probiotics also act by competitively binding to the adhesion sites by virtue of that it fights for cellular attachments.

It's been also proposed that probiotic bacteria inhibit pathogens by producing antagonistic components and competes for competition for nutrients (particularly iron in marine microbes), nutritional benefits such as improving feed digestibility and utilization, immune-stimulatory functions, and alteration of the enzymatic activity of pathogens (Seerengeraj 2018). Another possible MOA for probiotics is alteration in microbial flora through the synthesis of antimicrobial compounds (Rolfe 2000). Because, different types of bacteria (*Lactobacilli* and *Bifidobacteria*) produces antimicrobial compounds including bacteriocin. Bacteriocins are described as "compounds produced by bacteria that have a biologically active protein moiety and a bactericidal action". Furthermore, probiotics are reported to increase

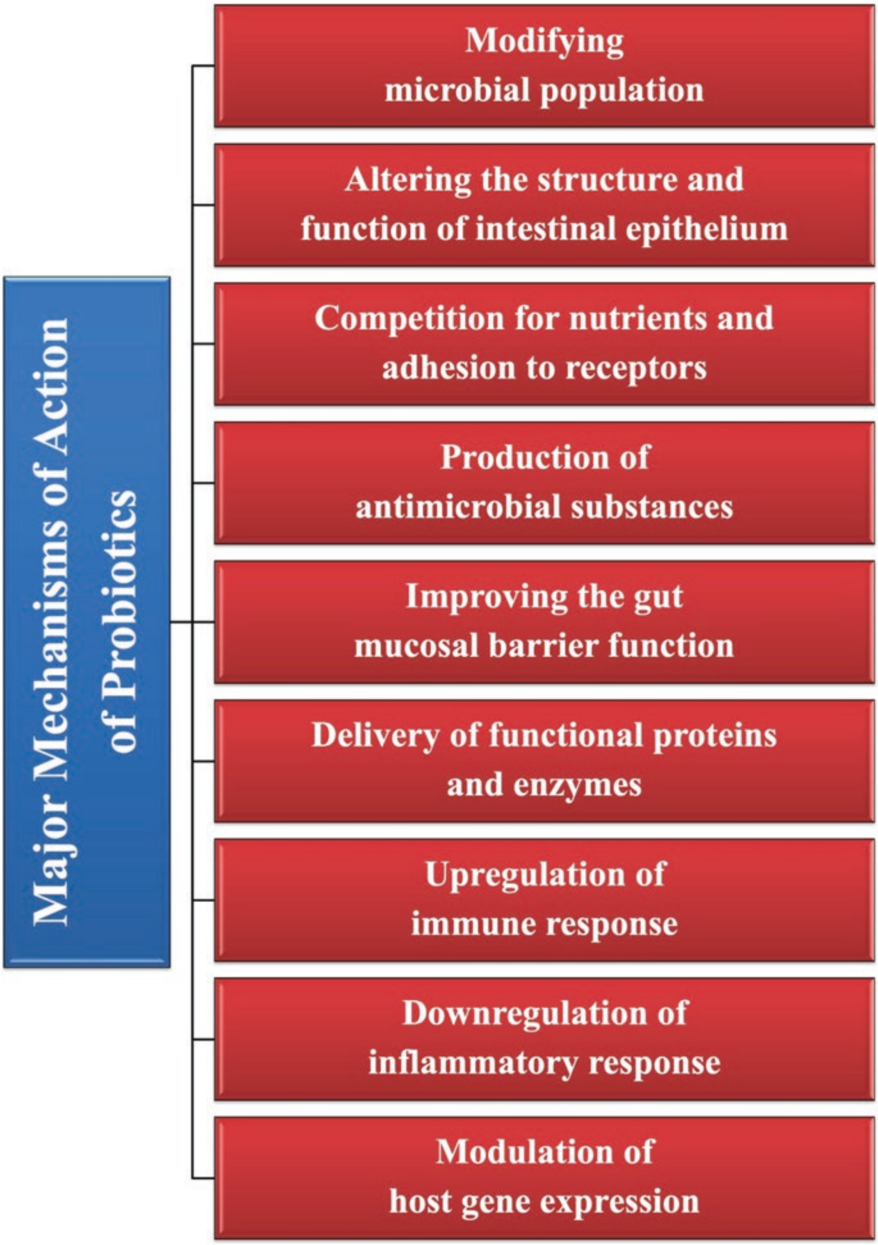

Fig. 6.2 Possible and major mechanism of action of probiotics

immunoglobulin-A (IgA) secretion, enhanced phagocytic activity of macrophages leads to increased immune response. Meanwhile, increase in IgA secretion causes decrease in the numbers of pathogenic microorganism as well as improves the condition of microflora in the intestinal tract. Therefore some of the research studies suggest that probiotics could not only fight intestinal or urogenital infections, but it could also help in inflammatory diseases, in allergic responses, even as an adjuvant in vaccination (Khalighi et al. 2016).

6.5 Bio-preservation Techniques Using Probiotic Organisms for Food Safety

Food safety and regulatory standards implementation in food production system is very crucial to ensure safe food production. Recently, development of noble chemical additives, new food pathogens and its source for causing food-borne illnesses has raised the concerns in food production system. In addition, extensive use of food preservative chemicals, antibiotic in food production system has forced the scientific communities to search more natural ways of food preservation (Akbar et al. 2016). Food preservation is a major hurdle in modern day food technology. Therefore, to present consumer a fresh, ready to eat, highly nutritious, minimally processed food to avoid contamination will improve the food preservation. Use of microorganisms and their natural by-products for bio-preservation has been commonly practiced throughout the history of mankind (Kamarudheen et al. 2014). The term bio-preservation states that preservation of food, extension of shelf-life as well as its food safety can be achieved by using living microbes and their metabolites.

Of note, the process of bio-preservation can be done by two different ways such as the inoculation of food matrix with target microorganisms, and the other one by using microbial metabolites in purified form, in particular bacteriocins (Gaggia et al. 2011). Moreover, the whole food fermentation depends on the selection of microorganism to control spoilage and make pathogen inactive. Therefore, a special interest has been shifted to a very important microorganisms i.e., LABs and their metabolites. LABs has been reported to show antimicrobial properties (like organic acids, carbon dioxide, diacetyl (2,3-butanedione), anti-fungal peptides, hydrogen peroxide and bacteriocins) and offer a unique texture and flavor to the food products (Singh 2018; Oluk and Karaca 2018). Currently these techniques are used in various dairy milk products as well as other food products. Various food product such as chicken meat, beef meat, ham, iceberg lettuce, golden delicious apples, non-fermented pickles, cold smoked salmon and cooked and fresh peeled shrimp shelf life is been improved using various microorganisms such as *E. faecium* PCD71, *L. fermentum* ACA-DC179, *L. sakei* 4808, *L. curvatus* CRL 705, *L. sakei* 10A, *Pseudomonas putida* LTH 5878, *L. mesemteroides* CM 135, CM160, PM249, *L. curvatus* LR 55, *C. divergens* V41, *L. casei* T3, *L. palntarum* Pe2, *C. piscicola* Sal3, *Leuconostoc gelidum* EU 2247 (Gaggia et al. 2011). They are non-pathogenic, bile tolerant and salt tolerant (Kamarudheen et al. 2014). Sea foods shelf-life and safety can be increased with the help of natural or controlled microbiota and/or their antimicrobial compounds (Nath et al. 2014). Therefore, bio-preservation offers the potential to improve the shelf-life and food safety suggesting a promising approach towards preserving food by natural means.

6.6 Beneficial Health Effects of Probiotics

Fermented foods comprising of beneficial bacteria have been for hundreds of years in our food are considered as probiotics. Recently, probiotics has been studied for both *in vitro* and *in vivo* and found to be clinically effective for the treatment of various diseases. Several scientific evidences has showed the significant role of probiotics in the prevention and management of different health problems such as diarrheal diseases, liver diseases, allergies, hypertension, inflammatory and immune response, detoxifying carcinogens and many more. Researches on probiotics for human consumption are yet rare, further *in vivo* studies are needed to determine the type of probiotic strains, health conditions, dosages, as well as to demonstrate their safety and limitation.

6.6.1 Prevention and Management of Diarrheal Diseases

Diarrheal disease is the second main cause of death in under-five aged children. It is also the main cause of malnutrition in this group and it kills around 525,000 children each year. Globally, the total number of cases of childhood diarrheal disease every year is about 1.7 billion (https://www.who.int/news-room/fact-sheets/detail/diarrhoeal-disease, 2017). In adults also, acute diarrhea is a familiar problem, its most popular etiology is viral gastroenteritis. Increases in travel, comorbidities and food-borne illnesses leads to more bacteria-related cases of acute diarrhea (Barr and Smith 2014). Several studies have been carried out to test the efficacy of probiotics in the prevention and management of the diarrheal diseases. These studies have reported the role of probiotics in the prevention and management of diarrheal diseases (Plaza-Díaz et al. 2018; Hempel et al. 2012; Goldenberg et al. 2017). The prevention and management of infective diarrhea, the remedy of frequent diarrhea caused by *Clostridium difficile*, in addition to the control of the diarrhea associated with antibiotics are the areas of interest of these researchers. Hospitalized children administered with probiotics, such as *Bifidobacteria* significantly prevent these children from diarrhea. One study showed that *Saccharomyces boulardii* (*S. boulardii*) decreases the duration, frequency, and hospitalization period of diarrhea, therefore, decreasing the treatment costs. In different clinical studies, *S. boulardii* was found to be active for the prophylactic as well as in the treatment of diarrhea, mainly antibiotic-associated diarrhea (Wada et al. 2010; Dash et al. 2017). The decline in duration and frequency of acute diarrhea within 24 h was also reported in Cochrane review of meta-analysis (https://www.who.int/news-room/fact-sheets/detail/diarrhoeal-disease, 2017; Shah et al. 2012).

Some probiotic strains, like *Lactobacillus rhamnosus GG (L. rhamnosus)*, *Lactobacillus reuteri (L. reuteri)*, and *S. boulardii*, looks like potent therapeutic agents for the improvement of the situation of acute diarrhea in children, when used therapeutically (Isolauri et al. 2002). *S. boulardii* was found to be an appropriate and new addition in the treatment of acute diarrhea in children. It reduces the frequency of stool, duration of illness and the number of episodes of diarrhea in a very short time (Billoo et al. 2006). Gill and Guarner (2004) reported that different strains of probiotics such as *L. rhamnosus*, *L. acidophilus*, *L. bulgaricus* and the yeast *S. boulardii* can decrease the incidence of antibiotic-related diarrhea in children as well as in adults. Beside, preventative use of probiotics was also reported to prevent hospitalized children from nosocomial diarrhea, which is the main dilemma in pediatric hospitals globally (Gill and Guarner 2004). Isolauri et al. (2002) showed in a controlled clinical research that probiotics like *L. rhamnosus*, *L. reuteri*, *L. casei* Shirota and *B. lactis* Bb12 can reduce the span of acute rotavirus diarrhea (Isolauri et al. 2002). Sur et al. (2011) have reported no difference in rehabilitation rates for adenovirus, rotavirus, norovirus, or astrovirus for children receiving *L. casei* Shirota compared with a control cohort (Sur et al. 2011). Dinleyici et al. (2011) in his study on children with *Blastocystis hominis* reported increased rate of clinical recovery and vanishing of cysts from the stool with probiotics.

Several MOA by which probiotics mediate their anti-diarrhea effect have been suggested; such as improvement of the epithelial barrier, increase in intestinal mucosa adhesion, and accompanying inhibition of pathogen adhesion, pathogenic microorganisms competitive inhibition, production of anti-microbial substances, and the immune system modulation (Bermudez-Brito et al. 2012; Dinleyici et al. 2011). Moreover, prevention of childhood diarrhea infection and antibiotic-associated diarrhea can be improved by using probiotics. It has been reported in many clinical studies that, probiotics can improve microbial imbalance and therefore constrain the generation of pathogens like *C. difficile* (Goldenberg et al. 2017; Urbańska et al. 2016). Generally, probiotics MOA in children and adults include colonization and normalization of perturbed intestinal bacterial communities, changes in the enzymatic activities linked with the carcinogens metabolism, as well as other toxic materials and synthesis of volatile fatty acids, which has a role in the conservation of energy homeostasis and organization of functionality in peripheral tissues. Additionally, probiotics also help in mucin synthesis and regulates the immune system as well as gut-associated lymphoid tissue activity (Plaza-Diaz et al. 2019).

6.6.2 Prevention and Management of Liver Diseases

Many types of liver diseases were reported globally, including diseases caused by viruses like Hepatitis A, B and C, in addition to the diseases caused by drugs and alcohol consumption such as the fatty liver and liver cirrhosis (Talwani et al. 2011). Cesaro et al. (2011) and Frazier et al. (2011) suggested that treatment and prevention of chronic liver diseases can be done by using probiotics. They reported that probiotics can prevent bacterial translocation and epithelial invasion, in addition to the fact that probiotics can inhibit bacterial mucosal adherence and synthesizing of antimicrobial peptides, at the same time reducing inflammation and stimulation of host immunity (Cesaro et al. 2011; Frazier et al. 2011). Liver disease complications could be decreased by modifying the microbiota either quantitatively or qualitatively (Eslamparast et al. 2013). Chávez-Tapia et al. (2015) reported that probiotics can modulate alterations in the gut microbiota, intestinal permeability, immune and inflammatory responses, and therefore, they can treat hepatic problems (Chavez-Tapia et al. 2015). Ranadheera et al. (2014) reported that probiotics have a big role in many liver diseases, mainly in some functional characteristics like adhesion and pro-inflammatory response (Ranadheera et al. 2014). Hong et al. (2015) showed that in a fatty diet model, *L. rhamnosus* and *L. acidophilus* moderately reduces the intrahepatic lymphocytes and TNF-α expression, also reverses irregular and decadent microvilli due to alcohol risk (Hong et al. 2015).

Different types of probiotics have a great effect on intestinal bacterial flora composition, which can show distinguished results and improvements on the metabolic health of individuals (Al-Muzafar and Amin 2017). Changed in gut flora is progressively known to play a significant important role in fatty liver disease (non-alcoholic) and is an important component of alcoholic liver disease (Kirpich and McClain 2012). In a clinical investigation involving alcoholic cirrhosis patients, who received *L. casei* Shirota three times a day for 28 days were reported to iterate neutrophil phagocytic capacity in cirrhosis, maybe due to alteration in TLR4 expression IL-10 ooze (Stadlbauer et al. 2008). Kirpich, and McClain (2012) suggested that the gut-liver axis has an important role in the pathogenesis of liver problems. Patients suffering from alcoholic cirrhosis, when received LAB showed a significant boost in liver function, by decrease in liver enzyme ALT (alanine aminotransferase) level and in tumor necrosis factor (TNF) level (Loguercio et al. 2002). When *B. bifidum* and *L. plantarum* 8PA3 were administered orally for a short period to patients with alcohol-induced liver injury, results showed that there was a significant recovery in the bowel flora in the injured liver patients, compared to the patients who received standard therapy alone (Kirpich et al. 2008).

Al-muzafar and Amin (2017) reported that a mixture of probiotic strains has a better advantage over the host health rather than a probiotic with single-strain. This mixture was reported to have an efficient effect for the management of non-alcoholic fatty liver disease via improving the leptin levels, liver function test, inflammatory markers, lipid profiles, and resist in hormone levels (Al-Muzafar and Amin 2017). They concluded that probiotics are a potential therapeutic agent that can control hepato-steatosis and associated diseases. Chen et al. (2007) reported that, in patients with hepatitis B and C, increasing the numbers of *Bifidobacteria* and *Lactobacillus* will lead to a reduction in endotoxemia and avoids the growth of pathogens (Chen et al. 2007). The main cause of liver disease is the abnormality in the gut flora. Therefore, a well-healthy GI tract prevents a high percentage of liver diseases (Imani Fooladi et al. 2013). Comparing probiotic administration with antibiotic treatment and surgery, it is safe, with no serious side effects, and low cost. Probiotics decreases the patho-physiological signs and ameliorate many types of liver diseases (Imani Fooladi et al. 2013).

6.6.3 Modulation of Inflammatory and Immune Response

Inflammation is the protective response of tissue to a noxious stimulus, resulting in both the elimination of harmful stimuli and the starting of the healing action (Pajarinen et al. 2019). Acute inflammation is noticed by capillary dilatation, leukocytic relocation and infiltration to the local area. This leads to the clinical manifestations of redness, heat, pain and loss of function (Loi et al. 2016). One of the most important mechanisms of probiotics on human health is their modulation of the immune system (Yan and Polk 2011). Gut microbiome alteration due to the consumption of probiotics, boosts the immune system and suppress inflammatory pathways. Multiple sclerosis, an inflammatory and autoimmune neurological problem that leads to demyelination can be healed due to this improvement in the immune system by probiotics (Morshedi et al. 2019). A decrease in gut dysbiosis and gut leaky after treatment with probiotics could reduce the production of inflammatory biomarkers and weaken extreme immune system stimulation (Hosseinifard et al. 2019; Fung et al. 2017). Kwon et al. (2013) and Lavasani et al. (2010) showed that probiotics can increase the differentiation of T cells toward Th2 and also increases the synthesis of Th2 cytokines like IL-10 and IL-4 (Kwon et al. 2013; Lavasani et al. 2010). Lescheid (2014) reported that probiotics have a powerful effect in the treatment of inflammatory disorders.

Some types of probiotic strains can mend hyper permeable epithelial barriers and thus indirectly adjust inflammation by locking potentially remarkable provenances of stimuli of chronic inflammation, including LPS. They are also important inducers of other substances that have prevalent roles in modulating inflammation, including butyrate and antimicrobial peptides. Additionally, specific probiotic strains bind to nucleotide-binding oligomerization domain receptors to directly affect the activity of many important signaling pathways, affecting inflammation via boosting production of more regulatory or suppressive cytokines like IL-10 and transforming growth factor-beta (TGF-β) (Lescheid 2014). Accordingly, administration of a combination of probiotic strains will modulate multiple signaling pathways, which could have a deep combined effect on the prevention and treatment of inflammation in a short time (Lescheid 2014). Probiotics have been reported to modulate central immune responses within the GI tract via modulating signaling pathways. The MOA of the probiotic are usually strain-specific and can have different responses within varied host cells (Llewellyn and Foey 2017). Probiotics such as *L. paracasei* CNCM I-1518 as well as *L. casei* CRL 431 were reported to stick through the Toll-like receptors and mediate immune stimulation into gastro intestinal epithelial cells (Galdeano and Perdigón 2004).

Fermentation processes are well-known for its ability to enhance the nutritional food quality by the enhancement of food nutrients. Therefore, probiotic fermented milk gets more attention recently. Consumption of probiotic fermented milk causes surges in the phagocytic and antimicrobial activity of spleen and peritoneal macrophages (Maldonado Galdeano et al. 2011). Appealingly, the cytokine produced by probiotics on immune cells stimulates the systemic immune response, with an increment in particular antibody production (Maldonado Galdeano et al. 2011). These antibodies were reported to have a significant role in lowering the infectious bacteria spreading to the liver and spleen after contaminating with *Salmonella* Typhimurium (Núñez et al. 2013). The probiotic bacteria spend around 72 h in the intestinal lumen, which is sufficient to stimulate modifications in the gut immune cells, developing the number of macrophages and dendritic cells of the lamina propria, and boosting their functionality, reflected in cytokines production (Maldonado Galdeano et al. 2011). Malnutrition leads to a substantial reduction in the defense mechanisms and increasing the susceptibility of the host to infections. Administration of probiotics will participate in restoring the thymus histology and stimulates the adaptive immune response (Núñez et al. 2013). As probiotic is been noticed to have a beneficial role in vaccine response (Zimmermann and Curtis 2018), the immunomodulatory effect of probiotic may have the possibility to help in COVID-19 infection. The ability of probiotics to regulate the gut microflora may in succession to modulate the immune system in a way that could be useful in COVID-19 (Adnan and Pramaningtyas 2020).

6.6.4 Prevention and Management of Allergies

Allergic diseases and it's prevalence in children has seen a surge apparently in the last few decades. Changing the intestinal microflora of an individual is been considered as a potential source of treatment and prevention in case of allergic disorders. Probiotics can change the microflora of the host; therefore, they may either prevent or improve allergies (Savilahti 2011). Using functional food enriched with *Lactobacilli* and *Bifidobacteria* have shown successful modulation in allergic rhinitis, food-related allergies and atopic problems (Prakash et al. 2014). Probiotics may have a positive effect for eczema prevention, and the World Allergy Organization (WAO) recommendations suggest using probiotics in lactating women, during pregnancy and in children with high risk of allergy (Zuccotti et al. 2015). Zuccotti et al. (2015) in a meta-analysis review reported that treatment with probiotics led to a marked reduction in the relative risk for eczema, compared with placebo and that the effect was most stated when a mixture of probiotic strains was used (Zuccotti et al. 2015).

One of the main reasons for developing allergy and their correlated diseases is exposure to environmental microbes (Tang 2005). An alteration of the Th1/Th2 cytokine balance, which leads to initiation of Th2 cytokines and the release of IL-4, IL-5 and IL-13 as well as IgE production, is the main cause of allergic disorders (Michail 2009). Administration of probiotics extremely changes the gut ecology by encouraging a change in the local microbiota and cytokine production (Winkler et al. 2007), and by virtue of that it positively affect allergic disorders. Few studies available that addressed the effectiveness of probiotic administration in the treatment or prevention of allergic conditions such as asthma, allergic rhinitis and food allergy, but these studies have not been conclusive yet and led to contradictory conclusions (Michail 2009; Giovannini et al. 2007; Hol et al. 2008). The oxymoron results and the effectiveness of probiotics in the prevention and management of allergy could be due to the large strains of heterogeneity, therapy duration, as well as the amount dose usage. Also, the results of these studies bring the authors to conclude that probiotics may have a beneficial effect in the above-mentioned allergic conditions, but the current clinical data are still not adequate to allow in clinical practices.

6.6.5 Prevention and Management of Hypertension

Hypertension or high blood pressure (BP) is a medical situation in which the BP in the arteries is persistently elevated. It is a high-risk factor for cardiovascular diseases, which is a leading non-communicable health problem worldwide. Probiotics have been reported to have an anti-hypertensive effect. Many studies carried out in spontaneously hypertensive rats showed that biologically active peptides that were obtained from fermented milk, could lower in hypertensive subjects (Miguel et al. 2006). Qi et al. (2020) in a meta-analysis study showed that probiotic consumption significantly reduced either systolic blood pressure (SBP) or diastolic blood pressure (DBP), but the SBP reduction was greater than DBP compared with the control groups, and suggest the use of probiotics as an anti-hypertensive agent (Qi et al. 2020). In a systematic review study, Khalesi et al. (2014) observed that when probiotics are consumed by the subjects, there is a significant change in SBP and DBP compared with control groups (Khalesi et al. 2014). When multiple strains of probiotics were used, there will be a higher reduction for both SBP and DBP compared to consumption of a single strain. Barrett et al. (2012) and Hernández-Ledesma et al. (2004) reported that particular probiotic strains like *Lactobacilli* and *Bifidobacteria* can produce short chain fatty acids (SCFAs), conjugated linoleic acid (CLA), γ-amino butyric acid (GABA), and angiotensin converting enzymes (ACE) inhibitory peptides, which were reported to have a hypotensive effect (Barrett et al. 2014; Hernández-Ledesma et al. 2004). Santisteban et al. (2016) suggested a new mechanism for the pathophysiology of hypertension involving a brain-gut-bone marrow triangular interaction (Santisteban et al. 2016).

The probiotics ability to lower the BP is been mainly consider due to the production of bioactive peptides during the fermentation processes, like the angiotensin-converting enzyme (ACE) inhibitory peptides (Robles-Vera et al. 2017). ACE-inhibitor tripeptides have been reported to reduce the progress of hypertension in hypertensive rats (Sipola et al. 2001). In another study, Hayakawa et al. (2004) revealed that incorporation of *L. casei* Shirota and *L. lactis* YIT 2027 strains in milk have shown to improve the mean SBP and DBP in mildly hypertensive patients (Hayakawa et al. 2004). Consumption of probiotics and probiotic fermented foods can improve the overall health status of individuals and reduces risk of developing cardiovascular diseases. Management of hypertension by consumption of probiotics is cross-linked with many different mechanisms, like improving lipid profile, bile acid deconjugation, and body mass index management. An enhancement in the absorption of nutrients, phytoestrogens and a lowering in plasma glucose levels may also influence the probiotic effect in hypertension regulation (Khalesi et al. 2014). Karbach et al. (2016) revealed that there is no difference in BP between germ-free and traditionally raised mice, which is consistent with previous study showing no effect in BP after a significant decrease in fecal microbial biomass caused by antibiotic treatment (Pluznick et al. 2013; Karbach et al. 2016). As it has been shown that probiotics and their fermented products can effectively lower inflammation and hypercholesterolemia and eventually reduces BP, this fact can support their administration in reducing the risk of cardiovascular diseases. Probiotics could be a cheap and reliable source of anti-hypertensive agents.

6.6.6 Prevention and Management of Metabolic Disorder (Diabetes)

Currently, diabetes has become an epidemic around the world affecting nearly 382 million people. According to the published data, it is assumed that each year around 1.3 million people die because of diabetes. As per International Diabetes Federation (IDF), it is projected that almost 629 million of world population will become diabetic by 2045 (Ashraf et al. 2020a). The intestinal microbiota exhibits crucial role for the non-digestible substrate fermentation such as endogenous intestinal mucus and dietary fibers. The intestinal microbiota is the most extensive and 2–10 folds higher than the number of cells that make our body and mostly found in small intestine and colon (Rad et al. 2017). Intestinal microbiota involved in a variety of aspects related to health as well as in curing the diseases (Lallès 2016). Diseases consist of varied metabolic disorders such as glucose intolerance, insulin resistance, diabetes obesity and metabolic syndrome. These microorganisms reveal an essential function in the permeability of GI mucosa and immune system, which are the significant factors in type 2 diabetes mellitus (T2DM). It was revealed that

T2DM is linked with intestinal microbiota dysbiosis (Ri et al. 2015; Wu et al. 2010). Intestinal microbiota dysbiosis may help in fat synthesis, development of adipose tissue, energy extraction from diet and leads to metabolic syndromes (Marchesi et al. 2016; Cani and Delzenne 2009; Blandino et al. 2016). Microbiota of intestinal tract also raises the adiposity, dysfunction of β-cell, systemic inflammation, metabolic endotoxemia, oxidative stress (Yoo and Kim 2016; Sun et al. 2020). Currently, modulation of intestinal microbiota performs great role in the prevention and treatment of dysbiosis allied with metabolic disorders (Druart et al. 2014).

In one study, it has been revealed that *L. rhamnosus* GG reduces gluconeogenesis in the liver and augments the insulin sensitizing hormone (Kim et al. 2013; Kim et al. 2014). Another study revealed about hypoglycemic and anti-diabetic effects of *Lactobacillus* spp. (Andrade-Velásquez et al. 2020). In an animal study of *Lactobacillus* spp. it was observed that, they reduce pro-inflammatory genes expression in mice and expresses beneficial effects in diabetic rats. Overall, numerous studies have been confirmed that probiotics and probiotics derived foods exhibit significant results in diabetes (Park et al. 2013). It has been observed that modulation of intestinal microbiota via probiotics is helpful to improve insulin-resistance (Rad et al. 2017; Cani and Delzenne 2009). Nevertheless, the efficiency of probiotics varies on different species. After clinical trials on T2DM patients, it has been reported that using fermented milk containing *B. lactis* Bb12 and *L. acidophilus* LA5 controls the reduction of anti-inflammatory cytokines and improves the glycemic control (Tonucci et al. 2017). It has also been found that probiotics decreases the blood sugar levels and insulin resistance through the improvement of inflammation. It has been reported that yoghurt with *Bifidobacterium* and *L. acidophilus* strain La-5 remarkably reduces the TNF- α and HbA1c (Mohamadshahi et al. 2014).

Probiotics are able to improve intestinal barrier function and decreases the microorganism's transmission along with their derivatives and leads to reduction in associated pro-inflammatory cytokines released through Toll-like receptor-4 signaling (Guha and Mackman 2001). Improvement in the antioxidant enzymes activities includes catalase, superoxide dismutase and glutathione peroxidase has been exhibited in other similar study of probiotics. Several strains of probiotic LAB have played antioxidant actions by several potential mechanisms that include scavenging of reactive oxygen species (ROS), chelation of metal ions, auto-oxidation inhibition and enzyme inhibition (Parle and Malik 2014). Gestational diabetes mellitus (GDM) rate is increasing across the world with other associated consequences including, overweight, obesity, preeclampsia etc. It produces acute and chronic complications to mothers as well as offspring (Petry 2020; Chu et al. 2007; Nijs and Benhalima 2020). Current therapy to control GDM is better for short term complication than long term complication. Probiotics contain the capability to avert GDM by altering metabolism (Barrett et al. 2014). Diet can influence the composition of microbiota along with gene expression with changing host metabolism. Modifying the microbiome inside the gut exhibits numerous effects. For instance, influence of inflammatory pathways, glucose and lipid metabolism and altering the nutrients absorption (Rad et al. 2017; Bäckhed et al. 2004). Clinical trials conducted on the normal weight pregnant women with the probiotic supplements and reported that GDM rate decreased from 34% to 13%. Probiotics supplement given to the patient has *L. rhamnosus* GG and *B. lactis* Bb12. It was found that blood glucose and HbA1 levels improved than control group those depend on healthy diets without any probiotics (Luoto et al. 2010).

6.6.7 Prevention and Management of Cardiovascular Diseases

Heart diseases (cardiovascular disorders) have remained the leading cause of deaths at the global level for the last 20 years. However, rate of deaths is now escalating than ever before. Heart diseases death rate rose nearly over two million since 2000, to almost nine million in 2019. 16% of world deaths are linked with heart diseases (WHO 2020). Cardiovascular disorders may be preventable up to 90% through avoiding the recognized risk factors. Presently measured practices to avert heart disorders includes, decrease in the intake of saturate fats, stop smoking, keep up the healthy diet, moderate work out and reduce body fat contents if obese or over weight (Habib et al. 2019; Ahmad 2019; McNeal et al. 2010). Probiotics and fermented foods have been employed as a health promoting agents for many years (Ahmad et al. 2013a; Ahmad et al. 2013b). Probiotic bacteria produce acids that control the production of cholesterol due to absorption of the fiber from intestine. Propionic acid exhibits remarkable result by reducing the cholesterol production by liver. Liver bile acids are broken down by probiotics, bile acids help the body in the digestion of fats and these bile acids are produced by the liver. The recycling of bile acids is done by liver to make use again and again. Break down of bile acids by liver decreases the concentration of bile acids and to maintain the regular production of bile acids, more cholesterol is required. Consequently, cholesterol is utilized by the liver to prepare bile acids and eventually cholesterol concentration decreases in the body. It has also been reported that probiotics get nourishment through cholesterol metabolism. Thus, owing to various functions of probiotics, these could be the best food substitutes to control various diseases linked with cholesterol such as peripheral vascular disease, stroke and other coronary heart diseases. Also, it could be the better replacement of pharmaceutical products (Peirotén et al. 2020; Saini and Saini 2009).

Probiotics exhibits the potency to maintain the regulatory T cells in the immune system. Innate and adaptive immune actions exhibit crucial role in the progress of many cardiac disorders, and probiotics proved to possess potent immunomodulatory actions in various studies. Dendritic cell's key role is to process the antigen material along with transfer to the cell surface of T cells of the immune system. They are capable to distinguish diverse microbial strains by pattern-recognition receptors expression that distinguishes the pathogen-associated molecular patterns. Probiotics bacteria encourages the dendritic cell pattern of maturation by releasing of little quantity of IL-12 and TNF-α with elevated IL-10 levels and restrain pro-inflammatory cells generation. *Bifidobacteria* remain in the intestines and they play significant role for the health by decreasing CD80 and CD40 expression and induces an upregulation of IL-10 emission. Consequently, anti-inflammatory and immunomodulatory actions produced by increasing the IL10-production (Abdolalipour et al. 2020; Saini et al. 2010; Madsen 2006). Raised low-density lipoprotein cholesterol (LDL-C) is a key threat for coronary heart diseases (CHD), and to overcome it, the main target is lipid lowering therapy (Virani et al. 2021; DiRienzo 2014; Mourikis et al. 2020). It is the need of the hour to find the LDL-C reducing agents. Recently, several probiotic strains such as *E. faecium* and *L. reuteri* have been searched with capability to decrease the LDL-C, in addition to other CHD risk factors (DiRienzo 2014). Several animal studies have suggested that probiotic strain have beneficial habits as presented in Table 6.1.

Table 6.1 Animal studies of probiotic strains on obesity and associated disorders that leads to cardiovascular diseases

Type of probiotic	Duration	Results	References
Lactobacillus paracasei CNCM I-4270	12 week with high fat diets	↑Infiltration in adipose tissue ↓Weight gain ↑ Glucose insulin homeostasis ↓Liver steatosis	Wang et al. (2015)
Lactobacillus plantarum ky1032 and *Lactobacillus curvatus* HY7601	10 week with high fat diets	↓ Fat accumulation and body weight gain, ↓ Leptin, plasma insulin, and cholesterol ↓ IL6, IL1β and TNFα in adipose tissue ↓ Fatty acid oxidation genes in the liver	Park et al. (2013)
Bifidobacterium adolescentis	12 weeks parallel high fat diets	↑Insulin sensitivity ↓ Visceral fat accumulation and body weight gain	Chen et al. (2012)
Lactocbacillus rhamnosus GG	4 weeks	↑Insulin sensitivity ↑ Glucose tolerance ↑Insulin stimulated Akt phosphorylation ↓ Skeletal muscle endoplasmic reticulum stress	Park et al. (2015)
Bifidobacteria adolescentis	12 week with high fat diets	↓ Steatosis and liver inflammation ↓ Body weight gain ↓ Development of ROS	Reichold et al. (2014)

6.6.8 Detoxification of Cancer-Causing Carcinogens

Globally, cancer is considered as the second-leading cause of death, and despite of the several advancements in recent drug discovery, there is still lot of research needed to counter adverse effects of drugs with the help of naturally derived medicines. Cancer represents broad categories of malignancies showing the key characteristic of uncontrolled proliferation, aided by various functional and regulatory changes, which causes spread of tumor cell throughout the body (Elkhalifa et al. 2021; Ashraf et al. 2020b; Ahmad et al. 2021). Meanwhile, several studies have demonstrated that there is a direct link between incidence of cancers and dietary habits. Since, intake of processed food has exposed human being to various ranges of toxic chemicals such as polycyclic aromatic hydrocarbons, heavy metals, acrylamide, mycotoxins, cyanotoxins, nitrosamines, phthalic acid esters, heterocyclic aromatic amines and polycyclic aromatic hydrocarbons which has been well-documented for producing mutagenic as well as carcinogenic effects (Khorshidian et al. 2016; Shoukat 2020). In addition, various other risk factors which causes cancer includes genetic factors as well as immune system of the individual's body. Currently, several reports suggest that intestinal microbiome shows very significant role in sustaining homeostasis in human body. Goldin and Gorbach were the first who conducted research studies to see the association between food and colon cancer, thereby they found the food enriched with LAB was able to reduce the colon cancer by 40% compared to control 70%. Probiotics have been found to modulate cancer cell's proliferation and apoptosis in both *in vitro* and *in vivo* studies. Furthermore, probiotic has gained substantial medical significance because of the several health benefits (Śliżewska et al. 2021).

Probiotic bacteria is been responsible for detection and detoxification of potential carcinogens, which causes cell proliferation or cell death leads and known as signaling molecules in the immune system (Górska et al. 2019). Among probiotic strains LAB are the most popular with various application in food and pharmaceutical industries. Shoukat (2020) reported that various probiotic strains including *Bifidobacteria*, LABs help in prevention colon cancer by reducing or detoxifying carcinogenic compounds. Probiotics including *Bifidobacteria* and LABs have been found to detoxify most of the carcinogens and *Bifidobacteria* have shown a significant non-toxic and non-pathogenic, and *in vivo* functional properties (Khorshidian et al. 2016; Śliżewska et al. 2021; Górska et al. 2019). Several studies suggest that *L. rhamnosus* GG, *L. pentosus*, *L. fermentum*, *L. acidophilus*, *L. helveticus*, *L. casei*, *L. lactis*; *Bifidobacterium*: lactis, adolescentis *Pediococcus pentosaceus*, *Bacillus subtilis* strains have a significant anti-proliferative effect on various human colon cancer cell lines (HGC-27, SW480, Caco-2, DLD-1, SW1116, HT-29 and HCT116), in addition it was also found to reduce the level of level of IL–8 (Altonsy et al. 2010; Borowicki et al. 2011; Orlando et al. 2012; Russo et al. 2007; Sadeghi-Aliabadi et al. 2014; Lopez et al. 2008). In addition, *L. casei* LBC80R, *L. acidophilus* CL1285, *Bifidobacterium longum* HY8001, *L. acidophilus* SNUL and *L. casei* YIT9029 has been reported to causes apoptosis or suppressed proliferation of human colorectal cells (LS513 & SNUC2A) as well as gastric carcinoma cells (SNU1) (Baldwin et al. 2010; Lee et al. 2004). Drug used for cancer treatment such as 5–fluorouracil causes diarrhea in cancer patient as one its side effect. *Bacillus polyfermenticus,* a probiotic strain has been found to lower the cell colony formation in human colonic epithelial cells (NMC460) (Śliżewska et al. 2021). Therefore based upon the potential application of probiotic, a novel probiotic based therapy could become an alternative approach to more invasive as well as costly treatment such as chemotherapy.

6.7 Regulation, Safety and Efficacy

Recently, probiotic market has grown throughout the world, both for probiotic food or probiotic as therapeutically supplementation is been in used to enhance health benefits. Regulations for the use of probiotic around the world vary, in other words probiotic is not much regulated until unless it has not make any specific claim related to the health benefits. Of note, probiotics are regulated mainly based upon the characteristics of food supplements and regulations are monitored on the legality of any claims, rather than its efficacy, safety and quality. Additionally, probiotic properties are usually strain-specific and in general safety and efficacy are majorly related to specific formulations, and should not be generalized to specific probiotic products (de Simone 2019). LAB is considered as one of the very well-known strains used for probiotic preparations and it has safe use for human food consumption since long time back. However, ingestion of probiotic for human consumption can't be guaranteed of zero risk factor. LAB safety in fermentation application is quite clear, but several other probiotic strains used in various food materials fermentation impact on final products such as its safety, health benefits and its sensory attribute (Mortazavian 2012; Gawai and Prajapati 2017).

Recently, various strains of probiotics such as *Lactobacilli* and *Bifidobacterium* currently used by severally internationally renowned food manufacturers and starter culture suppliers for productions of safe probiotics and its related food products (Tamime et al. 2007; Sanders 2003). According to previous studies, it is suggested that *Lactobacilli* and *Bifidobacterium* does not possess any risk factors with its usage as oral consumption by healthy individuals. The Joint FAO/WHO committee proposed a framework containing information regarding strain identification and functional characterization, followed by safety assessment. According to Joint FAO/WHO guideline, the minimum tests required to characterize safety are parameters for probiotic strains are as followed (Ray and Joshi 2014) To check the antibiotic resistance patterns, (Di Cagno et al. 2013) Identify the metabolic activities of strains, (Terefe 2016) Identify the toxin produced from fermentation or during the fermentation, (Bell et al. 2017) Does the strains has the hemolytic capability? (Kechagia et al. 2013) To check whether the probiotic strains have any infectivity in immunocompromised animals, (Guarner et al. 2012) Identify the side effects of probiotic strain in human model and (Nagpal et al. 2012) To perform the epidemiological surveillance of adverse incidents among the consumers (Gaggia et al. 2011; Mohamadshahi et al. 2014; Mishra et al. 2018).

Furthermore, several efficacy studies for probiotics have been performed to establish the product in recent times. A meta-analysis study of 11 probiotic species against the eight major GI diseases and revealed that probiotic species was highly effective in the treatment of antibiotic-associated diarrhea, infectious diarrhea, *Helicobacter pylori* eradication, *C. difficile* infection and pouchitis. At the same time these 11 probiotic strains showed poor efficacy against the traveler's diarrhea and necrotizing enterocolitis (Khalighi et al. 2016). Therefore, several observations made regarding the probiotic products and it clearly suggests that it help consumers with immunocompromised system or vulnerable people, such as the elderly, children and people with immune deficiencies (Peivasteh Roudsari et al. 2019). Few examples such as usage of probiotic product for children in day care unit under the randomized trial shows reduction in the respiratory infections as well as reduces the severity of illness (Hatakka et al. 2001). Therefore, the success of probiotic has fascinated genetic engineers to improve and produce genetically modified strains of probiotics for further applications. Currently, many probiotic products is been on the market since long time with no major safety issues and it can act differently in two consumers, hence the safety questions of probiotic product or active ingredient are very specific to the individual (Mishra et al. 2018). Meanwhile, usage of the probiotic strains should be completely non-pathogenic and should not cause any harm to the host (Peivasteh Roudsari et al. 2019).

6.8 Future Perspectives and Global Demands

The global market for probiotic supplements are continually expanding day by day. Rising awareness among the consumers regarding the prevention and management of several chronic diseases has led to an increase in demand of natural and safe health benefiting product such as probiotic. Various commercial products of probiotics are available around the world such as Aciforce (Biohorma® Natherland), Actimel (Danone® France), Activia (Danone®), Hellus (Tallinna Piimatoostuse AS® Estonian), Yakult (Yakult® Japan), which is predicted to upsurge the market share (Mishra et al. 2018). Currently, one area is being targeted for investigation of probiotic behavior via whole genome sequencing technology. This, amongst other features, will boost the functional aspects of probiotic LAB, and data will provide a good base for further LAB genetic manipulation (Zommiti et al. 2020). In addition to strains from the genera *Lactobacillus* and *Bifidobacterium*, strains from other genera, such as *Propionibacterium* and *Lactococcus*, commonly found in fermented foods, are likely to receive more attention. Strains from "new" probiotic genera are also likely to emerge, such as butyrate-producing *Roseburia* and *Clostridium*, or strains from the anti-inflammatory species *Faecalibacterium prausnitzii*. Furthermore, genetically modified probiotics should be anticipated and they may even target diseases for which there is currently no cure. Similarly, one could anticipate that more complex mixtures might be more efficacious, as they could provide a multitude of functions to microbiota in disarray. Furthermore, published report indicated that, the global probiotics market size was valued at USD 48.88 billion in 2019 and is projected to reach USD 94.48 billion by 2027, exhibiting a CAGR of 7.9 during the forecast period (https://www.fortunebusinessinsights.com/industry-reports/probiotics-market-100083). Furthermore in Canada, foods and beverages fortified with probiotics are expected to grow at a CAGR of 6.6% by 2022. Moreover, Europe is the second largest food and beverage probiotic market. Brazil leads the probiotic market with an estimated share of 52% in 2016 and a forecast CAGR of about 11% between 2017 and 2022. In Asia, China leads the probiotic market with an estimated 35.4% market share (https://bc30probiotic.com/wp-content/uploads/2019/11/GanedenBC30-Global-Probiotic-And-Digestive-Markets-Infographic.pdf).

6.9 Conclusion

Despite the public perception of benefits provided by probiotics, the evidence to conclusively link probiotic strains to improved characteristics of health or disease is lacking. This is due to the lack of large-scale research trials and insufficient understanding regarding probiotic interactions within the human system. This has driven scientific researches with the aspirations to uncover probiotic strains that provide conclusive evidence of improvements in health and disease outcomes. More in-depth research into individual probiotic strains, combined with the application of multiple advanced measurement techniques will provide a future direction for probiotic research and in turn, aims to provide useful data to translate into routine healthcare practice. Currently, probiotics has been classified for human health application and WHO has approved probiotics usage in human beings and these are generally recognized as safe. Therefore based upon our review, we can conclude that, probiotic can be considered for various health benefits, however its clinical safety in human beings are not very clearly studied. Further clinical studies are needed to see the effect on host and food and its adverse effects in high-risk consumers.

References

Abdolalipour E, Mahooti M, Salehzadeh A, Torabi A, Mohebbi SR, Gorji A, Ghaemi A (2020) Evaluation of the antitumor immune responses of probiotic Bifidobacterium bifidum in human papillomavirus-induced tumor model. Microb Pathog 145:104207

Adnan ML, Pramaningtyas MD (2020) Probiotics as promising immunomodulatory agents to prevent COVID-19 infection: a narrative review. Int J Med Stud 8(2):121–125

Adnan M, Patel M, Hadi S (2017) Functional and health promoting inherent attributes of Enterococcus hirae F2 as a novel probiotic isolated from the digestive tract of the freshwater fish Catla catla. PeerJ 5:e3085

Agerholm-Larsen L, Raben A, Haulrik N, Hansen AS, Manders M, Astrup A (2000) Effect of 8 week intake of probiotic milk products on risk factors for cardiovascular diseases. Eur J Clin Nutr 54(4):288–297

Ahmad F (2019) Ganoderma lucidum: a macro fungus with phytochemicals and their pharmacological properties. In: Plant and human health, volume 2 : phytochemistry and molecular aspects. Springer International Publishing, Cham, pp 491–515

Ahmad F, Panda B, Azad ZRAA (2013a) Simultaneous bioprospecting of Ganoderma lucidum OE 52 with Ganoderic acid B and C2 by submerged fermentation process. Adv Sci Focus 1:258–261

Ahmad F, Ahmad F, Azad ZRAA, Alam M, Ansari J, Panda B (2013b) Edible mushrooms as health promoting agent. Adv Sci Focus 1:189–196

Ahmad MF, Ahmad FA, Ashraf SA, Saad HH, Wahab S, Khan MI, Ali M, Mohan S, Hakeem KR, Athar MT (2021) An updated knowledge of black seed (Nigella sativa Linn.): review of phytochemical constituents and pharmacological properties. J Herbal Med 25:100404

Akbar A, Ali I, Anal A (2016) Industrial perspectives of lactic acid bacteria for biopreservation and food safety. J Anim Plant Sci 26:938–948

Al-Muzafar HM, Amin KA (2017) Probiotic mixture improves fatty liver disease by virtue of its action on lipid profiles, leptin, and inflammatory biomarkers. BMC Complement Altern Med 17(1):43

Alshammari E, Patel M, Sachidanandan M, Kumar P, Adnan M (2019) Potential evaluation and health fostering intrinsic traits of novel probiotic strain enterococcus durans F3 isolated from the gut of fresh water fish Catla catla. Food Sci Anim Resour 39(5):844–861

Altonsy MO, Andrews SC, Tuohy KM (2010) Differential induction of apoptosis in human colonic carcinoma cells (Caco-2) by Atopobium, and commensal, probiotic and enteropathogenic bacteria: mediation by the mitochondrial pathway. Int J Food Microbiol 137(2–3):190–203

Andrade-Velásquez A, Domínguez-Cañedo L, Melgar-Lalanne G (2020) Growth kinetic model, antioxidant and hypoglycemic effects at different temperatures of potential probiotic Lactobacillus spp. Revista Mexicana de Ingeniería Química 20:37–49

Ashraf SA, Elkhalifa AEO, Siddiqui AJ, Patel M, Awadelkareem AM, Snoussi M, Ashraf MS, Adnan M, Hadi S (2020a) Cordycepin for health and wellbeing: a potent bioactive metabolite of an entomopathogenic cordyceps medicinal fungus and its nutraceutical and therapeutic potential. Molecules (Basel, Switzerland) 25(12):2735

Ashraf SA, Adnan M, Patel M, Siddiqui AJ, Sachidanandan M, Snoussi M, Hadi S (2020b) Fish-based bioactives as potent nutraceuticals: exploring the therapeutic perspective of sustainable food from the Sea. Mar Drugs 18(5):265

Ashraf SA, Siddiqui AJ, Elkhalifa AEO, Khan MI, Patel M, Alreshidi M, Moin A, Singh R, Snoussi M, Adnan M (2021) Innovations in nanoscience for the sustainable development of food and agriculture with implications on health and environment. Sci Total Environ 768:144990

Bäckhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, Semenkovich CF, Gordon JI (2004) The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci U S A 101(44):15718–15723

Baldwin C, Millette M, Oth D, Ruiz MT, Luquet FM, Lacroix M (2010) Probiotic Lactobacillus acidophilus and L. casei mix sensitize colorectal tumoral cells to 5-fluorouracil-induced apoptosis. Nutr Cancer 62(3):371–378

Barr W, Smith A (2014) Acute diarrhea. Am Fam Physician 89(3):180–189

Barrett E, Ross RP, O'Toole PW, Fitzgerald GF, Stanton C (2012) γ-Aminobutyric acid production byculturable bacteria from the human intestine. Journal of applied microbiology, 113(2):411–417. https://doi.org/10.1111/j.1365-2672.2012.05344.x

Barrett HL, Dekker Nitert M, Conwell LS, Callaway LK (2014) Probiotics for preventing gestational diabetes. Cochrane Database Syst Rev 2014(2):Cd009951

Bell V, Ferrão J, Fernandes T (2017) Nutritional guidelines and fermented food frameworks. Foods (Basel, Switzerland) 6(8):65

Bergillos-Meca T, Navarro-Alarcón M, Cabrera-Vique C, Artacho R, Olalla M, Giménez R, Moreno-Montoro M, Ruiz-Bravo A, Lasserrot A, Ruiz-López MD (2013) The probiotic bacterial strain Lactobacillus fermentum D3 increases in vitro the bioavailability of Ca, P, and Zn in fermented goat milk. Biol Trace Elem Res 151(2):307–314

Bermudez-Brito M, Plaza-Díaz J, Muñoz-Quezada S, Gómez-Llorente C, Gil A (2012) Probiotic mechanisms of action. Ann Nutr Metab 61(2):160–174

Billoo AG, Memon MA, Khaskheli SA, Murtaza G, Iqbal K, Saeed Shekhani M, Siddiqi AQ (2006) Role of a probiotic (Saccharomyces boulardii) in management and prevention of diarrhoea. World J Gastroenterol 12(28):4557–4560

Blandino G, Inturri R, Lazzara F, Di Rosa M, Malaguarnera L (2016) Impact of gut microbiota on diabetes mellitus. Diabetes Metab 42(5):303–315

Borowicki A, Michelmann A, Stein K, Scharlau D, Scheu K, Obst U, Glei M (2011) Fermented wheat aleurone enriched with probiotic strains LGG and Bb12 modulates markers of tumor progression in human colon cells. Nutr Cancer 63(1):151–160

Cani PD, Delzenne NM (2009) The role of the gut microbiota in energy metabolism and metabolic disease. Curr Pharm Des 15(13):1546–1558

Cencic A, Chingwaru W (2010) The role of functional foods, nutraceuticals, and food supplements in intestinal health. Nutrients 2(6):611–625

Cesaro C, Tiso A, Del Prete A, Cariello R, Tuccillo C, Cotticelli G, Del Vecchio Blanco C, Loguercio C (2011) Gut microbiota and probiotics in chronic liver diseases. Dig Liver Dis 43(6):431–438

Chavez-Tapia NC, Mendiola-Pastrana I, Ornelas-Arroyo VJ, Noreña-Herrera C, Vidaña-Perez D, Delgado-Sanchez G, Uribe M, Barrientos-Gutierrez T (2015) Granulocyte-colony stimulating factor for acute-on-chronic liver failure: systematic review and meta-analysis. Ann Hepatol 14(5):631–641

Chen C, Li L, Wu Z, Chen H, Fu S (2007) Effects of lactitol on intestinal microflora and plasma endotoxin in patients with chronic viral hepatitis. J Infect 54(1):98–102

Chen J, Wang R, Li XF, Wang RL (2012) Bifidobacterium adolescentis supplementation ameliorates visceral fat accumulation and insulin sensitivity in an experimental model of the metabolic syndrome. Br J Nutr 107(10):1429–1434

Chu SY, Callaghan WM, Kim SY, Schmid CH, Lau J, England LJ, Dietz PM (2007) Maternal obesity and risk of gestational diabetes mellitus. Diabetes Care 30(8):2070–2076

de Simone C (2019) The unregulated probiotic market. Clin Gastroenterol Hepatol 17(5):809–817

Dash D, Dash M, Mohanty MD, Acharya N (2017) Efficacy of probiotic Saccharomyces boulardii as an adjuvant therapy in acute childhood Diarrhoea. J Nepal Pediatr Soc 36:250

De Melo Pereira GV, Neto DPDC, Junqueira ACDO, Karp SG, Letti LAJ, Júnior AIM, Soccol CR (2020) A review of selection criteria for starter culture development in the food fermentation industry. Food Rev Intl 36(2):135–167

Di Cagno R, Coda R, De Angelis M, Gobbetti M (2013) Exploitation of vegetables and fruits through lactic acid fermentation. Food Microbiol 33(1):1–10

Dinleyici EC, Eren M, Dogan N, Reyhanioglu S, Yargic ZA, Vandenplas Y (2011) Clinical efficacy of Saccharomyces boulardii or metronidazole in symptomatic children with Blastocystis hominis infection. Parasitol Res 108(3):541–545

DiRienzo DB (2014) Effect of probiotics on biomarkers of cardiovascular disease: implications for heart-healthy diets. Nutr Rev 72(1):18–29

Druart C, Alligier M, Salazar N, Neyrinck AM, Delzenne NM (2014) Modulation of the gut microbiota by nutrients with prebiotic and probiotic properties. Adv Nutr (Bethesda, Md) 5(5):624s–633s

Elkhalifa AEO, Alshammari E, Adnan M, Alcantara JC, Awadelkareem AM, Eltoum NE, Mehmood K, Panda BP, Ashraf SA (2021) Okra (Abelmoschus Esculentus) as a potential dietary medicine with nutraceutical importance for sustainable health applications. Molecules (Basel, Switzerland) 26(3):696

Eslamparast T, Eghtesad S, Hekmatdoost A, Poustchi H (2013) Probiotics and nonalcoholic fatty liver disease. Middle East J Dig Dis 5:129–136
Frazier TH, DiBaise JK, McClain CJ (2011) Gut microbiota, intestinal permeability, obesity-induced inflammation, and liver injury. JPEN J Parenter Enteral Nutr 35(5 Suppl):14s–20s
Fung TC, Olson CA, Hsiao EY (2017) Interactions between the microbiota, immune and nervous systems in health and disease. Nat Neurosci 20(2):145–155
FAO/WHO (2002) Working Group Report on Drafting Guidelines for the Evaluation of Probiotics in FoodLondon, Ontario, Canada, April 30 and May 1, 2002
Gaggia F, Di Gioia D, Baffoni L, Biavati B (2011) The role of protective and probiotic cultures in food and feed and their impact in food safety. Trends Food Sci Technol 22:S58–S66
Galdeano CM, Perdigón G (2004) Role of viability of probiotic strains in their persistence in the gut and in mucosal immune stimulation. J Appl Microbiol 97(4):673–681
Gawai K, Prajapati J (2017) Safety aspects of fermented and probiotic foods. Int J Fermented Foods 6(1):45–55
Gill HS, Guarner F (2004) Probiotics and human health: a clinical perspective. Postgrad Med J 80(947):516–526
Giovannini M, Agostoni C, Riva E, Salvini F, Ruscitto A, Zuccotti GV, Radaelli G (2007) A randomized prospective double blind controlled trial on effects of long-term consumption of fermented milk containing Lactobacillus casei in pre-school children with allergic asthma and/or rhinitis. Pediatr Res 62(2):215–220
Goldenberg JZ, Yap C, Lytvyn L, Lo CK, Beardsley J, Mertz D, Johnston BC (2017) Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. Cochrane Database Syst Rev 12(12):Cd006095
Górska A, Przystupski D, Niemczura MJ, Kulbacka J (2019) Probiotic Bacteria: a promising tool in Cancer prevention and therapy. Curr Microbiol 76(8):939–949
Guarner F, Khan AG, Garisch J, Eliakim R, Gangl A, Thomson A, Krabshuis J, Lemair T, Kaufmann P, de Paula JA, Fedorak R, Shanahan F, Sanders ME, Szajewska H, Ramakrishna BS, Karakan T, Kim N (2012) World gastroenterology organisation global guidelines: probiotics and prebiotics October 2011. J Clin Gastroenterol 46(6):468–481
Guha M, Mackman N (2001) LPS induction of gene expression in human monocytes. Cell Signal 13(2):85–94
Habib MAAM, Al MA, Kabir MR, Chowdhury MH, Tumpa FA, Nayeem J (2019) Probiotics for cardiovascular diseases, hypertension, hypercholesterolemia, and cancer condition: a summary of the evidence. Edu Q Rev 2(2). https://ssrn.com/abstract=3415273
Hatakka K, Savilahti E, Pönkä A, Meurman JH, Poussa T, Näse L, Saxelin M, Korpela R (2001) Effect of long term consumption of probiotic milk on infections in children attending day care centres: double blind, randomised trial. BMJ (Clin Res Ed) 322(7298):1327
Hayakawa K, Kimura M, Kasaha K, Matsumoto K, Sansawa H, Yamori Y (2004) Effect of a gamma-aminobutyric acid-enriched dairy product on the blood pressure of spontaneously hypertensive and normotensive Wistar-Kyoto rats. Br J Nutr 92(3):411–417
Hempel S, Newberry SJ, Maher AR, Wang Z, Miles JN, Shanman R, Johnsen B, Shekelle PG (2012) Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. JAMA 307(18):1959–1969
Hernández-Ledesma B, Amigo L, Ramos M, Recio I (2004) Angiotensin converting enzyme inhibitory activity in commercial fermented products. Formation of peptides under simulated gastrointestinal digestion. J Agric Food Chem 52(6):1504–1510
Hol J, van Leer EH, Elink Schuurman BE, de Ruiter LF, Samsom JN, Hop W, Neijens HJ, de Jongste JC, Nieuwenhuis EE (2008) The acquisition of tolerance toward cow's milk through probiotic supplementation: a randomized, controlled trial. J Allergy Clin Immunol 121(6):1448–1454
Hong M, Kim S, Han S, Kim DJ, Suk KT, Kim Y, Kim M, Kim M, Baik S, Ham Y (2015) Probiotics (Lactobacillus rhamnosus R0011 and acidophilus R0052) reduce the expression of toll-like receptor 4 in mice with alcoholic liver disease. PLoS One 10:e0117451

Hosseinifard ES, Morshedi M, Bavafa-Valenlia K, Saghafi-Asl M (2019) The novel insight into anti-inflammatory and anxiolytic effects of psychobiotics in diabetic rats: possible link between gut microbiota and brain regions. Eur J Nutr 58(8):3361–3375

Ibrahim SIO, Awadelkareem AM, Ashraf SA, Sabahelkhier MK (2018) Comparative studies on the physicochemical and microbiological characteristics of different animal Milk collected from the farms of Khartoum state, Sudan. Biosci Biotechnol Res Commun 11(3):387–392

Imani Fooladi AA, Mahmoodzadeh Hosseini H, Nourani MR, Khani S, Alavian SM (2013) Probiotic as a novel treatment strategy against liver disease. Hepat Mon 13(2):e7521

Isolauri E, Kirjavainen PV, Salminen S (2002) Probiotics: a role in the treatment of intestinal infection and inflammation? Gut 50(Suppl 3):Iii54-9

Kamarudheen N, George C, Priya C, Rao B (2014) Biopreservation of meat by probiotic bacteria isolated from dairy products. Pharm Lett 6:266–271

Karbach SH, Schönfelder T, Brandão I, Wilms E, Hörmann N, Jäckel S, Schüler R, Finger S, Knorr M, Lagrange J, Brandt M, Waisman A, Kossmann S, Schäfer K, Münzel T, Reinhardt C, Wenzel P (2016) Gut microbiota promote angiotensin II-induced arterial hypertension and vascular dysfunction. J Am Heart Assoc 5(9):e003698

Kechagia M, Basoulis D, Konstantopoulou S, Dimitriadi D, Gyftopoulou K, Skarmoutsou N, Fakiri EM (2013) Health benefits of probiotics: a review. ISRN Nutr 2013:481651

Khalesi S, Sun J, Buys N, Jayasinghe R (2014) Effect of probiotics on blood pressure: a systematic review and meta-analysis of randomized, controlled trials. Hypertension (Dallas, Tex: 1979) 64(4):897–903

Khalighi A, Behdani R, Kouhestani S (2016) Probiotics: a comprehensive review of their classification, mode of action and role in human nutrition. IntechOpen

Khorshidian N, Yousefi M, Hosseini H, Shadnoush M, Mortazavian A (2016) Potential Anticarcinogenic effects of lactic acid Bacteria and probiotics in detoxification of process-induced food toxicants. Iranian J Cancer Prev 9. https://doi.org/10.17795/ijcp-7920

Kim SW, Park KY, Kim B, Kim E, Hyun CK (2013) Lactobacillus rhamnosus GG improves insulin sensitivity and reduces adiposity in high-fat diet-fed mice through enhancement of adiponectin production. Biochem Biophys Res Commun 431(2):258–263

Kim SH, Huh CS, Choi ID, Jeong JW, Ku HK, Ra JH, Kim TY, Kim GB, Sim JH, Ahn YT (2014) The anti-diabetic activity of Bifidobacterium lactis HY8101 in vitro and in vivo. J Appl Microbiol 117(3):834–845

Kirpich IA, McClain CJ (2012) Probiotics in the treatment of the liver diseases. J Am Coll Nutr 31(1):14–23

Kirpich IA, Solovieva NV, Leikhter SN, Shidakova NA, Lebedeva OV, Sidorov PI, Bazhukova TA, Soloviev AG, Barve SS, McClain CJ, Cave M (2008) Probiotics restore bowel flora and improve liver enzymes in human alcohol-induced liver injury: a pilot study. Alcohol 42(8):675–682

Kwon HK, Kim GC, Kim Y, Hwang W, Jash A, Sahoo A, Kim JE, Nam JH, Im SH (2013) Amelioration of experimental autoimmune encephalomyelitis by probiotic mixture is mediated by a shift in T helper cell immune response. Clin Immunol (Orlando, Fla) 146(3):217–227

Lallès J-P (2016) Microbiota-host interplay at the gut epithelial level, health and nutrition. J Anim Sci Biotechnol 7(1):66

Laranjo M, Potes ME, Elias M (2019) Role of starter cultures on the safety of fermented meat products. Front Microbiol 10:853

Lavasani S, Dzhambazov B, Nouri M, Fåk F, Buske S, Molin G, Thorlacius H, Alenfall J, Jeppsson B, Weström B (2010) A novel probiotic mixture exerts a therapeutic effect on experimental autoimmune encephalomyelitis mediated by IL-10 producing regulatory T cells. PLoS One 5(2):e9009

Lee JW, Shin JG, Kim EH, Kang HE, Yim IB, Kim JY, Joo HG, Woo HJ (2004) Immunomodulatory and antitumor effects in vivo by the cytoplasmic fraction of Lactobacillus casei and Bifidobacterium longum. J Vet Sci 5(1):41–48

Lescheid D (2014) Probiotics as regulators of inflammation: a review. Func Foods Health Dis 4:299–311

Llewellyn A, Foey A (2017) Probiotic modulation of innate cell pathogen sensing and signaling events. Nutrients 9(10):1156

Loguercio C, De Simone T, Federico A, Terracciano F, Tuccillo C, Di Chicco M, Cartenì M (2002) Gut-liver axis: a new point of attack to treat chronic liver damage? Am J Gastroenterol 97(8):2144–2146

Loi F, Córdova LA, Pajarinen J, Lin TH, Yao Z, Goodman SB (2016) Inflammation, fracture and bone repair. Bone 86:119–130

Lopez M, Li N, Kataria J, Russell M, Neu J (2008) Live and ultraviolet-inactivated Lactobacillus rhamnosus GG decrease flagellin-induced interleukin-8 production in Caco-2 cells. J Nutr 138(11):2264–2268

Luoto R, Laitinen K, Nermes M, Isolauri E (2010) Impact of maternal probiotic-supplemented dietary counselling on pregnancy outcome and prenatal and postnatal growth: a double-blind, placebo-controlled study. Br J Nutr 103(12):1792–1799

Madsen K (2006) Probiotics and the immune response. J Clin Gastroenterol 40(3):232–234

Maldonado Galdeano C, Novotny Núñez I, de Moreno de LeBlanc A, Carmuega E, Weill R, Perdigón G (2011) Impact of a probiotic fermented milk in the gut ecosystem and in the systemic immunity using a non-severe protein-energy-malnutrition model in mice. BMC Gastroenterol 11:64

Marchesi JR, Adams DH, Fava F, Hermes GD, Hirschfield GM, Hold G, Quraishi MN, Kinross J, Smidt H, Tuohy KM, Thomas LV, Zoetendal EG, Hart A (2016) The gut microbiota and host health: a new clinical frontier. Gut 65(2):330–339

Mathur H, Beresford TP, Cotter PD (2020) Health benefits of lactic acid Bacteria (LAB) Fermentates. Nutrients 12(6):1679

McNeal CJ, Dajani T, Wilson D, Cassidy-Bushrow AE, Dickerson JB, Ory M (2010) Hypercholesterolemia in youth: opportunities and obstacles to prevent premature atherosclerotic cardiovascular disease. Curr Atheroscler Rep 12(1):20–28

Michail S (2009) The role of probiotics in allergic diseases, allergy, asthma, and clinical immunology: official journal of the Canadian Society of Allergy and. Clin Immunol 5(1):5

Miguel M, Recio I, Ramos M, Delgado MA, Aleixandre MA (2006) Antihypertensive effect of peptides obtained from Enterococcus faecalis-fermented milk in rats. J Dairy Sci 89(9):3352–3359

Mishra S, Behera P, Kar B, Ray R (2018) Advances in probiotics, prebiotics and nutraceuticals. In: Innovations in technologies for fermented food and beverage industries. Springer International Publishing, Cham, pp 121–141

Mohamadshahi M, Veissi M, Haidari F, Shahbazian H, Kaydani GA, Mohammadi F (2014) Effects of probiotic yogurt consumption on inflammatory biomarkers in patients with type 2 diabetes. Bioimpacts 4(2):83–88

Morshedi M, Hashemi R, Moazzen S, Sahebkar A, Hosseinifard E-S (2019) Immunomodulatory and anti-inflammatory effects of probiotics in multiple sclerosis: a systematic review. J Neuroinflammation 16(1):231

Mortazavian A (2012) The starter culture characteristics of probiotic microorganisms in fermented milks. Eng Life Sci 12:399–409

Mourikis P, Zako S, Dannenberg L, Nia AM, Heinen Y, Busch L, Richter H, Hohlfeld T, Zeus T, Kelm M, Polzin A (2020) Lipid lowering therapy in cardiovascular disease: from myth to molecular reality. Pharmacol Ther 213:107592

Nagpal R, Kumar A, Kumar M, Behare PV, Jain S, Yadav H (2012) Probiotics, their health benefits and applications for developing healthier foods: a review. FEMS Microbiol Lett 334(1):1–15

Nath S, Chowdhury S, Sarkar S (2014) Role of biopreservation in improving food safety and storage. Int. Journal of Engineering Research and Applications; 4(1) version 3, 26–32

Nijs H, Benhalima K (2020) Gestational diabetes mellitus and the long-term risk for glucose intolerance and overweight in the offspring: a narrative review. J Clin Med 9(2):599

Núñez IN, Galdeano CM, Carmuega E, Weill R, de Moreno de LeBlanc A, Perdigón G (2013) Effect of a probiotic fermented milk on the thymus in Balb/c mice under non-severe protein-energy malnutrition. Br J Nutr 110(3):500–508

Oluk CA, Karaca OB (2018) Chapter 18: The current approaches and challenges of biopreservation. In: Grumezescu AM, Holban AM (eds) Food safety and preservation. Academic, pp 565–597

Orlando A, Refolo MG, Messa C, Amati L, Lavermicocca P, Guerra V, Russo F (2012) Antiproliferative and proapoptotic effects of viable or heat-killed Lactobacillus paracasei IMPC2.1 and Lactobacillus rhamnosus GG in HGC-27 gastric and DLD-1 colon cell lines. Nutr Cancer 64(7):1103–1111

Pajarinen J, Lin T, Gibon E, Kohno Y, Maruyama M, Nathan K, Lu L, Yao Z, Goodman SB (2019) Mesenchymal stem cell-macrophage crosstalk and bone healing. Biomaterials 196:80–89

Park DY, Ahn YT, Park SH, Huh CS, Yoo SR, Yu R, Sung MK, McGregor RA, Choi MS (2013) Supplementation of Lactobacillus curvatus HY7601 and Lactobacillus plantarum KY1032 in diet-induced obese mice is associated with gut microbial changes and reduction in obesity. PLoS One 8(3):e59470

Park KY, Kim B, Hyun CK (2015) Lactobacillus rhamnosus GG improves glucose tolerance through alleviating ER stress and suppressing macrophage activation in db/db mice. J Clin Biochem Nutr 56(3):240–246

Parle M, Malik J (2014) Curd: a sedative with a bonus bowl of useful side effects. Int Res J Pharm 5:131–135

Peirotén Á, Gaya P, Álvarez I, Landete JM (2020) Production of O-desmethylangolensin, tetrahydrodaidzein, 6′-hydroxy-O-desmethylangolensin and 2-(4-hydroxyphenyl)-propionic acid in fermented soy beverage by lactic acid bacteria and Bifidobacterium strains. Food Chem 318:126521

Peivasteh Roudsari L, Karami H, Tajdar-Oranj B, Molaee-aghaee E, Sadighara P (2019) Probiotics and food safety: an evidence-based review. J Food Saf Hyg 5:50

Petry CJ (2020) Nutrition for gestational diabetes—Progress and potential. Nutrients 12(9):2685

Plaza-Díaz J, Ruiz-Ojeda FJ, Gil-Campos M, Gil A (2018) Immune-mediated mechanisms of action of probiotics and Synbiotics in treating pediatric intestinal diseases. Nutrients 10(1):42

Plaza-Diaz J, Ruiz-Ojeda FJ, Gil-Campos M, Gil A (2019) Mechanisms of action of probiotics. Adv Nutr (Bethesda, Md.) 10(suppl_1):S49–S66

Pluznick JL, Protzko RJ, Gevorgyan H, Peterlin Z, Sipos A, Han J, Brunet I, Wan LX, Rey F, Wang T, Firestein SJ, Yanagisawa M, Gordon JI, Eichmann A, Peti-Peterdi J, Caplan MJ (2013) Olfactory receptor responding to gut microbiota-derived signals plays a role in renin secretion and blood pressure regulation. Proc Natl Acad Sci U S A 110(11):4410–4415

Prakash S, Tomaro-Duchesneau C, Saha S, Rodes L, Kahouli I, Malhotra M (2014) Probiotics for the prevention and treatment of allergies, with an emphasis on mode of delivery and mechanism of action. Curr Pharm Des 20(6):1025–1037

Qi D, Nie XL, Zhang JJ (2020) The effect of probiotics supplementation on blood pressure: a systemic review and meta-analysis. Lipids Health Dis 19(1):79

Rad AH, Abbasalizadeh S, Vazifekhah S, Abbasalizadeh F, Hassanalilou T, Bastani P, Ejtahed HS, Soroush AR, Javadi M, Mortazavian AM, Khalili L (2017) The future of diabetes management by healthy probiotic microorganisms. Curr Diabetes Rev 13(6):582–589

Rakhmanova A, Khan ZA, Shah K (2018) A mini review fermentation and preservation: role of lactic acid bacteria. MOJ Food Process Technol 6(5):414–417

Ranadheera S, Evans C, Adams M, Baines S (2014) Effect of dairy probiotic combinations on in vitro gastrointestinal tolerance, intestinal epithelial cell adhesion and cytokine secretion. J Funct Foods 8:18–25

Ray R, Joshi V (2014) Fermented foods: past, present and future. In: Microorganisms and fermentation of traditional foods. CRC Press

Reichold A, Brenner SA, Spruss A, Förster-Fromme K, Bergheim I, Bischoff SC (2014) Bifidobacterium adolescentis protects from the development of nonalcoholic steatohepatitis in a mouse model. J Nutr Biochem 25(2):118–125

Rhee SJ, Lee JE, Lee CH (2011) Importance of lactic acid bacteria in Asian fermented foods. Microb Cell Factories 10(Suppl 1):S5

Ri W, Chao M, Xiaodan L, Huikun D, Yanli J, Yu W, Pingzhe J, Haisong W, Peipei T, Miao L, Ganggang N, Baicheng M, Minggang L (2015) Construction of yeast strains expressing long-acting glucagon-like peptide-1 (GLP-1) and their therapeutic effects on type 2 diabetes mellitus mouse model. Yi chuan = Hereditas 37(2):183–191

Robles-Vera I, Toral M, Romero M, Jiménez R, Sánchez M, Pérez-Vizcaíno F, Duarte J (2017) Antihypertensive effects of probiotics. Curr Hypertens Rep 19(4):26

Rolfe RD (2000) The role of probiotic cultures in the control of gastrointestinal health. J Nutr 130(2S Suppl):396s–402s

Russo F, Orlando A, Linsalata M, Cavallini A, Messa C (2007) Effects of Lactobacillus rhamnosus GG on the cell growth and polyamine metabolism in HGC-27 human gastric cancer cells. Nutr Cancer 59(1):106–114

Saad N, Delattre C, Urdaci M, Schmitter JM, Bressollier P (2013) An overview of the last advances in probiotic and prebiotic field. LWT Food Sci Technol 50(1):1–16

Sadeghi-Aliabadi H, Mohammadi F, Fazeli H, Mirlohi M (2014) Effects of Lactobacillus plantarum A7 with probiotic potential on colon cancer and normal cells proliferation in comparison with a commercial strain. Iran J Basic Med Sci 17(10):815–819

Saini R, Saini S (2009) Sugandha, probiotics: the health boosters. J Cutan Aesthet Surg 2(2):112

Saini R, Saini S, Sharma S (2010) Potential of probiotics in controlling cardiovascular diseases. J Cardiovasc Dis Res 1:213–214

Sanders ME (2003) Probiotics: considerations for human health. Nutr Rev 61(3):91–99

Santisteban MM, Kim S, Pepine C, Raizada M (2016) Brain-gut-bone marrow Axis: implications for hypertension and related therapeutics. Circ Res 118(8):1327–1336

Savilahti E (2011) Probiotics in the treatment and prevention of allergies in children. Biosci Microflora 30:119–128

Seerengeraj V (2018) Probiotics: the marvelous factor and health benefits. Biomed Biotechnol Res J (BBRJ) 2:1–8

Shah D, Choudhury P, Gupta P, Mathew J, Gera T, Gogia S, Mohan P, Panda R, Menon S (2012) Promoting appropriate Management of Diarrhea A systematic review of literature for advocacy and action: UNICEF PHFI Series on Newborn and Child Health, India. Indian Pediatr 49:627–649

Shimojo Y, Ozawa Y, Toda T, Igami K, Shimizu T (2018) Probiotic Lactobacillus paracasei A221 improves the functionality and bioavailability of kaempferol-glucoside in kale by its glucosidase activity. Sci Rep 8(1):9239

Shoukat S (2020) Potential anti-carcinogenic effect of probiotic and lactic acid bacteria in detoxification of benzo[a]pyrene: a review. Trends Food Sci Technol 99:450–459

Singh VP (2018) Recent approaches in food bio-preservation – a review. Open Vet J 8(1):104–111

Sipola M, Finckenberg P, Santisteban J, Korpela R, Vapaatalo H, Nurminen ML (2001) Long-term intake of milk peptides attenuates development of hypertension in spontaneously hypertensive rats. J Physiol Pharmacol 52(4 Pt 2):745–754

Stadlbauer V, Mookerjee RP, Hodges S, Wright GA, Davies NA, Jalan R (2008) Effect of probiotic treatment on deranged neutrophil function and cytokine responses in patients with compensated alcoholic cirrhosis. J Hepatol 48(6):945–951

Steinkraus KH (1992) Lactic acid fermentations, National Research Council (US) panel Washington (DC): applications of biotechnology to traditional fermented foods. Applications of biotechnology to fermented foods: report of an ad hoc panel of the board on science and Technology for International Development. National Academies Press (US), Washington, DC

Sugiharto S (2016) Role of nutraceuticals in gut health and growth performance of poultry. J Saudi Soc Agric Sci 15(2):99–111

Sun Z, Sun X, Li J, Li Z, Hu Q, Li L, Hao X, Song M, Li C (2020) Using probiotics for type 2 diabetes mellitus intervention: advances, questions, and potential. Crit Rev Food Sci Nutr 60(4):670–683

Sur D, Manna B, Niyogi SK, Ramamurthy T, Palit A, Nomoto K, Takahashi T, Shima T, Tsuji H, Kurakawa T, Takeda Y, Nair GB, Bhattacharya SK (2011) Role of probiotic in preventing acute diarrhoea in children: a community-based, randomized, double-blind placebo-controlled field trial in an urban slum. Epidemiol Infect 139(6):919–926

Śliżewska K, Markowiak-Kopeć P, Śliżewska W (2021) The role of probiotics in Cancer prevention. Cancers 13(1):20

Talwani R, Gilliam BL, Howell C (2011) Infectious diseases and the liver. Clin Liver Dis 15(1):111–130

Tamime AY, Saarela M, Søndergaard A, Mistry V, Shah N (2007) Production and maintenance of viability of probiotic micro-organisms in dairy products. In: Probiotic dairy products. Blackwell Science Ltd, Oxford, pp 39–72

Tang RB (2005) Risk factors associated with the development of asthma. J Chin Med Assoc 68(5):199–201

Terefe NS (2016) Food fermentation., Elsevier food science reference module. Elsevier, New York

Tonucci LB, Olbrich Dos Santos KM, Licursi de Oliveira L, Rocha Ribeiro SM, Duarte Martino HS (2017) Clinical application of probiotics in type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled study. Clin Nutr (Edinburgh, Scotland) 36(1):85–92

Urbańska M, Gieruszczak-Białek D, Szajewska H (2016) Systematic review with meta-analysis: Lactobacillus reuteri DSM 17938 for diarrhoeal diseases in children. Aliment Pharmacol Ther 43(10):1025–1034

Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Cheng S, Delling FN, Elkind MSV, Evenson KR, Ferguson JF, Gupta DK, Khan SS, Kissela BM, Knutson KL, Lee CD, Lewis TT, Liu J, Loop MS, Lutsey PL, Ma J, Mackey J, Martin SS, Matchar DB, Mussolino ME, Navaneethan SD, Perak AM, Roth GA, Samad Z, Satou GM, Schroeder EB, Shah SH, Shay CM, Stokes A, VanWagner LB, Wang NY, Tsao CW (2021) Heart disease and stroke Statistics-2021 update: a report from the American Heart Association. Circulation 143(8):e254–e743

Wada M, Nagata S, Saito M, Shimizu T, Yamashiro Y, Matsuki T, Asahara T, Nomoto K (2010) Effects of the enteral administration of Bifidobacterium breve on patients undergoing chemotherapy for pediatric malignancies. Support Care Cancer 18(6):751–759

Wang J, Tang H, Zhang C, Zhao Y, Derrien M, Rocher E, van Hylckama Vlieg JE, Strissel K, Zhao L, Obin M, Shen J (2015) Modulation of gut microbiota during probiotic-mediated attenuation of metabolic syndrome in high fat diet-fed mice. ISME J 9(1):1–15

WHO (2020) https://www.who.int/news/item/09-12-2020-who-reveals-leading-causes-of-death-and-disability-worldwide-2000-2019

Winkler P, Ghadimi D, Schrezenmeir J, Kraehenbuhl JP (2007) Molecular and cellular basis of microflora-host interactions. J Nutr 137(3 Suppl 2):756s–772s

Wu X, Ma C, Han L, Nawaz M, Gao F, Zhang X, Yu P, Zhao C, Li L, Zhou A, Wang J, Moore JE, Millar BC, Xu J (2010) Molecular characterisation of the faecal microbiota in patients with type II diabetes. Curr Microbiol 61(1):69–78

Yan F, Polk DB (2011) Probiotics and immune health. Curr Opin Gastroenterol 27(6):496–501

Yoo JY, Kim SS (2016) Probiotics and prebiotics: present status and future perspectives on metabolic disorders. Nutrients 8(3):173

Zimmermann P, Curtis N (2018) The influence of probiotics on vaccine responses – a systematic review. Vaccine 36(2):207–213

Zommiti M, Feuilloley MGJ, Connil N (2020) Update of probiotics in human world: a nonstop source of benefactions till the end of time. Microorganisms 8(12):1907

Zuccotti G, Meneghin F, Aceti A, Barone G, Callegari ML, Di Mauro A, Fantini MP, Gori D, Indrio F, Maggio L, Morelli L, Corvaglia L (2015) Probiotics for prevention of atopic diseases in infants: systematic review and meta-analysis. Allergy 70(11):1356–1371