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Probiotics-based foods and beverages as future foods and their overall safety and regulatory claims

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ABSTRACT

The increasing research on science and innovation has shifted consumer awareness from conventional to functional foods that are more nutritious and healthier. The ideation of functional food is based on the addition of probiotics that promote cognitive response, improved immune system, and general wellbeing. At a time when there is noproven therapy for global pandemic SARS-CoV-2 causing infectious viral disease COVID-19, alternative food and nutritional interventions through diet are studied like never before to limit the infection. Probiotics are live microorganisms that have the potential to modulate the human immune system and prevent such infection, which is why several safety issues during its administration must be addressed. While at the same time, it is necessary to update, reform, and tighten the policies and regulations for the food manufacturers dealing with such functional foods to protect consumers from false and misleading claims. This review paper attempts to extensively provide insights into safety and regulatory considerations for probiotic-based foods and beverages.

1. Introduction

With modernization and increasing trend towards a healthier society, consumers are concerned about diet, nutrition, and food safety for improved quality of life. Currently, the world is facing a challenge of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection as a global pandemic. Nutritional status has been tagged as one of the biggest risk factors for developing severe illness, including obesity and malnutrition amidst the SARS-CoV-2 pandemic (James et al., 2020). Healthy, nutritious, and functional foods are the only rational alternatives for survival in the current context that plays a vital role in strengthening the immune system to ward off these diseases (Aman and Masood, 2020).

The emerging consensus among consumers has prompted multi-stakeholders involved in food systems to divert the conventional approach of food production by either adding or increasing the health benefits that make food products more functional. Functional foods exceeds in providing health benefits beyond basic nutrition and are often termed as future foods. For foods to be marketed as a functional, it has to meet certain conditions that include conformation and meeting food safety regulation of a particular country or exporting then meeting international food safety standards, free access, and proof of health benefits when consumed normally as a balanced diet. Such functional foods prevalent in the market include probiotics, prebiotics, dietary supplements, vitamins, antioxidants, dietary fiber, and other phytochemicals (Annunziata and Vecchio, 2013; Cencic and Chingwaru, 2010; Corbo et al., 2014; Granato et al., 2020).

Among emerging functional foods in the market, probiotics-based foods and beverages are considered as one of the future foods that are more prominent with wider acceptability among consumers (Shi et al., 2016). This has skyrocketed its global market value of 42.55 billion USD in 2017 and is expected to reach 94.48 billion USD by 2024 (Insights, 2020). Asia and the Pacific region dominates these numbers while in Europe, regulations regarding health claims have shown a slow growth rate of probiotics foods and beverages (Yilmaz-Ersan et al., 2020). A huge amount of revenue and money is at stake when it comes to probiotics-based foods and beverages. One of the first probiotic fermented dairy beverages is Yakult which contains the probiotic *Lactobacillus casei shirota* (Katan, 2012).

Probiotics confer health benefits to the host when consumed in an adequate amount (Anal and Singh, 2007; Noomhorm et al., 2014). Such effects that are postulated after administration of probiotics in the food matrix which include; balancing the intestinal homeostasis by either eliminating or inhibition of microbial flora (Cordeiro et al., 2019; Khaneghah et al., 2020); boosting the immune system (Galdeano et al., 2019); reducing the risk of various cancers (Pino et al., 2020); enhancing lactose digestion (Oak and Jha, 2019); and other host-microbe benefits like prevention from cardiovascular diseases, diabetes, and some allergic reactions (Shafi et al., 2019; Soccol et al., 2010; West et al., 2011). In addition to this, changes in the microbiome of the intestinal tract occur upon the consumption of probiotics. The causes of this change dates

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back to our birthing process where humans are first exposed to these bacteria, which is the time when the body system recognizes them as desired or unnecessary. The body recognizes the desired bacteria necessary for developing immune system and is well tolerated throughout life (Vanderhoof and Young, 2008). The consumption of probiotics alters the gut microbiome through an immune response that would ultimately recognize them as useful and form a barrier in the intestinal tract for protection against pathogens.

Traditional fermented foods and drugs are known to contain probiotic microorganisms (Anal, 2019; Guimarães et al., 2020; Roobab et al., 2020; Zucko et al., 2020). Among these, fermented dairy products like cheese, yogurt, acidified milk, and drinking yogurt have been most widely accepted as vehicles for probiotic delivery. This is attributable to their unique physicochemical and nutritional abilities that provide them the buffering capacity in the harsh acidic conditions of the stomach (pH 2–3) for a viable number of probiotic survival in the lower gut (6 to 8 Log CFU/ mL) that can help them to exert potential therapeutic effects (Araújo et al., 2012; Kalicka et al., 2019; Linares et al., 2017; Reid, 2015; Tomar, 2019).

Although many probiotic strains are found to exert positive effects on human health, any adverse effects must be considered from a consumer safety perspective. In this regard, lactic acid bacteria (LAB), namely, *Lactococcus* and *Lactobacillus*, have been classified as generally recognized as safe (GRAS) (Wassenaar and Klein, 2008). However, opportunistic infections have been associated with some species of LAB (Cannon et al., 2005; Gasser, 1994). Thus, to assess the overall safety of probiotics-based foods and beverages, considerations on its origin and nature, pathogenicity, administration process, ability to carry antibiotic resistance genes or not, level of exposure, health status of the host, and its intended use must be considered (de Simone, 2019).

Along with safety, the regulatory frameworks have been established in many countries to protect consumers from any misleading claims by the intended use of probiotics. Various sets of regulatory claims are effective on the commercial market of many countries dependent on the intended use of probiotic foods, demographical conditions, and market dynamics (Melchor et al., 2019).

2. Potential of consumption of probiotics-based foods in COVID-19 pandemics and other viral infections

The World Health Organization (WHO) declared COVID-19 (a viral infectious disease caused by the SARS-CoV-2), a global pandemic on 11 March 2020. As of yet, there is no cure or treatment for this virus. With no proven and effective therapy against COVID-19, alternative strategies need to be developed that are focused on pathophysiological pathways. One such approach is developing future foods with probiotics. Traditionally fermented foods containing probiotic microorganisms have tremendous potential to prevent COVID-19. Past studies on the consumption of probiotic fermented milk reduced upper respiratory tract infections among healthy infants, children, adults, and the elderly (Makino et al., 2010; Merenstein et al., 2010; Shida et al., 2017). Kanauchi et al. (2018) reviewed the efficacy of probiotics in treating viral infections. *Lactobacillus casei shirota (LcS)* (common strain used in Yakult) ingestion was effective by reducing the plasma cytomegalovirus and epstein–barr virus antibody titres in highly physically active people (Gleeson et al., 2016). The effect of ingestion of *Lactobacillus rhamnosus GG* by healthy volunteers for six months against *rhinovirus* was evaluated. It was observed that the occurrence, infection rate, and severity of cold systems were reduced in subjects with rhinovirus infection than the control group (Kumpu et al., 2015).

Other reported studies showing positive effects of probiotics against viral infections include reduced risk of catching a common cold in elderly people by increasing natural killer cell activity by probiotic *Lactobacillus delbrueckii ssp. bulgaricus OLL1073R-1* (Sindhu et al., 2014), a significant decrease in the incidence of upper respiratory tract infections in healthy adults with high psychological stress by probiotic *Lactobacillus plantarum L-137* (Hirose et al., 2006), a significant decrease in the duration period of diarrhea in children aged 5 months to 5 years that are hospitalized by rotavirus using probiotic *Bifidobacterium lactis B94* (Erdoğan et al., 2012). These studies shed light on how probiotics can be useful against COVID-19. Based on available evidences, potential mechanisms to elucidate the action of probiotics against COVID-19 include enhancing the intestinal epithelial barrier, adhesion to intestinal epithelia, production of secondary metabolites as bacteriocins, host immune modulation, and competitive action against pathogens for nutrients (Plaza-Diaz et al., 2012).

Robles-Vera et al. (2017) stated the impacts of probiotics action against angiotensin converting enzyme (ACE), a potent vasoconstrictor. Probiotics produce bioactive peptides from food proteins during fermentation to inhibit the ACE enzyme by blocking the active sites (Ayyash et al., 2020). Even the debris left by dead probiotic cells act against the ACE enzyme (Miremadi et al., 2014). The production of proinflammatory cytokines are triggered in large quantities due to COVID-19 infection as an offensive inflammatory response in some patients known as cytokine storm (Huang et al., 2020). Several vital organs of human body including lungs, kidneys, brain, GI tract, and eyes are prone to damage due to this phenomenon (Bhaskar et al., 2020). This could be lessened by intake of probiotic based foods and beverages as indicated by several studies. Probiotics regulate the intestinal mucosal immune cells in the human GI tract by production of short chain fatty acids (SCFAs) (Xu et al., 2020). The colonizing probiotic bacteria at the gastrointestinal tract interact with the intestinal mucosa and communicate with the epithelial and mucosal lymphoid elements, which provoke the host defences in the gut (Shi and Walker, 2004). Han et al. (2007) reported the effectiveness of gut microbiota in combating respiratory tract disorders and infection as an immunological function. Baud et al. (2020) recently revealed the lists of some probiotics (*Lactobacillus casei*, *Lactobacillus gasseri*, *Bifidobacterium longum, Bifidobacterium bifidum*, *Lactobacillus rhamnosus*, *Lactobacillus plantarum, Bifidobacterium breve, Pediococcus pentosaceus*, and *Leuconostoc mesenteroides)* which could decrease the burden of the COVID-19. Considering such potential of probiotics, major food based manufacturing companies have incorporated these strains of probiotics into several products such as DanActive/Actimel fermented drink (Danone), Tribion harmonis (Merck), Shirota, Morinaga, and Medipharm (Baud et al., 2020). These promising results demonstrate the significance of probiotics as future foods in combating COVID-19 and other viral infections. Thus, probiotics rich foods and beverages are expected to enhance the immune systems and thus to control the risk of viral including COVID-19 infection (Gasmi et al., 2020).

3. Probiotics and host immunity

The global food consumption pattern and the emergence of ultra-processed foods have been associated with increased inflammation and other health issues rising to lower immune responsiveness. These dietary changes have been linked to imbalances in the human gut microbiome (Childs et al., 2019; Gibney et al., 2017; Monteiro et al., 2013; Sonnenburg and Sonnenburg, 2019). Researchers have shown probiotics to restore the gut microbiota and modulate the intestinal immune response in viral respiratory infections (Clua et al., 2017; de Vrese et al., 2005; Hao et al., 2015; Winkler et al., 2005). These studies reveal the immune-enhancing benefits of probiotics which has increased consumer demands for more such foods now and in the future.

The established and well-known action mechanisms of probiotics for boosting immunity is shown in **Fig. 1**. They do so by providing protection against the pathogens, secretion of antimicrobial substances, immunomodulation, production of short-chain fatty acids (SCFA), and competitive action for adhesion and nutritional sources (Ashaolu, 2020; Wan et al., 2019).

The primary site of action of probiotics is gut or the large intestine. When probiotics reach the gut (known as human bioreactor) through

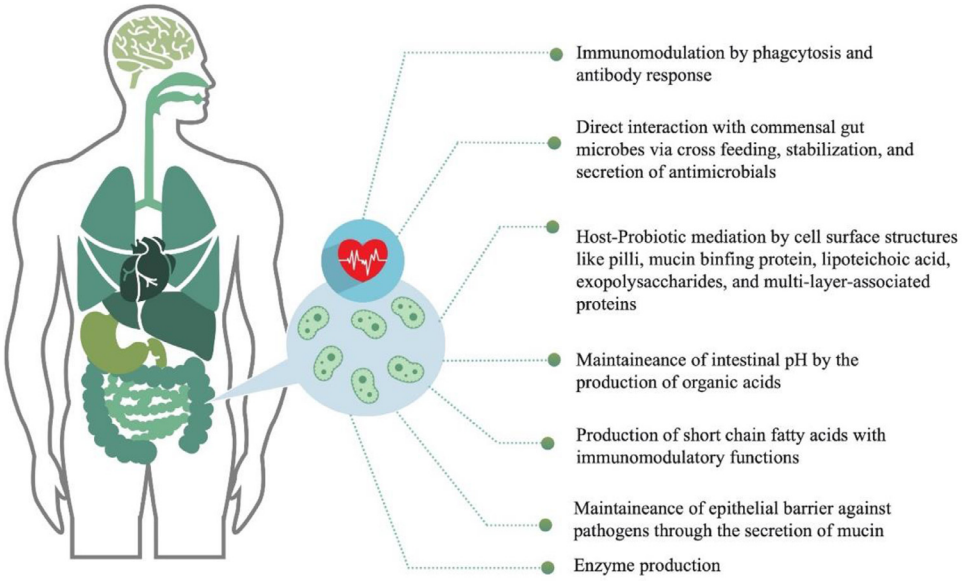

Fig. 1. Probiotics action mechanism for host immune enhancement.

direct supplementation or probiotics, the first significant step is adherence to the intestine's epithelium layer. Once probiotics colonize the gut, they ferment the foods producing short-chain fatty acids (SCFA). SCFAs are vital compounds that can inhibit histone deacetylases and improve antibody-antigen response. Other metabolites produced by probiotics include peptides, amino acids, and vitamins regulating the host immune system (Morais et al., 2020; Vinolo et al., 2011; Zhang et al., 2019). Thus, probiotics can modulate the host immune system by various mechanisms and maintain natural intestinal homeostasis. Then an immune response can be triggered which can be the case against SARS-CoV-2. However, various probiotics strain even within the same genus behave differently and the safety aspects must be considered before real-life applications.

4. Safety assessment

More than 420,000 deaths every year is accounted to food poisoning as per the World Health Organization (WHO) report (WHO, 2015). Part of this is because food which we consume for nutrients delivery, is also suitable hostage to the favourable growth of pathogenic microorganisms. Due to these, consumers are more conscious on future foods with beneficial microbes (Bian et al., 2016). Probiotics contain live bacteria that are added to food or food supplements. This is why a careful safety assessment (**Fig. 2**) needs to be carried out to check if the added probiotics are safe or harmful for consumption considering the possibility of theoretical side effects. The genetic study of probiotics while assessing its safety will certainly give an understanding on specific genes can suppress the expression of gene, interaction with food-borne pathogens, and their toxins while accounting the safety of probiotics as future foods. Proving probiotics safety, however, is a challenging task to provide evidence for the absence of all virulence properties. This property is sometimes strain-specific, too, which makes it more challenging. Along with this, the emergence of antimicrobial resistance in the bacteria helps transfer pathogenic genes into the probiotics (Wassenaar and Klein, 2008). Considering all these challenges, here we discuss the fundamental practices of safety assessment of the probiotics.

4.1. Non-pathogenicity

The probiotic strain used in foods and beverages must be non-pathogenic and should not pose a risk to the host. The most commonly used probiotic microorganisms for foods and beverages belong to *Lactobacilli* and *Bifidobacteria* that are generally considered safe to the host (Adams and Marteau, 1995). *Lactococcus lactis* and *Lactobacilli* are classified as generally recognized as safe (GRAS) in the United States (Salminen et al., 1998). Their existence and occurrence support the safety of these strains in food as normal commensals and inhabitants of mammalian flora. Along with that, established safety claims over a diverse range of food products, including presence in the traditionally fermented foods worldwide, corroborates this conclusion (Marteau, 2002).

Some *Lactobacillus* species have been associated with opportunistic infections. Cannon et al. (2005) reported the pathogenicity of over 200 documented cases of *Lactobacillus* infections. In this study, species *casei* and *rhamnosus* were most associated with endocarditis and bacteremia, with associated infections not limited to peritonitis, abscesses, and meningitis. Similarly, Saxelin et al. (1996) assessed the safety of *Lactobacilli* to detect the presence of bacteremia during a 4-year period (1989–1992) in southern Finland. *Lactobacilli* were identified in eight patients among 3317 blood culture isolates, of which five had a severe bacteremic complication. Bacterial species like *Escherichia coli* and *Enterococcus* possess both non-pathogenic variants and pathovars (Franz et al., 2003). Hence it is important to consider that the attribute pathogen associated with probiotics for food application is strain-specific rather than species-specific. Thus, the general conclusions on the safety of probiotic strain do not apply to all given species strains. To prove non-pathogenicity, strain-specific evidence is required to establish the claim (Wassenaar and Klein, 2008).

For proving the non-pathogenicity of probiotic bacteria in foods and beverages, evidence surrounding pathogenic features like production of toxin, survivability, and replication in the bloodstream along with invasion and translocation must be revealed systemically (Bernardeau et al., 2006). Notably, some bacteria possess the ability to take up DNA from the environment into its genome. This might affect non-pathogenic bacteria, which could gain virulence genes while in the gut. The horizontal gene transfer due to the uptake of foreign DNA from the environment could expose probiotic bacteria to acquire antimicrobial resistance. This could be transferred to pathogenic bacteria from non-pathogenic probiotics during microbial-host-pathogen interactions in the gut with adverse health consequences. Thus, the non-pathogenicity of probiotics in foods and beverages must be assessed in terms of their pathogenicity, virulence repertoire, antibiotic resistance, and ability to acquire foreign DNA.

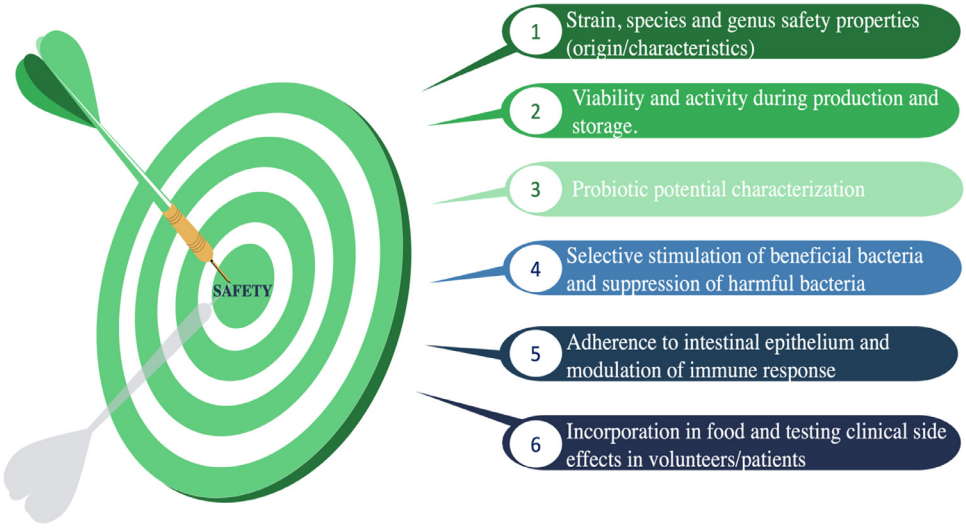

Fig. 2. General procedure for the safety evaluation of probiotics for application in foods and beverages.

4.2. Absence of virulome in probiotics

The safety of probiotics-based foods and beverage is of utmost importance, especially with the rise of public consciousness towards probiotics and functional foods. This warrants detailed safety over functional evaluation which traditionally includes microbiological and phenotypical assays to confirm the absence of virulence genes. Virulence genes (virulome) represents the bacteria associated genes that are essential for a bacterium to affect eukaryotic cells (like humans) by invasion, colonization, immune evasion, suppression of host immune response and acquire nutrition from the host (Wassenaar et al., 2015). Hence, an additional whole-genome sequence is essential for the safety evaluation of a strain earmarked for probiotic use. The criterion would be the complete absence of virulome from probiotic bacteria and transferrable genes to relevant antibiotics in clinical practice.

Though the absence of virulence factors in probiotic strain would mean its acceptability for commercial application, proving such genes in a bacterium is an equally daunting task for several reasons. Firstly, virulome for all (entero) pathogen is not yet well characterized. The pathogenic mechanism of some pathogens like *Campylobacter jejuni* is still unknown, meaning the bacteria demonstrates virulome through unknown mechanisms, which is not yet detected (Wassenaar and Blaser, 1999). Secondly, probiotics in the gut exhibit virulence like properties and this is where a distinction between colonization and virulence becomes difficult, though both of them are related. Thus, it becomes difficult to define which properties of bacteria help them adhere and attach to the gut epithelium (ability of probiotic strain as colonization) and responsible for the disease (Wassenaar and Klein, 2008).

Pieniz et al. (2015) evaluated the presence of virulence factors in *Enterococcus durans* LAB18s isolated from frescal cheese. The study was aimed to detect virulence factors like adhesion, aggregation and biofilm formation using PCR with specific primers. The results showed a negative for all virulence factors studied, suggesting the safety of strain for use in food and feed applications. However, Wassenaar et al. (2015) studied the virulence genes in Symbioflor2 (DSM 17,252), a probiotic product with six different *Escherichia coli*. The authors reported several virulence-associated genes in a probiotic product, which did not account for pathogenicity. A similar study was conducted by Binnewies et al. (2006) where the authors studied complete bacterial genomes for ten years, only to discover that virulence genes are quite common in commensals. Thus, proving the absence of virulence genes in a probiotic strain for food application does account for its safety; however, methodology and its interpretations are yet to be streamlined, even when the whole genome sequence will be available.

4.3. Absence of antibiotic resistance in probiotics

Antibiotic resistance has been common in microorganisms due to its indiscriminate use in human and veterinary medicine, that pose serious problems when treating microbial infections. (Saarela, 2019; Thapa et al., 2020). Bacteria can resist the effects of medication that was once effective against the microbe (D'Costa et al., 2011). This acquired ability of bacteria to change its nature should be avoided in probiotics for food applications. Though it is unsure whether these antibiotic resistance genes would affect the host's health, they could transfer the genes to potential pathogenic bacteria in the gut, which may pose serious health issues. Proving the absence of antibiotic resistance in a given bacterial strain is relatively straightforward compared to complexities involved with proving the absence of virulence factors.

Antibiotic resistance in bacteria may be due to acquired or intrinsic properties. Intrinsic resistance to medication is naturally occurring and specific to species while acquired resistance occurs from DNA of foreign bacteria is incorporated into the host bacteria or due to genetic mutations (Blair et al., 2015; Munita and Arias, 2016). Lactic Acid Bacteria (LAB) also possess an array of antibiotic resistance intrinsically but most of these are non-transmissible (Gueimonde et al., 2013). The antibiotic resistance of LAB could be due to chromosomal, transposon or plasmid located genes. *Lactobacilli* with non-transmissible antibiotic resistance genes do not possess a safety concern. *Lactobacillus rhamnosus* and *Lactobacillus casei* along with several other species of *lactobacilli* are resistant (intrinsically) to vanomycin. The usual species contains vanomycin activity precursor with D-alanine as a terminating end while the resistant species contains peptidoglycan precursor with D-lactate as a terminating end. These species of *Lactobacilli* resistant to vanomycin intrinsically have a demonstrated history of safe use as a probiotic. No other evidence is obtained that shows if it could transfer the resistance to other bacteria (Saarela et al., 2000). A systematic approach to approval of enterococci as antibiotic resistance to vanomycin is shown illustrated in **Fig. 3**.

Plasmid-linked antibiotic resistance occurs in *Lactobacilli* species though it is uncommon, so safety considerations must be considered. The possibility of genes encoding antibiotic resistance, especially with strains isolated from the intestine, do exist in common probiotic *Lactobacilli* and *Bifidobacteria* as they contain plasmid (FAO, 2006). This necessitates further research into antibiotic resistance properties in traditional probiotic strains linked with *Lactobacilli* and *Bifidobacteria.*

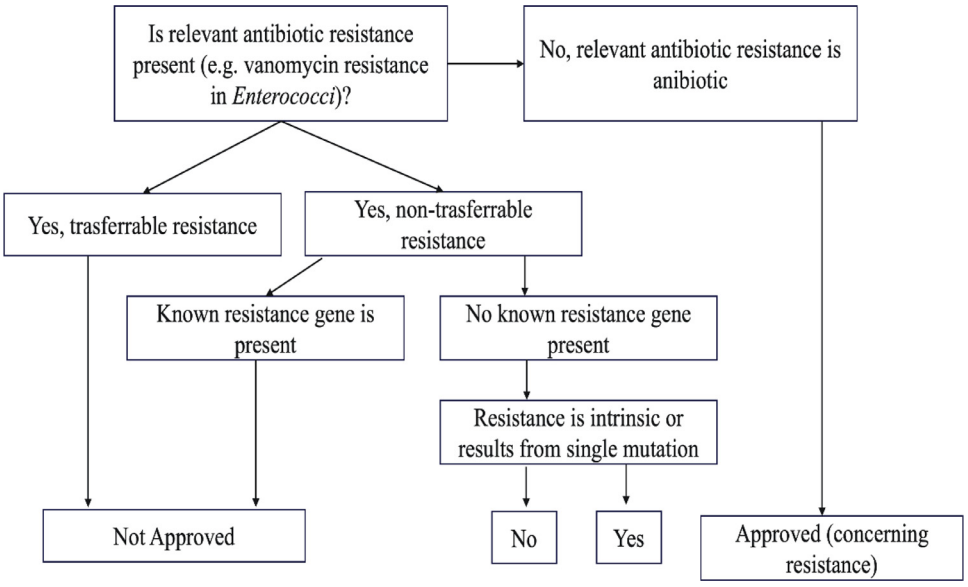

Fig. 3. Decision scheme for approval of probiotic bacteria (enterococci) resistance to vancomycin.

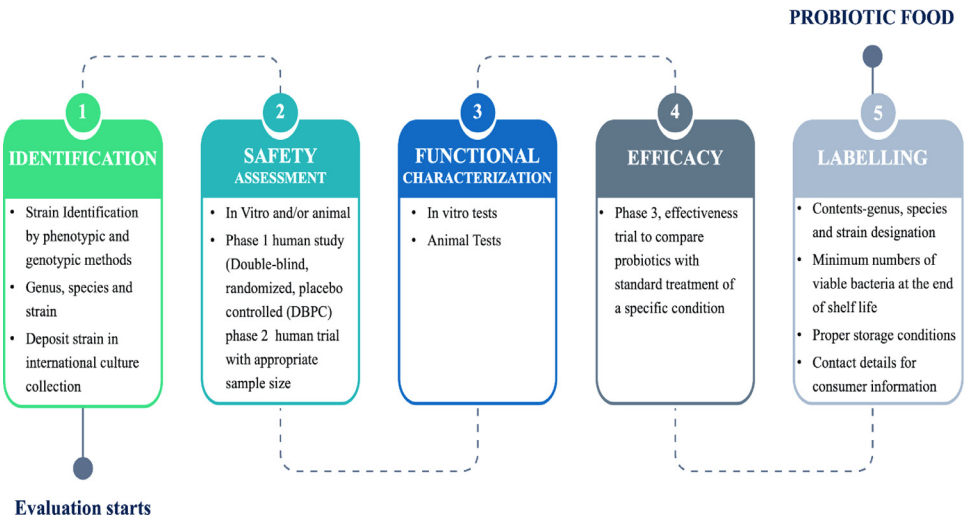

Fig. 4. Overall safety and functional evaluation of probiotic for use in food applications.

5. FAO/WHO report on the evaluation of safety of probiotics in food and beverages

The joint FAO/WHO consortium was held during 1–4 October 2001 in Cordoba, Argentina recognized a growing demand for probiotic-based foods and beverages in the market, which needs to be streamlined with proper guidelines, systematic approach and assessment of probiotic safety before it reaches to the consumers. The consultation group also set forth the evaluation techniques for probiotics in food leading to added health benefits (**Fig. 4**). The dedicated working group aimed to identify and outline the minimum requirements of probiotics in food for any food to be labeled as "Probiotic Food" (FAO/WHO, 2002).

5.1. *Screening of microorganism*

The first step for any potential probiotics for food application starts with isolation and identification. The identification of species should be performed by using 16s RNA methods and verified with a combination of phenotypic and genotypic tests. The information on the presence of plasmid as an extrachromosomal genetic elements should be supported by the strain characteristics (FAO/WHO, 2002; Zielińska et al., 2018).

5.2. *Screening probiotic potential* in vitro

It is essential to substantiate the efficacy of identified microbes by various *in vitro* and potentially *in vivo* tests with human clinical trials with probiotic claimed foods and beverages. Normally characteristics such as tolerance to bile acid, gastric juice resistance, adherence to human epithelial cells, ability to reduce pathogen in the gut, antimicrobial activity, bile salt hydrolase activity and safety assessment are conducted to elucidate the probiotic potential of a given microbe (Zielińska et al., 2018).

Some traditional probiotic species of the bacteria used in foods like *Bifidobacterium, Lactobacillus*, and *Streptococcus*, including yeast such as *Saccharomyces boulardii* are considered as GRAS (Bagchi, 2014). However, the FAO/WHO working group recommends safety assessment as evidence to certify given probiotics in food application. Safety assessment of probiotic prescribed by the working group includes the following:

a Production of undesirable metabolites and its evaluation (e.g., D-lactate production and bile salt deconjugation)
b Presence of potential antimicrobial resistance factors
c Possible side effects in human clinical studies

d Epidemiological post-market assessment of adverse effects in consumers
e Hemolytic activity
f Toxin production and toxicity

Casarotti et al. (2017) studied the safety and probiotic potential of *Lactobacillus* strains isolated from mozzarella cheese. The safety assessment of ten *Lactobacillus* strains including *Lactobacillus fermentum* SJRP30, *Lactobacillus casei* SJRP37, SJRP66, SJRP141, SJRP145, SJRP146, and SJRP169, and *Lactobacillus delbrueckii* subsp. *bulgaricus* SJRP50, SJRP76, and SJRP149 were analyzed based on resistance to antibiotics, virulome factors, degradation of mucin and hemolytic activity. Their results demonstrate that all strains were resistant to antibiotics; however, it was limited to intrinsic resistance. Limited virulome or virulence genes were present and in this study the strains did not show any hemolytic activity and mucin degradation. Overall, *L. fermentum* SJRP30 and *L. casei* SJRP145 and SJRP146 were reported to be safe. Da Silva et al. (2019) assessed the safety of lactic acid bacteria isolated from goat milk. Antibiotic resistance, gelatinase production, hemolytic activity as safety related virulence factors were studied in isolated LAB. The results show that the selected LAB strains are safe against tested parameters. Sanders et al. (2005) reported that *in vitro* studies tend to provide more relevant information about strain characterization, genomic analysis, DNA-based identification, and viability measurement. These studies purely assess the probiotic strain against the suggested indicators from the FAO/WHO working group.

Some other studies have reported beneficial substances from probiotics. Kalhoro et al. (2019) identified bacteriocin-like inhibitory substance (BLIS) producing strains from probiotic *Lactobacillus paraplantarum BT-11*. Akbar et al. (2019) isolated *Lactococcus lactis subsp. lactis* from fermented milk and assessed the antimicrobial potential of LAB isolates. The antibmicrobial activity of the LAB was determined against major foodborne pathogens like *Salmonella typhimurium, Staphylococcus aureus, E. coli*, and *Listeria monocytogenes*. The bacteriocin as an antimicrobial metabolite from LAB reduced the number of target bacteria in milk by 10-fold after 24 h of incubation. A similar study was reported by Kumaree et al. (2015) where the authors investigated the potential of probiotic *Lactobacillus plantarum* isolated from freshwater catfish against major fishborne pathogens (*Streptococcus agalactiae, S. typhimurium, E. coli,* and *Klebsiella pneumoniae*). These studies and approaches should be included in the safety assessment of probiotics intended for foods and beverages, which will help understand an array of probiotic safety in a holistic manner.

5.3. *Human and animal studies* in vivo

The expert working group encourages the results from *in vitro* to understand the probiotic mechanism and encourages animal studies for substantiation of safety concerns. The procedure for human clinical studies regarding the administration of probiotic-based foods and beverages can be explained in four phases (Gupta, 2016).

a Safety assessment (Phase 1)
b Efficacy (Phase 2)
c Effectiveness (Phase 3)
d Surveillance (Phase 4)

The safety assessment in the first phase follows the screening of isolates in detail, following the procedure recommended by the working group. The animal studies are then essential to evaluate the efficacy (Sanders et al. (2005). The animal studies' results need to be carefully interpreted, referring to human physiology, pathology, anatomy, test group, and a range of other factors involved. The third stage involves the study of effectiveness of either probiotic strain or such foods by conducting human trials. This study is dependent on the regulations, the type of probiotic microorganisms used in foods and beverages and studied sample population. As safety is of paramount significance, the trials with probiotics in foods and beverages shall be carefully planned and supervised by an approved authorizing body. Shane et al. (2010) believes that coordinated collaborative effort between medical practitioner, consumer, microbiologist, industrial representative, and regulatory agencies is important to the quality and safety of trial involving probiotic foods. In general, functional foods like probiotic foods are examined in open-label studies. Hence, a placebo effect cannot be ignored as different matrices can affect microbe viability and alter the effect on the host (Zielińska et al., 2018).

5.4. *Health claims and labeling of probiotic-based foods and beverages*

One of the major concerns about probiotic-based foods and beverages is health claims and labeling that are too specific without scientific evidence and facts. They are at times merely used as a gimmick for promotion. Concerning this, it is recommended that the use of the word "probiotic" on only those foods and beverages that contain live microorganisms of well-defined strain with a considerable number of cells that deliver benefits to the host. Clear and precise labeling should be placed on probiotic foods which need to be verified by regulating body or agency. Failure to do so may result in unwanted health side effects and potential penalties as per the law and legislation.

Temmerman et al. (2003) studied 55 probiotic products in European markets for labeling issues which showed inappropriate and mislabeling in 40% of dairy products and other food supplements. Lewis et al. (2016) further studied 16 probiotic foods to determine if the claims on *Bifidobacteria* in the product describe the labeling claims in the packaging using DNA-based methods, only to report that the observed *Bifidobacteria* differs from the one listed as an ingredient. Surprisingly, only 1 out of 16 probiotics perfectly matched its label. There are more than 10,000 additional studies that use the term "probiotics" in PubMed since the inception of FAO/WHO (2002) safety evaluation report. This progress in scientific and clinical studies drives the future direction for probiotic-based foods and beverages. However, many misuses of the word "probiotic" have been found, as manufacturers use it without meeting specific criteria. Thus, the following adjustments were recommended during a high-level meeting at the ISAPP (International Scientific Association for Probiotics and Prebiotics) (Hill et al., 2014):

a Updating the FAO/WHO definitions for probiotics with minor grammar correction as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host,"
b It is now required to include the microorganisms species in the "probiotics" definition after it has passed necessary clinical studies with beneficial effects on the host,
c Specific claims (like health, nutritional, functional, and those beyond "contains probiotics") must be further substantiated,
d The term probiotics are not applied for cultures associated with traditionally fermented foods with no evidence of a health benefit.
e The word probiotics can be used for the defined strains from human samples with adequate safety and efficacy evidence.

Currently, manufacturers of probiotics-based foods and beverages do not need to specify the bacterial strain as a labeling requirement along with the number of live microorganisms and their shelf-viability. This regulatory requirement needs to be updated with the emerging trends of future foods with probiotics. However, many misuses of the word "probiotic" have been found, as manufacturers use it without meeting specific criteria. This is where regulatory bodies need to invigilate and protect the consumer from false and misleading claims.

6. Regulatory framework and labeling claims associated with probiotic-based foods and beverages

The traditional concepts of sound health have changed dramatically over the years due to increased awareness of consumers towards gastrointestinal health and how it affects the whole body. Focusing on this,

Table 1
Probiotic foods and beverage categorization in major countries.

S.N.	Country	Category	Regulatory authority	References
1	USA	Drugs	FDA	(FDA, 2015)
		Dietary supplements	DSHEA	(FDA, 2006)
			BLA	(Maughan et al., 2004)
		Biological product	FDA	(Degnan, 2008)
		Live therapeutic agent	DSHEA	(Arora and Baldi, 2015; Degnan, 2012)
		Medical Food		
2	Europe	Functional Food	FUFOSE	(Saxelin, 2008)
3	Japan	Probiotics	FAO/WHO	(FAO/WHO, 2002)
		Functional foods and nutraceuticals	MHLW, FOSHU	(Amagase, 2008; Nagata and Yamada, 2008)
4	China	Functional foods	SFDA	(Yang, 2016)
5	Canada	Natural health products	FDA	(Arora and Baldi, 2017)
6	Brazil	Functional food	ANVISA	(Frietas, 2006)
7	Thailand	Functional Food	Thai FDA	(FDA, 2011)
8	Malaysia	Functional food	FSQD	(Stanton and Emms, 2011)
9	India	Functional food Drugs	FSSA, PFA, FDA	(Sharma et al., 2013)

FAO/WHO=Food and Agricultural Organization/World Health Organization, MHLW=Ministry of Health and Welfare, FOSHU=Food for Specified Health Use, FUFOSE=Functional Food Science in Europe, SFDA=State Food and Drug Administration, ANVISA=National Health Surveillance Agency Brazil, FSANZ=Food Standards Australia and New Zealand, DSHEA=Dietary Supplement Health and Education Act, BLA=Biologic License Application, PFA=Prevention of Food Adulteration Act, FSQD=Food Safety and Quality Division, NPCB=National Pharmaceutical Control Bureau.

a large number of food products labeled as probiotics are found globally. The misuse of "probiotic" started to take place for marketing tactics. Hence, many countries enacted a legal framework by establishing agencies with food and labeling requirements, claims permitted and associated penalties to protect consumers from misleading claims (Peivasteh-Roudsari et al., 2019). The rationale was to harmonize the market with a stringent framework that oversights the safety and regulatory aspects of probiotic-based foods and beverages.

The broad-spectrum framework to develop regulatory policies and labeling claims for probiotic and probiotic-based foods & beverages includes its safety, efficacy, quality control and health claim regulations (de Simone, 2019). When a probiotic makes a health claim for the treatment, therapy, prevention or diagnosis, it is classified into "drug" as in medical or therapeutic product and regulated as such (Venugopalan et al., 2010). Under this condition, the existing laws and regulations will be applied for probiotics as a drug. However, majority of probiotics as drugs do not make specific health claims due to complexities associated with in vivo clinical studies with patients. The probiotics which do not make specific health claims either as a probiotic pill or capsule or those incorporated in food are classified as dietary or food supplements (Arora and Baldi, 2017; de Simone, 2019; Melchor et al., 2019). The categorization of probiotic foods and beverages in major countries is shown in **Table 1**.

Japan is the global leader where probiotics are commercially available as both foods, neutraceutical and drug. It is the first country to implement regulation on functional foods and nutraceuticals in 1991. **Fig. 5** illustrates the three different categories as established in Japan for foods that claim health benefits:

FOSHU (Foods for specialized health issues)

a FFC (Foods with functional claims)
b FNFC (Foods with nutrient functional claims)

The approval process for foods with mentioned claims under FOSHU typically takes at least one year to complete with a detailed review process through scientific evidence accepted by the expert committee. For any substantiation, clinical trials and epidemiological studies are a mandatory requirement (Japan, 2017). Along with this, human clinical data and animal studies are also required for the review of claims for the functional food product. The requirement also states that the data for this process must be statistically significant with a well-designed study (long period studies with a sufficient number of subjects). FFC claims does not need pre-approval unlike FOSHU. Food manufacturers may use the FFC based on a piece of scientific evidence through either (1) a clinical trial using a product and involving human studies or (2) a systematic literature review (Japan, 2013).

The USA has become another hub for open-minded market when it comes to alternative therapies that include probiotics. Some of the unique features of US market for probiotic-based foods and beverages include: generally lack of fermented foods and its lower consumption; strong fear for all bacteria since the discovery of penicillin and understanding of what bacteria can do; increasing incidence of foodborne illness; skepticism of advertising claims for natural probiotic food products (Vanderhoof and Young, 2008).

Regulatory issues remain an area of concern for the probiotic-based foods and beverages in USA particularly when it comes to what the industry needs to know and how to protect the consumers from false claims. Currently, the products are regulated depending on their intended use. The regulatory bodies involved are US Food and Drug Administration (FDA) and Dietary Supplement Health and Education Act (DSHEA) that policies safety, labeling and health claims for the products. As per the existing guidelines.

- Dietary supplement: If a probiotic is used as a dietary supplement, it is considered "foods" and regulated by DSHEA/FDA.
- Drug: If a probiotic is solely to be used for medical therapeutic purpose, then it is considered as "drug" and regulated by FDA
- Biological product: For probiotics to be used as a biological product, approval is necessary via Biologic License Application (BLA) and regulated by FDA.

The United States Food and Drug Administration (USFDA) also regulates certain claims for conventional probiotic foods and beverages, including health claims, structure claims, function, and nutrient content claims. Health claims need to be pre-authorized by the FDA by submitting a petition, which is rare. Generally, these products petition for

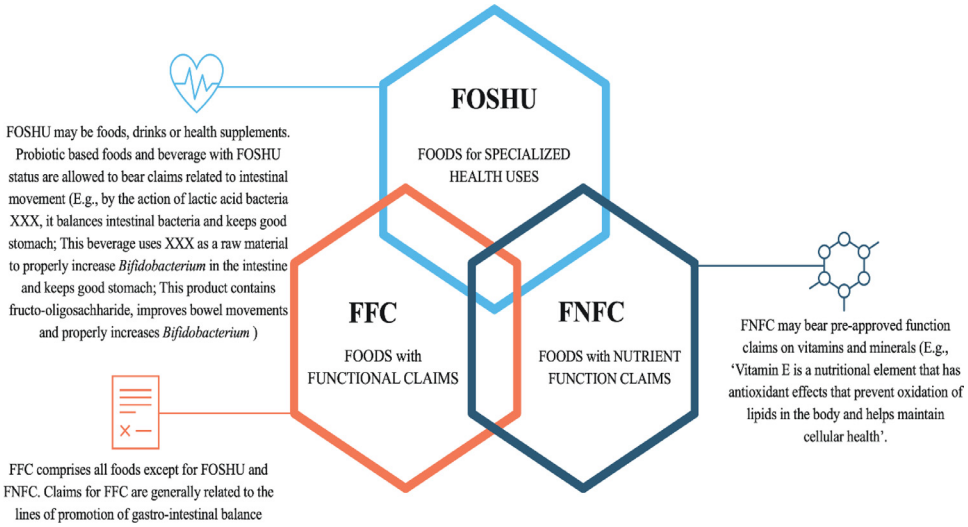

Fig. 5. Different types of health claims established in Japan.

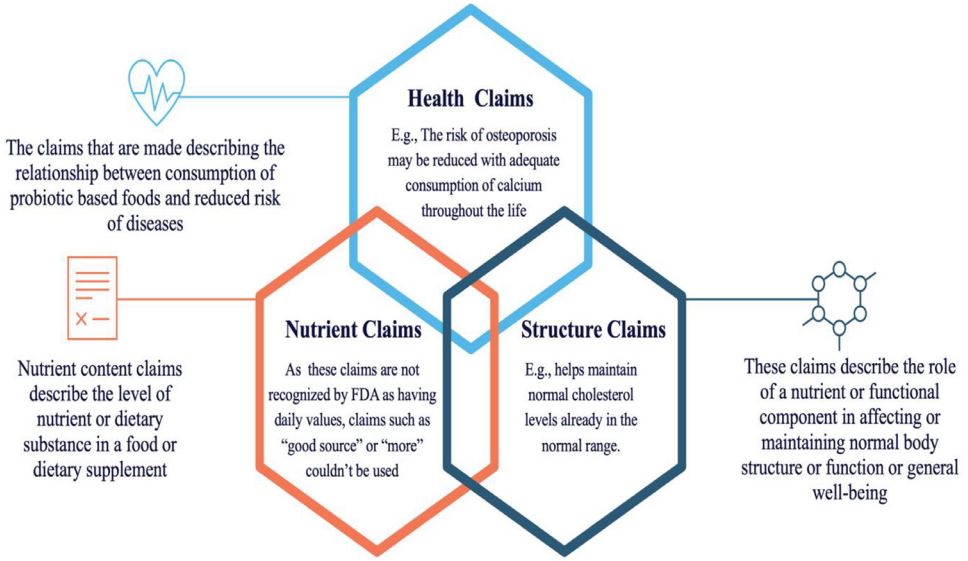

Fig. 6. Different types of claims regulated by FDA in the USA for probiotic foods and beverages.

structure and nutrient-based claims for which FDA premarket review or approval is not required. However, a notification must be made to the commission of FDA 30 days prior to the marketing of probiotic-based products. The approach of the Federal Trade Commission (FTC) which relies on tests, analysis, research, studies, evidence-based on the professionals, is adopted by FDA on approval of these claims, using the procedures generally accepted in the profession to yield accurate and reliable results. This is how the claims are substantiated and any probiotic-based foods and beverages thus sees the light of the day going through this regulatory process in the United States of America (**Fig. 6**).

Europe implemented a regulatory commission in 1995 especially on probiotics-based functional food. After Japan, Europe was second to define the probiotic-based functional foods and beverages, with a developed market, of which a large segment is composed of probiotic dairy products like yogurts and fermented milk (Stanton et al., 2001). The probiotic foods and supplements are regulated under the Food Products Directive and Regulation (regulation 178/2002/EC; directive 2000/13/EU). Before the products are marketed to the consumers, as per the European laws, all the ingredients including microbial cultures present in the foods must undergo a Qualified Presumption of Safety (QPS) for safety assessment test (**Fig. 7**) (EFSA, 2005; Leuschner et al., 2010). Despite many applications submitted to the European Food Safety Authority (EFSA), there are no approved health claims for probiotics in the region. As a result, consumers are faced with labels employing the Latin term for a particular strain of bacteria, which is not easily understood and creates confusion rather than clarity (van Loveren et al., 2012). European Food Safety Authority (EFSA), as it stands, is the regulatory body along with FUFOSE for functional foods including probiotics in the European market. One of the regulations that makes it a hurdle to recognize the benefits of probiotics is that the EU prohibits it from having medical claims. If this did not exist, nutritional treatments would have easily been approved as drugs without going through the costly procedures. Despite this, the prohibition is also considered a legal fiction because promotion of health and disease prevention is largely the same thing. EFSA indicated that it would allow health claims based on the ability of probiotics to reduce infections. This abolishes the distinction between health claims and medical claims to some extent (Herman et al., 2019).

China has a specific list of microorganisms permitted for food use, including *Bifidobacterium animalis* and *Bifidus bacterium*. However, safety requirements in the usage of these foods are not enacted. In general, the production of these prebiotics and probiotics should be in line with the

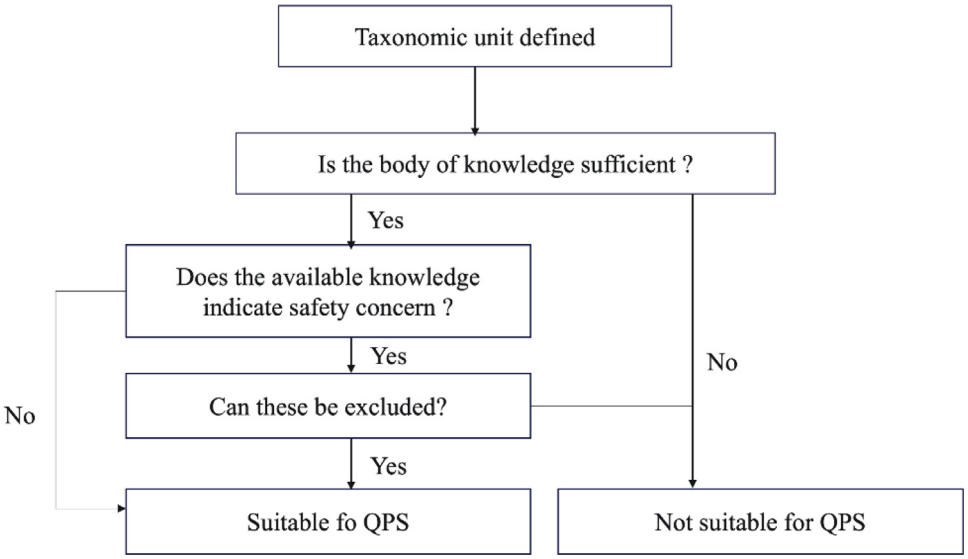

Fig. 7. Qualified Presumption of Safety (QPS) for safety assessment test.

National Food Safety Standard of the Chinese Government. The Chinese law clearly defines definitions for food claims such as the following:

a Conventional foods mark the presence of a specific ingredient in the label of regular foodstuffs. This states that probiotics fall under the scope of 'nutritional components' for this purpose.
b On the other hand, health foods aim to improve bodily functions but not to the extent of treating a disease. There are currently 28 health functions (i.e., enhance immunity, increase bone density) that can be claimed as healthy foods. There is no limit on which health function to use in prebiotic and probiotic foods; however, functions like 'enhance immunity' and 'regulate gastrointestinal flora can be used for probiotic foods. Foods that contain probiotics and aiming to be healthy food require a pre-market registration and takes 18–24 months to be completed.

Similarly, Brazil imposed a regulation in 2018 for both probiotics and prebiotics to assure consumers' safety in taking in the products and ensure that the claims should have scientific proof. Pre-authorization of claims and application with claims must register with Agência Nacional de Vigilância Sanitária (ANVISA), known as Brazil National Health Surveillance Agency through an online petitioning system that is the same with every other food processed. Proposed claims regarding probiotic substances require information including the character of microorganism, the antimicrobial resistance profile, determination of hemolytic activity and potential, proofs of potential adverse effect, efficacy, and viability.

Association of Southeast Asian Nations (ASEAN) is no exception to the growing demands of probiotics in the market. More and more probiotic-based foods and beverages are being introduced into the region to meet this demand surge. The region consists of 10 countries with over 650 million population making it the third-largest market globally. All countries in the region have standards or regulations related to probiotics except Cambodia, Lao PDR, Myanmar, and Vietnam. The rest of the countries in the region have followed EFSA based model for the approval of safety and regulatory claims related to probiotic-based foods and beverages (Poon, 2018).

In Australia and New Zealand, the requirements for making a general level health claim in probiotic-based foods and beverages are based on the FSANZ (FOOD Standards Australia New Zealand) Food Standards Code.

Probiotics are considered natural health products and Canadian Food and Drugs approve packaging acts, specifically under Natural Health Products Regulations.

7. Conclusion and future perspectives

Growing health concerns and subsequent shift towards functional foods have expanded the horizon for probiotic-based foods and beverages. At a time when the world is gripped with COVID-19 pandemic, dietary interventions through the ingestion of these future foods are considered effective nutritional therapy considering that we do not have a cure or treatment to the SARS-CoV-2 as of yet. This has led to more research and innovations on the traditional and next-generation probiotics for food products. The nearest future may also see the emergence of more food application of probiotics. With this looming horizon of probiotics as future foods, safety must be considered. The basic idea behind the application of probiotics in food for ages has been "do more good than harm," however, the emergence of some safety issues alongside a growing number of novel strains accounts for its safety evaluation. The major safety considerations are that the strains shall be of human origin and isolated from the human GI tract, the absence of pathogenicity and virulence factors, should not promote any disease-related activities and should not consist of any transferrable antibiotic resistance genes. Apart from safety, the regulatory framework is also necessary at the same time in order to protect the consumer from false and misleading claims while at the same time harmonizing the trade market. Each country and region has different sets of legislation, policies and government guidance documents as the clinical evidence and human trials are very hard to get approved. The standards, policy, and regulations improve with time continuously, but the expeditiously growing market of probiotic-based foods and beverages require more intensive efforts to assure consumers' safety.

Author contributions

Sushil Koirala has drafted this manuscript with input and supervision of Prof. Anil Kumar Anal.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Adams, M., Marteau, P., 1995. On the safety of lactic acid bacteria from food. Int. J. Food Microbiol. 27 (2–3), 263. doi:10.1016/0168-1605(95)00067-T.

Akbar, A., Sadiq, M.B., Ali, I., Anwar, M., Muhammad, N., Muhammad, J., Shafee, M., Ullah, S., Gul, Z., Qasim, S., 2019. Lactococcus lactis subsp. lactis isolated from fermented milk products and its antimicrobial potential. CyTA J. Food 17 (1), 214–220. doi:10.1080/19476337.2019.1575474.

Amagase, H., 2008. Current marketplace for probiotics: a Japanese perspective. Clin. Inf. Dis. 46 (Supplement_2), S73–S75. doi:10.1086/523338.

Aman, F., Masood, S., 2020. How nutrition can help to fight against COVID-19 pandemic. Pak. J. Med Sci. 36 (COVID19–S4). doi:10.12669/pjms.36.COVID19-S4.2776.

Anal, A.K., 2019. Quality ingredients and safety concerns for traditional fermented foods and beverages from Asia: a review. Fermentation 5 (1), 8. doi:10.3390/fermentation5010008.

Anal, A.K., Singh, H., 2007. Recent advances in microencapsulation of probiotics for industrial applications and targeted delivery. Trends Food Sci. Technol. 18 (5), 240–251. doi:10.1016/j.tifs.2007.01.004.

Annunziata, A., Vecchio, R., 2013. Consumer perception of functional foods: a conjoint analysis with probiotics. Food Qual. Prefer. 28 (1), 348–355. doi:10.1016/j.foodqual.2012.10.009.

Araújo, E.A., dos Santos Pires, A.C., Pinto, M.S., Jan, G., Carvalho, A.F., 2012. Probiotics in dairy fermented products. In: Rigobelo, E.C. (Ed.), Probiotics. Rennes: CC, United Kingdom, pp. 129–148. doi:10.5772/51939.

Arora, M., Baldi, A., 2015. Regulatory categories of probiotics across the globe: a review representing existing and recommended categorization. Indian J. Med. Microbiol. 33 (5), 2. doi:10.4103/0255-0857.150868.

Arora, M., Baldi, A., 2017. Comparative study of regulatory framework for probiotics: current status and future recommendations. Appl. Clin. Res. Clin. Trials Regul. Aff. 4 (2), 140–156. doi:10.2174/2213476X04666170620100145.

Ashaolu, T.J., 2020. Immune boosting functional foods and their mechanisms: a critical evaluation of probiotics and prebiotics. Biomed. Pharmacother. 130, 110625. doi:10.1016/j.biopha.2020.110625.

Ayyash, M., Olaimat, A., Al-Nabulsi, A., Liu, S.-.Q., 2020. Bioactive properties of novel probiotic lactococcus lactis fermented camel sausages: cytotoxicity, angiotensin converting enzyme inhibition, antioxidant capacity, and antidiabetic activity. Food Sci. Anim Resour. 40 (2), 155. doi:10.5851/kosfa.2020.e1.

Bagchi, T., 2014. Traditional food & modern lifestyle: impact of probiotics. Indian J. Med Res. 140 (3), 333. Retrieved from: https://www.ijmr.org.in/text.asp?2014/140/3/333/143764 .

Baud, D., Agri, V.D., Gibson, G.R., Reid, G., Giannoni, E., 2020. Using probiotics to flatten the curve of coronavirus disease COVID-2019 pandemic. Front. Public Health 8. doi:10.3389/fpubh.2020.00186.

Bernardeau, M., Guguen, M., Vernoux, J.P., 2006. Beneficial lactobacilli in food and feed: long-term use, biodiversity and proposals for specific and realistic safety assessments. FEMS Microbiol. Rev. 30 (4), 487–513. doi:10.1111/j.1574-6976.2006.00020.x.

Bhaskar, S., Sinha, A., Banach, M., Mittoo, S., Weissert, R., Kass, J.S., Rajagopal, S., Pai, A.R., Kutty, S., 2020. Cytokine storm in COVID-19—Immunopathological mechanisms, clinical considerations, and therapeutic approaches: the REPROGRAM consortium position paper. Front. Immun. 11, 1648. doi:10.3389/fimmu.2020.01648.

Bian, X., Muhammad, Z., Evivie, S.E., Luo, G.-.W., Xu, M., Huo, G.-.C., 2016. Screening of antifungal potentials of Lactobacillus helveticus KLDS 1.8701 against spoilage microorganism and their effects on physicochemical properties and shelf life of fermented soybean milk during preservation. Food Control 66, 183–189. doi:10.1016/j.foodcont.2016.02.004.

Binnewies, T.T., Motro, Y., Hallin, P.F., Lund, O., Dunn, D., La, T., Hampson, D.J., Bellgard, M., Wassenaar, T.M., Ussery, D.W., 2006. Ten years of bacterial genome sequencing: comparative-genomics-based discoveries. Funct. Integr. Genom. 6 (3), 165–185. doi:10.1007/s10142-006-0027-2.

Blair, J.M., Webber, M.A., Baylay, A.J., Ogbolu, D.O., Piddock, L.J., 2015. Molecular mechanisms of antibiotic resistance. Nat Rev Microbiol. 13 (1), 42–51. doi:10.1038/nrmicro3380.

Cannon, J., Lee, T., Bolanos, J., Danziger, L., 2005. Pathogenic relevance of Lactobacillus: a retrospective review of over 200 cases. Eur. J. Clin Microbiol. Infect Dis. 24 (1), 31–40. doi:10.1007/s10096-004-1253-y.

Casarotti, S.N., Carneiro, B.M., Todorov, S.D., Nero, L.A., Rahal, P., Penna, A.L.B., 2017. In vitro assessment of safety and probiotic potential characteristics of Lactobacillus strains isolated from water buffalo mozzarella cheese. Ann. Microbiol. 67 (4), 289–301. doi:10.1007/s13213-017-1258-2.

Cencic, A., Chingwaru, W., 2010. The role of functional foods, nutraceuticals, and food supplements in intestinal health. Nutrients 2 (6), 611–625. doi:10.3390/nu2060611.

Childs, C.E., Calder, P.C., Miles, E.A., 2019. Diet and immune function. Nutrients 11 (8), 1933. doi:10.3390/nu11081933.

Clua, P., Kanmani, P., Zelaya, H., Tada, A., Kober, A., Salva, S., Alvarez, S., Kitazawa, H., Villena, J., 2017. Peptidoglycan from immunobiotic Lactobacillus rhamnosus improves resistance of infant mice to respiratory syncytial viral infection and secondary pneumococcal pneumonia. Front. Immunol. 8, 948. doi:10.3389/fimmu.2017.00948.

Corbo, M.R., Bevilacqua, A., Petruzzi, L., Casanova, F.P., Sinigaglia, M., 2014. Functional beverages: the emerging side of functional foods: commercial trends, research, and health implications. Compr Rev. Food Sci. Food Saf. 13 (6), 1192–1206. doi:10.1111/1541-4337.12109.

Cordeiro, M., Souza, E., Arantes, R., Balthazar, C., Guimarães, J., Scudino, H., Silva, H., Rocha, R., Freitas, M., Esmerino, E., 2019. Fermented whey dairy beverage offers protection against Salmonella enterica ssp. enterica serovar Typhimurium infection in mice. J. Dairy Sci. 102 (8), 6756–6765. doi:10.3168/jds.2019-16340.

D'Costa, V.M., King, C.E., Kalan, L., Morar, M., Sung, W.W., Schwarz, C., Froese, D., Zazula, G., Calmels, F., Debruyne, R., 2011. Antibiotic resistance is ancient. Nature 477 (7365), 457–461. doi:10.1038/nature10388.

Silva, Da, A., L., Neto, J.H.P.L., Cardarelli, H.R., 2019. Safety and probiotic functionality of isolated goat milk lactic acid bacteria. Ann. Microbiol. 69 (13), 1497–1505. doi:10.1007/s13213-019-01533-z.

de Simone, C., 2019. The unregulated probiotic market. Clin. Gastroenterol. Hepatol. 17 (5), 809–817. doi:10.1016/j.cgh.2018.01.018.

de Vrese, M., Winkler, P., Rautenberg, P., Harder, T., Noah, C., Laue, C., Ott, S., Hampe, J., Schreiber, S., Heller, K., 2005. Effect of Lactobacillus gasseri PA 16/8, Bifidobacterium longum SP 07/3, B. bifidum MF 20/5 on common cold episodes: a double blind, randomized, controlled trial. Clin Nutr. 24 (4), 481–491. doi:10.1016/j.clnu.2005.02.006.

Degnan, F.H., 2008. The US food and drug administration and probiotics: regulatory categorization. Clin. Infect. Dis. 46 (Supplement_2), S133–S136. doi:10.1086/523324.

Degnan, F.H., 2012. Clinical studies involving probiotics: when FDA's investigational new drug rubric applies—and when it may not. Gut Microbes 3 (6), 485–489. doi:10.4161/gmic.22158.

European Food Safety Authority (EFSA), 2005. Qualified presumption of safety of micro-organisms in food and feed (9291990124). EFSA J. 5 (12), 587. doi:10.2903/j.efsa.2007.587.

Erdoğan, Ö., Tanyeri, B., Torun, E., Gönüllü, E., Arslan, H., Erenberk, U., Öktem, F., 2012. The comparition of the efficacy of two different probiotics in rotavirus gastroenteritis in children. J. Trop Med doi:10.1155/2012/787240.

FAO/WHO, 2002. Guidelines for the Evaluation of Probiotics in Food. Report of a Joint FAO/WHO Working Group on Drafting Guidelines for the Evaluation of Probiotics in Food https://www.who.int/foodsafety/fs_management/en/probiotic_guidelines.pdf/.

Thai Food and Drug Administration (Thai FDA), 2011. Re: Use of Probiotic Microorganisms in Foods. Ministry of Public Health http://food.fda.moph.go.th/law/data/announ_moph/V.English/No.%20339%20Use%20of%20Probiotic%20Microorganisms%20in%20Foods.pdf/.

United States Food and Drug Administration (FDA), Development & approval process of drugs. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/ (Accessed 6 September 2020)

United States Food and Drug Administration (FDA), Federal food, drug, and cosmetic act. http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcact/default.htm/ (Accessed 10 October 2020).

Franz, C.M., Stiles, M.E., Schleifer, K.H., Holzapfel, W.H., 2003. Enterococci in foods—a conundrum for food safety. Int J. Food Microbiol. 88 (2–3), 105–122. doi:10.1016/S0168-1605(03)00174-0.

Frietas, D., Nutraceuticals in Latin America: Brazil and beyond at Latin America: nutraceutical boom or bust? https://www.nutraceuticalsworld.com/issues/2006-07/view_features/nutraceuticals-in-latin-america-brazil-and-beyond/ (Accessed 11 October 2020).

Galdeano, C.M., Cazorla, S.I., Dumit, J.M.L., Vélez, E., Perdigón, G., 2019. Beneficial effects of probiotic consumption on the immune system. Ann. Nutr. Metab. 74 (2), 115–124. doi:10.1159/000496426.

Gasmi, A., Noor, S., Tippairote, T., Dadar, M., Menzel, A., Bjørklund, G., 2020. Individual risk management strategy and potential therapeutic options for the COVID-19 pandemic. Clin Immunol. 108409. doi:10.1016/j.clim.2020.108409.

Gasser, F., 1994. Safety of lactic acid bacteria and their occurrence in human clinical infections. Bull. Inst. Pasteur. 92 (1), 45–67.

Gibney, M.J., Forde, C.G., Mullally, D., Gibney, E.R., 2017. Ultra-processed foods in human health: a critical appraisal. Am J. Clin Nutr. 106 (3), 717–724. doi:10.3945/ajcn.117.160440.

Gleeson, M., Bishop, N.C., Struszczak, L., 2016. Effects of Lactobacillus casei Shirota ingestion on common cold infection and herpes virus antibodies in endurance athletes: a placebo-controlled, randomized trial. Eur. J. Appl. Physiol. 116 (8), 1555–1563. doi:10.1007/s00421-016-3415-x.

Granato, D., Barba, F.J., Bursać Kovačević, D., Lorenzo, J.M., Cruz, A.G., Putnik, P., 2020. Functional foods: product development, technological trends, efficacy testing, and safety. Annu. Rev. Food Sci. Technol. 11, 93–118. doi:10.1146/annurev–food-032519-051708.

Gueimonde, M., Sánchez, B., de los Reyes-Gavilán, C.G., Margolles, A., 2013. Antibiotic resistance in probiotic bacteria. Front. Microbiol. 4, 202. doi:10.3389/fmicb.2013.00202.

Guimarães, J.T., Balthazar, C.F., Silva, R., Rocha, R.S., Graça, J.S., Esmerino, E.A., Silva, M.C., Sant'Ana, A.S., Duarte, M.C.K., Freitas, M.Q., 2020. Impact of probiotics and prebiotics on food texture. Curr. Opin. Food Sci. 33, 38–44. doi:10.1016/j.cofs.2019.12.002.

Gupta, R.C., 2016. Nutraceuticals: Efficacy, Safety and Toxicity, First ed. Academic Press, United States.

Han, M.K., McLaughlin, V.V., Criner, G.J., Martinez, F.J., 2007. Pulmonary diseases and the heart. Circulation 116 (25), 2992–3005. doi:10.1161/circulationaha.106.685206.

Hao, Q., Dong, B.R., Wu, T., 2015. Probiotics for preventing acute upper respiratory tract infections. Cochrane Database. Syst. Rev. 3 (2). doi:10.1002/14651858.CD006895.pub3.

Herman, L., Chemaly, M., Cocconcelli, P.S., Fernandez, P., Klein, G., Peixe, L., Prieto, M., Querol, A., Suarez, J.E., Sundh, I., 2019. The qualified presumption of safety assessment and its role in EFSA risk evaluations: 15 years past. FEMS Microbiol. Lett. 366 (Supplement_1), i17–i23. doi:10.1093/femsle/fny260.

Hill, C., Guarner, F., Reid, G., Gibson, G.R., Merenstein, D.J., Pot, B., Morelli, L., Canani, R.B., Flint, H.J., Salminen, S., 2014. Expert consensus document: the International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat. Rev. Gastroenterol. Hepatol. 11 (8), 506. doi:10.1038/nrgastro.2014.66.

Hirose, Y., Murosaki, S., Yamamoto, Y., Yoshikai, Y., Tsuru, T., 2006. Daily intake of heat-killed Lactobacillus plantarum L-137 augments acquired immunity in healthy adults. J. Nutr. 136 (12), 3069–3073. doi:10.1093/jn/136.12.3069.

Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., 2020. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395, 497–506. doi:10.1016/S0140-6736(20)30183-5.

Fortune Business Insights, 2020. Probiotics Market Size, Share and Industry Analysis by Microbial Genus (Lactobacillus, Bifidobacterium, Yeast), by Application (Functional Food and Beverage, Dietary Supplement, Animal Feed), by Distribution Channel (Supermarkets/Hypermarkets, Pharmacies/Health Stores, Convenience Stores, Online Retail), and Regional Forecast 2018-2025. Fortune Business Insights https://www.fortunebusinessinsights.com/industry-reports/infographics/probiotics-market-100083/.

Government of Japan, Overview of FOSHU. https://www.caa.go.jp/policies/policy/food_labeling/health_promotion/pdf/food_labeling_cms206_200122_04.pdf/ (Accessed 1 September 2020).

Government of Japan, Food labelling and probiotic health claims. https://www.caa.go.jp/policies/policy/food_labeling/health_promotion/pdf/health_promotion_170606_0001.pdf/ (Accessed 1 September 2020).

James, P.T., Ali, Z., Armitage, A.E., Bonell, A., Cerami, C., Drakesmith, H., Jobe, M., Jones, K.S., Liew, Z., Moore, S.E., 2020. Could nutrition modulate COVID-19 susceptibility and severity of disease? A systematic review. medRxiv doi:10.1101/2020.10.19.20214395.

Kalhoro, M.S., Visessanguan, W., Nguyen, L.T., Anal, A.K., 2019. Probiotic potential of Lactobacillus paraplantarum BT-11 isolated from raw buffalo (Bubalus bubalis) milk and characterization of bacteriocin-like inhibitory substance produced. J. Food Process. Preserv. 43 (8), e14015. doi:10.1111/jfpp.14015.

Kalicka, D., Znamirowska, A., Pawlos, M., Buniowska, M., Szajnar, K., 2019. Physical and sensory characteristics and probiotic survival in ice cream sweetened with various polyols. Int. J. Dairy Technol. 72 (3), 456–465. doi:10.1111/1471-0307.12605.

Kanauchi, O., Andoh, A., AbuBakar, S., Yamamoto, N., 2018. Probiotics and paraprobiotics in viral infection: clinical application and effects on the innate and acquired immune systems. Curr. Pharm. Des. 24 (6), 710–717. doi:10.2174/1381612824666180116163411.

Katan, M., 2012. Why the European food safety authority was right to reject health claims for probiotics. Benef. Microbes 3 (2), 85–89. doi:10.3920/BM2012.0008.

Khaneghah, A.M., Abhari, K., Eş, I., Soares, M.B., Oliveira, R.B., Hosseini, H., Rezaei, M., Balthazar, C.F., Silva, R., Cruz, A.G., 2020. Interactions between probiotics and pathogenic microorganisms in hosts and foods: a review. Trends Food Sci. Technol. 95, 205–218. doi:10.1016/j.tifs.2019.11.022.

Kumaree, K.K., Akbar, A., Anal, A.K., 2015. Bioencapsulation and application of Lactobacillus plantarum isolated from catfish gut as an antimicrobial agent and additive in fish feed pellets. Ann. Microbiol. 65 (3), 1439–1445. doi:10.1007/s13213-014-0982-0.

Kumpu, M., Kekkonen, R., Korpela, R., Tynkkynen, S., Järvenpää, S., Kautiainen, H., Allen, E., Hendley, J., Pitkäranta, A., Winther, B., 2015. Effect of live and inactivated Lactobacillus rhamnosus GG on experimentally induced rhinovirus colds: randomised, double blind, placebo-controlled pilot trial. Benef. Microbes 6 (5), 631–639. doi:10.3920/BM2014.0164.

Leuschner, R.G., Robinson, T.P., Hugas, M., Cocconcelli, P.S., Richard-Forget, F., Klein, G., Licht, T.R., Nguyen-The, C., Querol, A., Richardson, M., 2010. Qualified presumption of safety (QPS): a generic risk assessment approach for biological agents notified to the European food safety authority (EFSA). Trends Food Sci. Technol. 21 (9), 425–435. doi:10.1016/j.tifs.2010.07.003.

Lewis, Z.T., Shani, G., Masarweh, C.F., Popovic, M., Frese, S.A., Sela, D.A., Underwood, M.A., Mills, D.A., 2016. Validating bifidobacterial species and subspecies identity in commercial probiotic products. Pediatr. Res. 79 (3), 445–452. doi:10.1038/pr.2015.244.

Linares, D.M., Gomez, C., Renes, E., Fresno, J.M., Tornadijo, M.E., Ross, R.P., Stanton, C., 2017. Lactic acid bacteria and bifidobacteria with potential to design natural biofunctional health-promoting dairy foods. Front. Microbiol. 8, 846. doi:10.3389/fmicb.2017.00846.

Makino, S., Ikegami, S., Kume, A., Horiuchi, H., Sasaki, H., Orii, N., 2010. Reducing the risk of infection in the elderly by dietary intake of yoghurt fermented with Lactobacillus delbrueckii ssp. bulgaricus OLL1073R-1. Br J. Nutr. 104 (7), 998–1006. doi:10.1017/S000711451000173X.

Marteau, P.R., 2002. Probiotics in clinical conditions. Clin. Rev. Allergy. Immunol. 22 (3), 255–273. doi:10.1007/s12016-002-0011-0.

Maughan, R.J., King, D.S., Lea, T., 2004. Dietary supplements. J. Sports Sci. 22 (1), 95–113. doi:10.1080/0264041031000140581.

Melchor, S.R., Skoblikov, L., Schütte, B.Urazbaeva, A., Szajkowska, A., Wernaart, B., Franssens, N.T., Vaskoska, R.S. (Eds.), 2019. The regulatory framework for the use of probiotics claims in food and food supplements around the world: a comparative analysis. The Functional Field of Food Law: Reconciling the Market and Human Rights 155–169. doi:10.3920/978-90-8686-885-8_10.

Merenstein, D., Murphy, M., Fokar, A., Hernandez, R.K., Park, H., Nsouli, H., Sanders, M.E., Davis, B.A., Niborski, V., Tondu, F., 2010. Use of a fermented dairy probiotic drink containing Lactobacillus casei (DN-114 001) to decrease the rate of illness in kids: the DRINK study A patient-oriented, double-blind, cluster-randomized, placebo-controlled, clinical trial. Eur J. Clin Nutr. 64 (7), 669–677. doi:10.1038/ejcn.2010.65.

Miremadi, F., Ayyash, M., Sherkat, F., Stojanovska, L., 2014. Cholesterol reduction mechanisms and fatty acid composition of cellular membranes of probiotic Lactobacilli and Bifidobacteria. J. Funct Foods 9, 295–305. doi:10.1016/j.jff.2014.05.002.

Monteiro, C.A., Moubarac, J.C., Cannon, G., Ng, S.W., Popkin, B., 2013. Ultra-processed products are becoming dominant in the global food system. Obes. Rev. 14, 21–28. doi:10.1111/obr.12107.

Morais, A.H., Passos, T.S., Maciel, B.L., da Silva-Maia, J.K., 2020. Can Probiotics and diet promote beneficial immune modulation and purine control in coronavirus infection? Nutrients 12 (6), 1737. doi:10.3390/nu12061737.

Munita, J.M., Arias, C.A., 2016. Mechanisms of antibiotic resistance. Microbiol. Spectr. VMBF 4 (2), 481–511. doi:10.1128/microbiolspec.VMBF-0016-2015.

Nagata, J., Yamada, K., 2008. Foods with health claims in Japan. Food Sci. Technol. Res. 14 (6), 519. doi:10.3136/fstr.14.519.

Noomhorm, A., Ahmad, I., Anal, A.K., 2014. Functional Foods and Dietary Supplements: Processing Effects and Health Benefits, First ed. John Wiley & Sons, United States.

Oak, S.J., Jha, R., 2019. The effects of probiotics in lactose intolerance: a systematic review. Crit Rev. Food Sci. Nutr. 59 (11), 1675–1683. doi:10.1080/10408398.2018.1425977.

Peivasteh-Roudsari, L., Pirhadi, M., Karami, H., Tajdar-oranj, B., Molaee-Aghaee, E., Sadighara, P., 2019. Probiotics and food safety: an evidence-based review. J. Food Hyg. Saf. 5 (1), 50. doi:10.18502/jfsh.v5i1.3878.

Pieniz, S., de Moura, T.M., Cassenego, A.P.V., Andreazza, R., Frazzon, A.P.G., de Oliveira Camargo, F.A., Brandelli, A., 2015. Evaluation of resistance genes and virulence factors in a food isolated Enterococcus durans with potential probiotic effect. Food Control 51, 49–54. doi:10.1016/j.foodcont.2014.11.012.

Pino, A., de angelis, M., chieppa, M., caggia, C., randazzo, C., 2020. Gut microbiota, probiotics and colorectal cancer: a tight relation. World J. Cancer Res. e1456. doi:10.32113/wcrj_20201_1456.

Plaza-Diaz, J., Muñoz-Quezada, S., Gomez-Llorente, C., Gil, A., 2012. Probiotic mechanisms of action. Ann. Nutr Metab. 61, 160–174. doi:10.1159/000342079.

Poon, W.M., Understanding today's probiotics regulations in South East Asia. https://www.probiotaasia.com/wp-content/uploads/2018/10/Wai-Mun-Poon.pdf/ (Accessed 8 December 2020).

Reid, G., 2015. The growth potential for dairy probiotics. Int. Dair. J. 49, 16–22. doi:10.1016/j.idairyj.2015.04.004.

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. doi:10.1007/s11906-017-0723-4.

Roobab, U., Batool, Z., Manzoor, M.F., Shabbir, M.A., Khan, M.R., Aadil, R.M., 2020. Sources, formulations, advanced delivery and health benefits of probiotics. Curr. Opin. Food Sci. 32, 17–28. doi:10.1016/j.cofs.2020.01.003.

Saarela, M., Mogensen, G., Fonden, R., Mättö, J., Mattila-Sandholm, T., 2000. Probiotic bacteria: safety, functional and technological properties. J. Biotechnol. 84 (3), 197–215. doi:10.1016/S0168-1656(00)00375-8.

Saarela, M.H., 2019. Safety aspects of next generation probiotics. Curr. Opin. Food Sci. 30, 8–13. doi:10.1016/j.cofs.2018.09.001.

Salminen, S., von Wright, A., Morelli, L., Marteau, P., Brassart, D., de Vos, W.M., Fondén, R., Saxelin, M., Collins, K., Mogensen, G., 1998. Demonstration of safety of probiotics—a review. Int. J. Food Microbiol. 44 (1–2), 93–106. doi:10.1016/S0168-1605(98)00128-7.

Sanders, M.E., Tompkins, T., Heimbach, J.T., Kolida, S., 2005. Weight of evidence needed to substantiate a health effect for probiotics and prebiotics. Eur J. Nutr. 44 (5), 303–310. doi:10.1007/s00394-004-0527-6.

Saxelin, M., 2008. Probiotic formulations and applications, the current probiotics market, and changes in the marketplace: a European perspective. Clin. Infect. Dis. 46 (Supplement_2), S76–S79. doi:10.1086/523337.

Saxelin, M., Chuang, N.-.H., Chassy, B., Rautelin, H., Mäkelä, P.H., Salminen, S., Gorbach, S.L., 1996. Lactobacilli and bacteremia in southern Finland, 1989–1992. Clin. Infect. Dis. 22 (3), 564–566. doi:10.1093/clinids/22.3.564.

Shafi, A., Naeem Raja, H., Farooq, U., Akram, K., Hayat, Z., Naz, A., Nadeem, H.R., 2019. Antimicrobial and antidiabetic potential of synbiotic fermented milk: a functional dairy product. Int. J. Dairy Technol. 72 (1), 15–22. doi:10.1111/1471-0307.12555.

Shane, A.L., Cabana, M.D., Ellis, C.L., Heimbach, J.T., Hempel, S., Hummelen, R., Lynch, S., Merenstein, D.J., Sanders, M.E., Tancredi, D.J., 2010. Guide to designing, conducting, publishing, and communicating results of clinical studies involving probiotic applications in human participants. Gut Microbes 1 (4), 243–253. doi:10.4161/gmic.1.4.12707.

Sharma, S., Arora, M., Baldi, A., 2013. Probiotics in India: current status and future prospects. Pharm. Aspire 1, 1–12.

Shi, H.N., Walker, A., 2004. Bacterial colonization and the development of intestinal defences. Can J. Gastroenter. 18, 690421. doi:10.1155/2004/690421.

Shi, L.H., Balakrishnan, K., Thiagarajah, K., Ismail, N.I.M., Yin, O.S., 2016. Beneficial properties of probiotics. Trop. Life Sci. Res. 27 (2), 73. doi:10.21315/tlsr2016.27.2.6.

Shida, K., Sato, T., Iizuka, R., Hoshi, R., Watanabe, O., Igarashi, T., Miyazaki, K., Nanno, M., Ishikawa, F., 2017. Daily intake of fermented milk with Lactobacillus casei strain Shirota reduces the incidence and duration of upper respiratory tract infections in healthy middle-aged office workers. Eur. J. Nutr. 56 (1), 45–53. doi:10.1007/s00394-015-1056-1.

Sindhu, K.N., Sowmyanarayanan, T.V., Paul, A., Babji, S., Ajjampur, S.S., Priyadarshini, S., Sarkar, R., Balasubramanian, K., Wanke, C.A., Ward, H.D., 2014. Immune response and intestinal permeability in children with acute gastroenteritis treated with Lactobacillus rhamnosus GG: a randomized, double-blind, placebo-controlled trial. Clin. Infect. Dis. 58 (8), 1107–1115. doi:10.1093/cid/ciu065.

Soccol, C.R., Vandenberghe, L.P.d.S., Spier, M.R., Medeiros, A.B.P., Yamaguishi, C.T., Lindner, J.D.D., Pandey, A., Thomaz-Soccol, V., 2010. The potential of probiotics: a review. Food Technol. Biotechnol. 48 (4), 413–434.

Sonnenburg, E.D., Sonnenburg, J.L., 2019. The ancestral and industrialized gut microbiota and implications for human health. Nat. Rev. Microbiol. 17 (6), 383–390. doi:10.1038/s41579-019-0191-8.

Stanton, C., Gardiner, G., Meehan, H., Collins, K., Fitzgerald, G., Lynch, P.B., Ross, R.P., 2001. Market potential for probiotics. Am. J. Clin. Nutr. 73 (2), 476s–483s. doi:10.1093/ajcn/73.2.476s.

Stanton, E., Emms, S., 2011. Malaysia's markets for functional foods, nutraceuticals and organic foods: an introduction for Canadian producers and exporters. The counsellor and regional agri-food trade commissioner, Southeast Asia, and the high commission of Canada in Malaysia.

Temmerman, R., Pot, B., Huys, G., Swings, J., 2003. Identification and antibiotic susceptibility of bacterial isolates from probiotic products. Int. J. Food Microbiol. 81 (1), 1–10. doi:10.1016/S0168-1605(02)00162-9.

Thapa, S.P., Shrestha, S., Anal, A.K., 2020. Addressing the antibiotic resistance and improving the food safety in food supply chain (farm-to-fork) in Southeast Asia. Food Control 108, 106809. doi:10.1016/j.foodcont.2019.106809.

Tomar, O., 2019. The effects of probiotic cultures on the organic acid content, texture profile and sensory attributes of Tulum cheese. Int. J. Dairy Technol. 72 (2), 218–228. doi:10.1111/1471-0307.12574.

van Loveren, H., Sanz, Y., Salminen, S., 2012. Health claims in Europe: probiotics and prebiotics as case examples. Annu. Rev. Food Sci. Technol. 3, 247–261. doi:10.1146/annurev-food-022811-101206.

Vanderhoof, J.A., Young, R., 2008. Probiotics in the United States. Clin. Inf. Dis. 46 (Supplement_2), S67–S72. doi:10.1086/523339.

Venugopalan, V., Shriner, K.A., Wong-Beringer, A., 2010. Regulatory oversight and safety of probiotic use. Emerg. Infect. Dis. 16 (11), 1661. doi:10.3201/eid1611.100574.

Vinolo, M.A., Rodrigues, H.G., Nachbar, R.T., Curi, R., 2011. Regulation of inflammation by short chain fatty acids. Nutrients 3 (10), 858–876. doi:10.3390/nu3100858.

Wan, M.L.Y., Forsythe, S.J., El-Nezami, H., 2019. Probiotics interaction with foodborne pathogens: a potential alternative to antibiotics and future challenges. Crit. Rev. Food Sci. Nutr. 59 (20), 3320–3333. doi:10.1080/10408398.2018.1490885.

Wassenaar, T., Zschüttig, A., Beimfohr, C., Geske, T., Auerbach, C., Cook, H., Zimmermann, K., Gunzer, F., 2015. Virulence genes in a probiotic E. coli product with a recorded long history of safe use. Eur. J. Microbiol. Immunol Bp 5 (1), 81–93. doi:10.1556/eujmi-d-14-00039.

Wassenaar, T.M., Blaser, M.J., 1999. Pathophysiology of campylobacter jejuni infections of humans. Microbes Infect. 1 (12), 1023–1033. doi:10.1016/S1286-4579(99)80520-6.

Wassenaar, T.M., Klein, G., 2008. Safety aspects and implications of regulation of probiotic bacteria in food and food supplements. J. Food Prot. 71 (8), 1734–1741. doi:10.4315/0362-028X-71.8.1734.

West, N.P., Pyne, D.B., Cripps, A.W., Hopkins, W.G., Eskesen, D.C., Jairath, A., Christophersen, C.T., Conlon, M.A., Fricker, P.A., 2011. Lactobacillus fermentum (PCC®) supplementation and gastrointestinal and respiratory-tract illness symptoms: a randomised control trial in athletes. Nutr. J. 10 (1), 30. doi:10.1186/1475-2891-10-30.

Winkler, P., De Vrese, M., Laue, C., Schrezenmeir, J., 2005. Effect of a dietary supplement containing probiotic bacteria plus vitamins and minerals on common cold infections and cellular immune parameters. Int. J. Clin. Pharmacol. Ther. 43 (7). doi:10.5414/CPP43318.

WHO, 2015. WHO's First Ever Global Estimates of Foodborne Diseases Find Children Under 5 Account for Almost One Third of Deaths. News Release, Geneva, Switzerland https://www.who.int/news/item/03-12-2015-who-s-first-ever-global-estimates-of-foodborne-diseases-find-children-under-5-account-for-almost-one-third-of-deaths.

Xu, K., Cai, H., Shen, Y., Ni, Q., Chen, Y., Hu, S., Li, J., Wang, H., Yu, L., Huang, H., 2020. Management of corona virus disease-19 (COVID-19): the Zhejiang experience. Zhejiang Da Xue Xue Bao Yi Xue Ban 49 (1). doi:10.3785/j.issn.1008-9292.2020.02.02.

Yang, M.S., 2016. Regulatory aspects of nutraceuticals: Chinese perspective. In: Grumezescu, A. (Ed.), Nutraceuticals. Elsevier, New York, pp. 947–957.

Yilmaz-Ersan, L., Ozcan, T., Akpinar-Bayizit, A., 2020. Assessment of socio-demographic factors, health status and the knowledge on probiotic dairy products. Food Sci. Hum. Well doi:10.1016/j.fshw.2020.05.004.

Zhang, C.-x., Wang, H.-y., Chen, T.-x., 2019. Interactions between intestinal microflora/probiotics and the immune system. BioMed Res. Int. doi:10.1155/2019/6764919.

Zielińska, D., Sionek, B., Kołożyn-Krajewska, D., 2018. Safety of probiotics. In: Grumezescu, A., Holban, A.M. (Eds.), Diet, Microbiome and Health. Elsevier, New York, pp. 131–161.

Zucko, J., Starcevic, A., Diminic, J., Oros, D., Mortazavian, A.M., Putnik, P., 2020. Probiotic–friend or foe? Curr. Opin. Food Sci. 32, 45–49. doi:10.1016/j.cofs.2020.01.007.