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The Benefit Roles of Micro- and Macro-Algae in Probiotics

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Abstract: The present review deals with the probiotics and effect of micro- and macro-algae supplementation on fermented dairy products. Today the world's attention has drawn on the health advantages of using probiotics in human consumption. Probiotics are living bacteria and yeasts that are good for Human beings. Probiotics are fermented foods contain microorganisms which have beneficial impacts on the host. The utilization of probiotic microorganisms delivers a protective impact on the gut flora. Probiotics have beneficial concerns for microbial disorder of the gut. Some indication has come to light about the beneficial effects, either for the host or the gut microbiota, of some foods and food ingredients. The most promising seem to be polysaccharides or their derivatives, and they include the dietary fibers. The polysaccharides from marine micro- and macro-algae act as prebiotics. The prebiotics have the possibility of using to modulate the microbiome, and, consequently, prevent certain human diseases. If prebiotics combined with probiotics they will form what is termed as synbiotics. A synbiotic activates the growth and the metabolism of one or a limited number of health promoting bacteria. On the other side, algae are emerging as dietary supplements. Researcher thought about the combination of algae in fermented dairy products as medium. Their effort was to enhance the functionality of food quality with addition of algae into it. Algae are rich source of proteins, vitamins, minerals and used mainly as a health supplements. Algae contain plenty of gut-supporting nutrition and produce beneficial bacteria when it undergoes fermentation helps in digestion. Addition of algae enhanced the viability of probiotic bacteria, acidity of food, and storage quality. There was more viability during storage to deliver more probiotics to human at time of their consumption. In the future, the possibility of using algae to modulate the microbiome, and, consequently, prevent certain human diseases is expected.
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Introduction

The nutrition quality is essential for human health because of the cardiovascular diseases, food poisoning, obesity, allergy, and cancer, that is consider the disease of the twenty-first century. There are large number of probiotics now available in fermented dairy products like yoghurt, cheese, curd, and ice-cream. All these products contain diverse group of microorganisms belonging to lactic acid bacteria. Some of them are natural inhabitants of the intestinal tract and others as fermentative lactic acid bacteria used in the food industry for improving flavor, texture, processing, and preservative properties. Probiotic strains such as Lactobacillus, Streptococcus, Bifidobacterium, Lactococcus, and Saccharomyces have been endorsed in food products due to their supposed health benefits (Puupponen *et al*. 2002). The positive effect of the probiotics include inhibition of constipation in elderly people, preventing diarrhea, increasing the body's immunity (Schiffrin *et al*. 1995), lactose intolerance, reduction in cholesterol levels in blood and prevention of cancer (Lee *et al.* 2007) and side effects associated with cancer (Markowiak and Śliżewska 2017). Apart from these therapeutic benefits, probiotics also offer protection against many opportunistic human pathogens (Collado *et al.* 2006). Probiotic bacteria may reduce and improve mutagenic enzymes such as β-glucuronidase, nitroreductase, and choloylglycine hydrolase (Roos and Katan 2000). Majority of scientific reports also show the benefits of probiotics on gastrointestinal diseases, nonalcoholic fatty liver disease, obesity, insulin resistance syndrome, and type 2 diabetes (FAO 2002, Hill *et al.* 2014).

Prebiotic was described as a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria already resident in the colon, thus improving the host's health and wellbeing (Roberfroid 1993, Gibson and Roberfroid 1995). Food and Agriculture Organisation (FAO)/WHO describes prebiotics as a nonviable food component that deals health benefit (s) on the host associated with modulation of the microbiota (Pandey

et al. 2015). The prebiotic is a "selectively fermented conferring benefits upon host health" (Gibson *et al.* 2010). The presence of prebiotics in the diet may lead to inhibition of the development of pathogens, reducing the occurrence and duration of diarrhea, increases the absorption of minerals, inhibition of colon cancer and providing relief from symptoms associated with intestinal bowel disorders. Prebiotics can be used as a probiotics substitute or as a supplementary support for them. Prebiotics can be obtained naturally from sources like vegetables, fruits, and grains consumed in our daily life but are also artificially prebiotic products such as: lactulose, galactooligosaccharides, and fructooligosaccharides (Pokusaeva *et al*. 2010). Some oligo- and polysaccharides (PS), accepted as prebiotics, are part of algal PS. It is known that both micro- and macroalgae are rich sources of most of these compounds, some of them already demonstrated to possess prebiotic properties as well (Zhang *et al*. 2010).

The term "synbiotic" described union between probiotics and prebiotics synergistically acting of health (Gibson and Roberfroid 1995). Synbiotic is attributed to the products where a prebiotic compound selectively improves a probiotic microorganism (Cencic and Chingwaru 2010). The main aim of this type of combination is the improvement of probiotic microorganism's survival in the gastrointestinal tract. Therefore, synbiotic have both probiotic and prebiotic assets and were designed to solve the probiotics survival in the gastrointestinal tract (Rioux *et al.* 2005). A combination of both prebiotic and probiotic in a single product should assurance a greater effect, compared to the action of the probiotic or prebiotic alone (Bengmark 2005, Panesar *et al.* 2009). The introduction of probiotics, prebiotics, or synbiotics into human diet is favourable for the intestinal microbiota and the human health. They may be consumed in the form of dairy products, raw vegetables and fruit or fermented pickles.

Recently, a tendency has been started to add algal biomasses into fermented milks to increase the functional product characteristics via promoting viability of probiotics and to improve the nutritional characteristics (Varga *et al*. 2002). Algae contain high-quality proteins, abundant amino acids, unsaturated fatty acids, high-antioxidant components, minerals, and many types of vitamins. It co-addition of algae and probiotics encourages growth and increases viability and acid production of the probiotic bacteria (Webb 1982). Therefore, prebiotics from algae are an attractive alternative source for promoting the growth *of Lactobacillus* and *Bifidobacterium* spp. which are the widely studied probiotic strains of lactic acid bacteria. Algae and lactic acid bacteria gives new opportunity in the taste, color, flavors, texture and quality, some more fermented food and with addition of traditional fermented food in same cost.

1. Probiotics

The word "probiotic" means "for life" and is in use to name bacterial association with beneficial effects on human and animal health (Fioramonti *et al*. 2003). Markowiak and Sli˙zewska (2017) and (Kerry *et al*. 2018) described probiotics as microorganisms and substances stimulating the growth of other microorganisms which contribute to intestinal microbial balance. Probiotics contain live nonpathogenic bacteria that produce metabolites which impart these probiotics their health promoting properties. The beneficial effect of probiotic is exerted by the microorganisms when consumed in adequate amounts as part of food (Shyamala *et al.* 2016). Probiotics provide health benefits, act as food and nutritional supplements as well as biologics and pharmaceuticals.

Regular use of probiotics could improve the quality of life and decreases the dependence on drugs and medical costs **(**Yadav *et al*. 2015**).** Probiotics are usually consumed after the antibiotic therapy, which destroys the microbial flora present in the digestive tract. Probiotics may successfully inhibit the development of pathogenic bacteria, such as *Salmonella enteritidis* (Carter *et al*. 2017), *Staphylococcus* (Sikorska and Smoragiewicz 2013), *Clostridium perfringens* (Schoster *et al*. 2013), *Yersinia* (De Montijo-Prieto *et al*. 2015), *Escherichia coli* (Chingwaru *et al*. 2017), *Campylobacter jejuni* (Jimmy Saint-Cyr *et al.* 2017), and thus prevented food poisoning. A positive effect of probiotics on digestion processes, treatment of candidoses (Kumar *et al*. 2013), food allergies (Heczko *et al*. 2005, Thomas and Greer 2010), and dental caries (Nase *et al*. 2001) has been confirmed. Probiotic microorganisms are natural producers of vitamins B, enhance the absorption of vitamins and mineral compounds, stimulate the generation of organic acids and amino acids, and increase the efficiency of the immunological system (Sanders *et al.* 2007, Nova *et al*. 2007). Probiotic microorganisms may be able to produce enzymes, such as esterase, lipase, and co-enzymes A, Q, NAD, and NADP. Some products of probiotics' metabolism may also show antibioticanti-cancerogenic, and immunosuppressive properties (Ishikawa *et al.* 2005, Schellenberg *et al*. 2006).

1.1 Probiotic Microorganisms

Probiotic products may contain one or more selected microbial strains belong mostly to *Lactobacillus*, *Lactococcus*, *Streptococcus*, *Enterococcoccus*, *Pediococcus*, *Leuconostoc*, and *Bifidobacterium* (Shyamala *et al*. 2016). Moreover, strains of *Bacillus* and some yeast strains like

Saccharomyces boulardii are commonly used in probiotic products (Simon 2005). Lactic acid bacteria (LAB) are defined as a major group of probiotic bacteria. Members of the LAB are usually subdivided into two groups based on their carbohydrate metabolism (Vasiljevic and Shah 2008). The homo-fermentative group consisting of *Lactococcus*, *Pediococcus*, *Enterococcus*, *Streptococcus*, and some lactobacilli utilize the glycolytic pathway to transform a carbon source chiefly into lactic acid. Versus homo-fermenters, hetero-fermentative bacteria produce equimolar amounts of lactate, CO_2, ethanol, or acetate from glucose exploiting phosphoketolase pathway.

Lactic acid bacteria (LAB) are functional classification of Gram-positive, non-flagellated rods or coccobacilli, non-spore-forming, nonpathogenic, and nontoxigenic (Barbosa *et al.* 2005). They are preferring anaerobic conditions, but are aerotolerant, acid-tolerant, catalase-negative bacterial species, and strictly fermentative, producing lactic acid as main end product of carbohydrate fermentation (Penaloza-Vazquez 2016). LAB is affected by several factors such as bacterial interactions, pH, oxygen availability, presence of secretions, and level of specific substrates. In addition, they have the character of health promoters in the human gastrointestinal and genitourinary tracts (Coppi *et al*. 1985). The probiotics either a single strain or a mixture of two or more strains are added to foods, particularly fermented milk products. A single strain may display different benefits when used individually and in combination. The different bacterial strains of the same species are constantly unique, and may have specific effects on human health. Probiotic effects are very strain specific and cannot be generalized. Lactic acid fermentation is a process where lactic acid bacteria, mainly the *Lactobacillus* species, convert sugar into lactic acid, which acts as a preservative (Ayichew *et al*. 2017). Prior to refrigeration and pasteurization, fermentation allowed food to be stored and preserved for later use, preventing spoilage by the natural defenses of lactic acid producing bacteria (Amel *et al*. 2014).

Bifidobacteriumis a genus of lactic acid producing, Gram-positive, rod-shaped, non-motile, non-spore forming, a catalase-negative, and anaerobic bacteria. They are common constituents of the indigenous microbiota in the human intestinal tract (Jungersen *et al.* 2014]. Bifidobacteria are microorganisms of paramount importance in the intestinal tract of humans (Hammes and Vogel 1995). The bifidobacteria are established shortly after birth and their number decreases with increasing age of an individual (Mandel *et al.* 2010).

Lactobacilli and Bifidobacteria remain stable elements of the normal intestinal microbiota, maintaining their important functions throughout life, and their dysbiosis is associated with a plethora of pathological conditions (Gerritsen *et al*. 2011). Numerous studies with different strains of Lactobacillus and Bifidobacterium have been performed in vitro and in vivo, in humans and animal models to investigate their immunomodulatory properties and probiotic potential to treat various infectious, allergic and inflammatory conditions (Tojo *et al*. 2014).

Few non-bacterial microorganisms such as yeasts, the most common genus is *Saccharomyces*, are commercialized as probiotics (Holzapfel *et al*. 2001). The *Saccharomyces boulardii*, *S. cerevisiae*, and *S. cerevisiae* var. *boulardii* have potential probiotic effect. They are able to tolerate low pH and bile and protect against bacterial infections by the reduction of the intestinal inflammatory response (Gasser 1994). Additionally, *Saccharomyces* encourages intestinal mucosa by secreting polyamines and trophic factors contributing to the increase in host immune defense (Buts and de Keyser 2006). The microorganism to be considered probiotic, it must survive passage through the stomach and maintain its viability and metabolic activity in the intestine (van der Aa Kühle *et al.* 2005).

1.2 Requirements for probiotic strains

According to FAO, probiotic strains must meet both safety and functionality criteria. Probiotic strains are considered to be non-pathogenic, lactic acid producer, short generation time, acid and bile tolerant, effective adhesion to gut lining, genetically stable, anti-genotoxic property, robust processing conditions, and therapeutic agents (Servin and Coconnier 2003). The Qualified Presumption of Safety (QPS) concept involves some criteria of the safety assessment of bacterial supplements, including absence of the risk of acquired resistance to antibiotics and the history of safe usage (Anadón *et al*. 2006, Gaggia *et al.* 2010). Probiotic strains have to meet the requirements associated with the technology of their production. Probiotics have to be able to survive and maintain their properties throughout the storage and distribution processes (Lee 2009). The probiotic products should have a minimum concentration of 10^6CFU/ml or gram. A total of some $10^8$to 10^9probiotic microorganisms should be consumed daily for the probiotic effect to be transferred to the consumer (Huys *et al.* 2013). Furthermore, the strains must be able to grow under commercial and manufacture conditions and should keep viability under normal storage conditions.

LAB and bifidobacteria tend to be auxotrophic for some of the 20 amino acids and have nutrient requirements that need to be satisfied from the external environment to grow (Fenster *et al*. 2019). The power of evaluating the metabolism, genome, gene expression, and protein expression provides critical knowledge of strains that is useful for

assessing strain-dependent nutritional needs and the ultimate performance of the manufactured product (Siragusa *et al.* 2014). Also, analyzing the sterilized medium prior to inoculation and after fermentation provides empirical results for nutritional needs and limitations. Understanding the composition of complex raw ingredients, yeast extracts, yeast peptones, milk, and other complex nitrogen sources provides an opportunity to adjust the medium and procedure to achieve better strain performance.

1.3 Sources of probiotics

The food products containing probiotic strains is a wide and can be found in dairy and non-dairy products. The main products existing in the market are dairy-based ones including fermented milks, milk powder, yogurts, cheese, buttermilk, and ice cream, the latter accounting for the largest sales (Stanton *et al*. 2001). Nondairy food applications include soy based products, nutrition bars, cereals, and a variety of juices as appropriate means of probiotic delivery to the consumer (Ewe *et al.* 2010). The factors that must be addressed in evaluating the effectiveness of the incorporation of the probiotic strains into such products are, besides safety, the compatibility of the product with the microorganism and the maintenance of its viability through food processing, packaging, and storage conditions (Kechagia *et al*. 2013).

Yogurt is the most common source of probiotics. Yogurt is a bacterial fermented food products produce with combine effects of *Lactobacillus bulgaricus* and *Streptococcus thermophiles* (Yadav *et al*. 2015). A symbiotic blend of two major bacteria are present in a 1:1 ratio- *S. thermophilus* and *L. bulgaricus*. Acid is produced by *S.thermophiles*, whereas aroma components are formed by *L. bulgaricus*. Rate of acid production is much higher when they grow together in comparison to individual growth. *S. thermophilus* grows faster and produces both acid and carbon dioxide which stimulates the growth of *L. bulgaricus*. Whereas, proteolytic activity of *L. bulgaricus* produces stimulatory peptides and amino acids which is utilized by *S. thermophilus*. Generally freshly prepared yogurt contains 10^9 cells/gram. Yogurt starter cultures modify milk sugar (lactose) into lactic acid in the milk and consequently milk clot or form soft gel (Iqbal *et al.* 2014). Lactic acid is responsible for giving yogurt its characteristics and also denatures and precipitates casein, resulting in a semisolid consistency. Yoghurt is considered as healthy fermented food for human beings due to its high digestibility, and bioavailability of its protein, energy, calcium, and other nutrients.

Probiotics are also available in supplements consisting of freeze dried bacteria in tablets, capsules and powders. Selection of probiotic product depends on type of bacteria and type of beneficial effect expected (Hamilton-Miller 2004). There are thousands of strains of probiotics and all of them show different beneficial effects.

1.4 Mechanism of probiotic action

Probiotics have several functions in human organisms. The beneficial effect of probiotics, involve multiple and various influences on the host in different ways: 1. Antagonism through the production of antimicrobial substances (de Vrese *et al.* 2001), 2. Competition with pathogens for adhesion to the epithelium and for nutrients (Guillot 2003), 3. Immunomodulation of the host (Isolauri *et al.* 2001), and 4. Inhibition of bacterial toxin production (Brandao *et al.* 1998). Probiotic microorganisms are attributed a high therapeutic potential in obesity, insulin resistance syndrome, type 2 diabetes, and other pathologies (Cerdó *et al*. 2019). In humans, the better lactose digestion occurs in lactose malabsorbers who consumed yoghurt.

Numerous studies assessed the use of probiotics in the treatment of lactose intolerance irritable bowel syndrome, and the prevention of colorectal cancer (Geier *et al*. 2006) and peptic ulcers (Lesbros-Pantoflickova *et al.* 2007). Other studies confirmed the effect of the probiotic on the elimination of oxalates with urine, which may potentially reduce the risk of urolithiasis (Lieske *et al*. 2005). The consumption of probiotics-containing dairy products results in the reduction of blood cholesterol, which may be helpful in the prevention of cardiovascular diseases, and cerebral stroke (Simons *et al*. 2006). Probiotics have also demonstrated their inherent effects in alleviating symptoms of allergy, AIDS, respiratory and urinary tract aging, fatigue, autism, and osteoporosis (Harish and Varghese 2006).

An important role in the action of probiotics is played by species- and strain-specific traits, such as: cellular structure, cell surface, size, metabolic properties, and substances secreted by microorganisms (Lima-Filho *et al.* 2000). The use of a combination of probiotics demonstrating various mechanisms of action may provide enhanced protection offered by a bio-therapeutic product.

1.4.1 Antimicrobial Activity

Probiotic activity can fight pathogenic bacteria by secreting antibacterial substances and defenses, decreasing luminal pH, blocking bacterial adherence and translocation (Cerdó *et al.* 2019). Probiotic bacteria, especially strains of *Lactobacilli*, produce lactic, acetic, and propionic acids and thus lowering the capacity of pH, leading to inhibition of the growth of a wide range of gram negative pathogenic bacteria (Vanderpool *et al*. 2008). Some *Lactobacillus* species inhibit growth of *Salmonella enterica* by the production of lactic acid (Trejo *et al*. 2006).

The probiotic microorganisms produce substances such as hydrogen peroxide and short-chain fatty acids which have the ability to inhibit the replication of pathogens (Oelschlaeger 2010). The production of hydrogen peroxide by LAB is antagonistic to *Staphilococcus aureus* (Vasiljevic and Shah 2008). Short-chain fatty acids (propionic-, butyric-, and acetic acid) are repeatedly found at various concentrations in the human colon. Their presence in the colon affects biological processes, such as growth, metabolism, and differentiation of the intestinal epithelial cells (Koninkx and Malago 2008).

The LAB may be able to produce bacteriocins, and some antibiotics. Three main groups of bacteriocins are lantibiotics, nonlantibiotics, and large heat-labile protein (O'Sullivan *et al.* 2002). The primary mechanism of bacteriocin action is by forming pores in the cytoplasmic membrane of sensitive bacteria, but they can also interfere with essential enzyme activities in sensitive species. In addition, several strains of Bifidobacteria have been found to produce bacteriocin-like compounds toxic to both gram-negative and gram-positive bacteria (Vanderpool *et al*.2008).

1.4.2 Enhancement of barrier function

In the intestine, only one layer made up of epithelia cells conform a physical barrier between the intestinal lumen, the lamina propria, and the mucosal-associated lymphoid tissue. Additionally, goblet cells (simple columnar epithelial cells) secret a mucus able to separate the bacteria from the lumen, preventing colonization of the epithelium (Martens *et al*. 2018). Therefore, epithelial barrier disruption will lead to different illnesses such as inflammatory bowel disease (Xu *et al.* 2018), autoimmune diseases (Gavin *et al*. 2018), celiac disease (Lamacchia *et al*. 2018), or enteric infections (Kumar *et al*. 2018).

Probiotic bacteria have the ability to adhere to the epithelial cells thus blocking pathogens (Guo *et al.* 2017). The intestinal normal flora can improve host defense by occupying the gut in large numbers and diversity. Consequently, they can inhibit the colonization of the host by pathogens, produce modified bile acids, volatile fatty acids, and antimicrobial compounds. Some mechanisms concerning the effect of probiotics on *H. pylori* have been proposed including competition for adhesion sites, enhanced gut barrier function, and production of antimicrobial substances (Vasiljevic and Shah 2008). Also, it has been stated that several Lactobacillus species can block pathogenic *E. coli* invasion and its adhesion (Mattar *et al*.2002, Mack *et al*. 2003). Resta-Lenert and Barrett (2019) observed that the administration of *Lactobacillus acidophilus* and *S. thermophilus* enhanced cytoskeletal and tight junction protein structures in epithelial cell lines exposed to *E. coli*.

The role of probiotics in inhibition of the bacterial toxin production is based on toxin inactivation and the removal of toxins from the body by adsorption. Probiotic bacteria interfere with the pathogen-receptor or toxin receptor interactions (Koninkx and Malago2008). Probiotics in the gastrointestinal tract decrease adhesion of both pathogens and their toxins to the intestinal epithelium. Several strains of Lactobacilli and Bifidobacteriaare able to compete with pathogenic bacteria for intestinal epithelial cell binding, and they can displace pathogenic bacteria.

1.4.3 Immunomodulation

Probiotic-induced immunological stimulation is manifested by the increased production of immunoglobulins, enhanced activity of macrophages and lymphocytes, and stimulate γ- interferon production. Probiotics may influence the congenital and acquired immunological system through metabolites, components of the cellular wall, and DNA, recognized by specialized cells of the host (Oelschlaeger 2010). The probiotics play an important role in the response of cytokine to the inflammatory activity. Probiotics might exert their anti-inflammatory activity by inhibiting the secretion of inflammatory cytokines (Shida and Nanno 2008).

Probiotics are able to make control over epithelial cells, monocytes, dendritic cells, macrophages, and lymphocytes through different mechanisms (Otte and Podolsky 2004). The epithelial cells can perceive and distinguish pathogenic bacteria, through cytokine production and signal transduction. Kalinina, and Knight (2018) observed that exopolysaccharide secreted by a commensal bacterium, *B. subtilis*, can generate inhibitory dendritic cells. It has been observed that *L. casei* has the ability to induce the production of IL-12 and IL-10 by macrophages (Kaji *et al.* 2018); thereby, probiotics may be applied as immunomodulators.

Dietary associated with probiotic organisms might be one of the approaches by which a "healthy" microbiota can be modulated and maintained. Different bacterial strains have shown beneficial anti-obesity effects, such as a reduction in tissue inflammation, leptin levels, adiposity, endotoxemia, body weight, and energy intake (Torres-Fuentes *et al.* 2017). Furthermore, some probiotic microorganisms are natural producers of vitamins, and products of their metabolism may also show antibiotic, anticancerogenic, and immunosuppressive properties (Kumar *et al.* 2017), which could contribute to the maintenance of beneficial gut bacteria.

1.5 Side effects of probiotics

There are risks related to the probiotic therapy concerned with immune compromised individuals or critically ill or hospitalized patients (Mercenier *et al*. 2010). Probiotics may theoretically be responsible for four types of side effects: systemic infections, deleterious metabolic activities, excessive immune stimulation, and gene transfer (Musa *et al*. 2009). Very few cases of opposing actions have been reported in humans consuming probiotics (Marteau 2001). Some opposing effects of probiotics, including nausea, vomiting, abdominal pain, rash, diarrhea and constipation, (McFarland *et al*. 2009), thirst and constipation with *S. boulardii* use (McFarland *et al*. 1994), bloating and flatulence with *L. rhamnosus* GG use (Lawrence *et al*. 2005) have been reported.

Probiotics are also grouped into two classes based on their risk to health. Risk group 1 (No risk) consists of Lactobecillus and Bfidobacteria (De Vrese and Schrezenmeir 2008). Risk group 2 (small risk) contains *L. rhamnosus* and *Bfidobacterium dentium.* Probiotics which are mostly considered as safe are *Lactococcus* and *Lactobacillus*. On the other hand, Enterococcus, Streptococcus and Lactobacillus contain some opportunistic bacteria (Iqbal *et al*. 2014). There was a case of liver abscess reported in a diabetic patient who was consuming dairy products containing *L. rhamnosus* GG (Rautio *et al.* 1999). Kunz *et al*. (2004) and Land *et al.* (2005) stated cases of *Lactobacillus sepsis* associated with probiotic use in children. A case of recurrent *B. subtilis* septicemia has also been reported in an immune-compromised patient (Oggioni *et al*. 1998) after the use of probiotics containing *B. subtilis*. In addition most probiotic species are resistant to most of the antibiotics. The resistance may be transmissible as present in plasmid mediated resistance (Iqbal *et al*. 2014).

Pharmaceutical companies should keep in mind the potential of health risk of probiotics before adding these into products. Before launching any probiotic product, the safety profile of that particular probiotic species should be evaluated to avoid occurrence of any unexpected harmful effect.

1.6 Safety aspects of probiotics

The selection criteria of probiotic strains is determined by many factors such as resistance to pancreatic enzymes, acid, and bile, preferably of human origin, documented health effects, known safety, and good technological properties, especially the potential probiotics (Seppo *et al*. 2002).

Certain strains of probiotic bacteria have been found to be free of risk factors like transferable antibiotic resistances, cancer-promoting and/or putre-factive enzymes and metabolites, hemolysis, activation of thrombocyte aggregation, or mucus degradation in the mucus layer of the GIT.

Probiotic effects are strain specific, thus each individual bacterial strain must be tested separately for health benefit in question, and the effects described for one strain cannot be directly applied to others (Suresh *et al*. 2013). Lactobacilli fall into the category of organisms classified as "generally regarded as safe" (Haukioja *et al*. 2006). Organisms that are safe along with lactobacilli, are Lactococci, Bifidobacterium and yeast. There are other probiotic organisms, such as Enterococcus, Bacillus, and other spore forming bacteria, as well as Streptococci, that are not generally regarded as safe but have been used as probiotics.

The factors that must be addressed in the evaluation of safety of probiotics include the following: (i) metabolic activity; (ii) the intrinsic properties of the microbes; (iii) pathogenicity; and (iv) infectivity and virulence factors comprising toxicity (Salminen and von Wright 1998, Anadón *et al*. 2016). Probiotic safety required the absence of pathogenicity and infectivity. In addition, the probiotic bacteria should not produce harmful substances by metabolic activity. Platelet-aggregating activity, mucus degradation activity, and antibiotic resistance should be also tested (Ishibashi and Yamazaki 2001). Thus, the probiotics must retain their viability during transit through the stomach and small intestine as well during the storage and manufacturing process of functional food.

The use of probiotic is safe in most cases. Probiotic use should be avoided in patients having abnormal gastrointestinal mucosal barrier, immune-compromised patients, patients with central venous catheters and children with short gut syndrome (Suresh *et al*. 2013).

1.7 The Technology of probiotics

Probiotics are very sensitive to many environmental factors. These factors include intrinsic parameters of the product like pH, titratable acidity, oxygen, water activity, presence of salt, sugar and other compounds (H_2O_2, bacteriocins, artificial flavoring and coloring agents), processing parameters including fermentation conditions (temperature, heat treatment, cooling and storage conditions of the product, packaging materials, scale of production), and finally microbiological parameters (strain of probiotics employed, rate and proportion of inoculation) (Grattepanche and Lacroix 2013, Putta *et al.* 2018). In addition, a number of other suitable food components including non-specific substrates, plants and their extracts, metabolites of microorganisms and gastric juice, bile acid and pancreatic juice, colonization/survival *in vivo* and functional and physiological aspects (adherence to intestinal epithelium/tissue/virulence, antagonism to pathogens, antimicrobial activity, stimulation/suppression of immune response, selective stimulation of beneficial

bacteria and clinical side effects in volunteers/patients) (Gibson *et al.* 2003).

Some authors presented improvements in fermentation technologies for enhancing the performance of probiotic bacteria during fermentation, downstream processing, and utilization in commercial products, and for improving functionality in the gut (Doleyres and Lacroix 2005, Lacroix *et al*. 2005). Membrane systems with continuous feeding of fresh medium, where cells are retained in the bioreactor by an ultrafiltration or microfiltration membrane, are an interesting technological possibility (Soccol *et al.* 2010). Lacroix and Yildirim (2007) reported that cell immobilization can be used to perform high cell density fermentations for both cell and metabolite production.

The most investigated method for improvement of probiotic survival and delivery of bioactive compounds is encapsulation. Probiotics encapsulation is known to stimulate stability, facilitate handling and storage of probiotic cultures and protect sensitive probiotic lactic acid bacteria from oxygen, freezing and acidic conditions during production, storage and gastrointestinal transit (Ebrahimi *et al*. 2018). Microencapsulation is defined as a technology of packaging solids, liquids or gaseous materials in miniature, sealed capsules that can release their contents at controlled rates under the influences of specific conditions (Anal and Stevens 2005, Anal *et al*. 2006). A microcapsule consists of a semipermeable, spherical, thin, and strong membrane surrounding a solid/liquid core, with a diameter varying from a few microns to 1 mm (Krasaekoopt *et al.* 2003). Encapsulation in hydrocolloid beads entraps or immobilizes the cells within the bead matrix (Anal and Singh 2007). Food-grade polymers such as carrageenan, alginate, carboxymethyl cellulose, chitosan, gelatin, and pectin are mainly applied using various microencapsulation technologies (Krasaekoopt *et al.* 2003). The most widely used encapsulating material is alginate which extracted from various species of algae (Smidsrod *et al*. 1972). The use of alginate is favored because of its simplicity, biocompatibility, and low cost (Tanaka *et al*. 1984, Martinsen *et al.* 1989). Other materials used with the emulsion technique which avoid the release of the cultures in the food product are chitosan (Groboillot *et al*. 1993), gelatin (Hyndman *et al.* 1993), mixture of k-carrageenan and locust bean gum (Audet *et al.* 1989), and cellulose acetate phthalate (Rao *et al*. 1989).

2. Prebiotics

Prebiotics are defined as "non-viable food component that associated with modulation the growth and activity of specific bacterial species in the colon that are considered health-supporting" (Gibson *et al*. 2017, Markowiak and Sli˙zewska 2017). Prebiotics have a long history of safe use and have been known for their health benefits in humans, including an increase in the bioavailability of minerals, prevention of gastrointestinal (GI) infections, modulation of the immune system, modification of inflammatory conditions, regulation of metabolic disorders, and reduction on the risk of cancer (Roberfroid *et al*. 2010, Anadón *et al*. 2016). Various prebiotics have been observed to improve bowel function in the elderly. The fermentation of prebiotics by colonic bacteria increases the bacteria biomass, leading to an increased fecal output (Yatsunenko *et al*. 2012). During fermentation, the SCFAs, butyrate, propionate, and acetate are formed, which are efficiently absorbed to epithelial cells and circulation.

2.1 Prebiotic selection criteria

Prebiotics are dietary fiber (non-digestible food ingredient), are not affected by heat, cold, acid, or time, provide a wide range of health benefits, and nourish the good bacteria that everyone already has in their gut (Nagpal and Kaur 2011). Prebiotics are naturally present in a variety of foods such as vegetables, whole grains, and fruits and consumption of which is encouraged in national and international dietary guidelines (WHO 2018). The following may be mentioned as such potential sources: bananas, tomatoes, berries, artichokes, asparagus, garlic, onions, chicory, green vegetables, legumes, as well as oats, linseed, barley, and wheat (Crittenden and Playne 2008). Some artificially produced prebiotics are lactulose, galactooligosaccharides, fructooligosaccharides, maltooligosaccharides, cyclodextrins, and lactosaccharose. Thus, prebiotics are commercially extracted and concentrated from fruits and vegetables through the hydrolysis of polysaccharides from dietary fibers or starch, or through enzymatic generation. The non- digestible oligosaccharides known as fructans and galactans are widely accepted as prebiotics (Gibson *et al*. 2017). All currently accepted prebiotics are carbohydrates, but polyphenols and polyunsaturated fatty acids may fit the criteria in time as evidence gathers.

2.2 Prebiotic effects

It is generally accepted that prebiotics have a selective effect on the microbiota that results in improved health of the host. Prebiotics exert an osmotic effect in the GIT as long as they are not fermented; when they are fermented by endogenous flora (exhibit their prebiotic effect) they increase intestinal gas production (Roberfoid and Slavin 2000).

Prebiotics act like growth factors in particular commensal bacteria (*Lactobacillus* sp.), which can both improve gut barrier function through protection of the epithelial tight junction during external stress (Seth *et al*. 2008). Currently accepted prebiotics

increase Bifidobacteria in the human gut (So *et al*. 2018). This is thought to benefit human health through the displacement of pathogens and modulation of the immune system (Wallace *et al*. 2011). Bifidobacteria metabolize substrates with chain lengths of the size of oligosaccharides (Gibson *et al*. 2017). Prebiotic compounds are able to modulate the gut microbiota composition especially *Bifidobacteria* (Roberfroid *et al*. 2010). The prebiotics make changes in the mucosal surface of the colon and the transepithelial transport of the short chain fatty acid, furthermore the transport of cationic minerals is stimulated by the lowered pH of the lumen.

Prebiotics may be used as an alternative to probiotics or as an additional support for them. Long-term stability during the shelf-life of food, resistance to processing, and physical and chemical properties may promote prebiotics as a competition to probiotics (Van Den Abbeele *et al.* 2013, Sivieri *et al*. 2014). Furthermore, resistance to acids, bile salts, and proteases present in the gastrointestinal tract may be considered as other favorable properties of prebiotics. Additionaly, prebiotics cause a reduction of intestinal pH and maintain the osmotic retention of water in the bowel (Crittenden and Playne 2009). However, it should be considered that an overdose of prebiotics may lead to diarrhea and flatulence. When prebiotics used at correct doses, they do not stimulate any adverse effects. Prebiotic substances are not allergenic and do not proliferate the abundance of antibiotic-resistance genes. The effect of the removal of selected pathogens achieved by the use of prebiotics may be inferior to antibiotics, but the properties mentioned above make them a natural substitute for antibiotics (Crittenden and Playne 2009).

3. Synbiotics

In symbiotic is a mixture of probiotics and prebiotics that positively affects the host by improving the survival and implantation of live microbial dietary supplements in the gastrointestinal tract (Gibson and Roberfroid 1995b, Gourbeyre *et al*. 2011). The aim of that combination is the improvement of survival of probiotic microorganisms in the gastrointestinal tract. Synbiotics have both probiotic and prebiotic properties and were produced in order to overcome some possible difficulties in survival of probiotics in the gastrointestinal tract (Rioux *et al*. 2005). Probiotics beneficially influence the intestinal equilibrium, and constitute a protective barrier for the alimentary tract. Prebioticssupply energy and nutrients for probiotic bacteria (Blay *et al.* 1999, Gibson 2003). Thus, an appropriate combination of both components in a single product should confirm a superior effect, compared to the activity of the probiotic or prebiotic alone (Bengmark 2005, Panesar *et al*. 2009**).** The health effect of synbiotics is probably associated with the individual combination of a probiotic and prebiotic (De Vrese and Schrezenmeir 2008, Scavuzzi *et al*. 2014).

3.1 Synbiotic selection criteria

Most of probiotic strains and prebiotics considered in the process of designing a synbiotic formula should meet all the criteria presented in "Selection criteria and requirements for probiotic strains" and "Prebiotic selection criteria" (Markowiak and Śliżewska 2017). The first aspect to be taken into account when composing a synbiotic formula should be a selection of an appropriate probiotic and prebiotic, exerting a positive effect on the host's health when used separately. A prebiotic should selectively stimulate the growth of microorganisms, having a beneficial effect on health, with simultaneous absent stimulation of other microorganisms. A combination of Bifidobacterium or Lactobacillusgenus bacteria with fructooligosaccharides in synbiotic products seems to be the most popular (Markowiak and Slizewska 2017).

3.2 Mechanism of action of synbiotics

In spite of probiotic is essentially active in the small and large intestine, and the effect of a prebiotic is observed mainly in the large intestine, the combination of the two may have a synergistic effect (Hamasalim 2016). Prebiotics are used mostly as a selective medium for the growth of a probiotic strain, fermentation, and intestinal passage. That combination of components leads to the creation of viable microbiological dietary supplements, and ensuring an appropriate environment allows a positive impact on the host's health. Two modes of synbiotic action are known (Manigandan *et al.* 2012): (1) Action through the improved viability of probiotic microorganisms; (2) Action through the provision of specific health effects.

The stimulation of probiotics with prebiotics results in the modulation of the metabolic activity in the intestine with the maintenance of the intestinal biostructure, development of beneficial microbiota, and inhibition of potential pathogens present in the gastrointestinal tract (De Vrese and Schrezenmeir 2008). Synbiotics result in reduced concentrations of undesirable metabolites, as well as the inactivation of nitrosamines and carcinogenic substances. Their use leads to a significant increase of levels of short-chain fatty acids, ketones, carbon disulphides, and methyl acetates, which potentially results in a positive effect on the host's health (Manigandan *et al.* 2012). The therapeutic properties of synbiotics include antibacterial, anticancerogenic, and anti-allergic effects. They also counteract decay processes in the intestine and prevent constipation and diarrhoea. It turns out that synbiotics may be highly efficient in the

prevention of osteoporosis, reduction of blood fat and sugar levels, regulation of the immunological system, and treatment of brain disorders associated with abnormal hepatic function (Pandey *et al*. 2015).

4. The viability of probiotic fermented milks

Functional foods are foods that have at least a certain nutritional highlight in addition to their regular nutritional properties along with having confirmed medicinal outcome to the consumer. They are produced by adding at least a chemical or microbial ingredient to a food-base, such as milk and milk products. Probiotics and synbiotics are functional foods with microbial enrichment (Nehir and Simsek2012). One of the best food-bases for production of functional foods is fermented milks, due to the fact that they are inherently known as healthy foods, are regularly consumed by the vast majority of people in their long-term diet. Fermented milks are widely manufactured throughout the world. Yogurt is considered as the most popular fermented milk in the world (Korbekandi *et al*. 2011). Fermented milks are considered as the most popular and consumed probiotic products.

The major factor in the production of probiotic fermented milks is loss of viability of probiotics during the fermentation process, and during the refrigerated storage and these organisms often show poor viability when marketed (Mortazavian *et al*. 2007). In fermented milks, many factors influence the viability of probiotic cultures such as pH, titratable acidity, the presence of other microorganisms, temperature, oxygen content, nutrients, growth factors, food additives, application of new technologies such as microencapsulation, and formulation of products (Mohammadi and Mortazavian 2010, Korbekandi *et al.* 2011).

To enhance the nutritional attributes of fermented milks, via promoting the viability of probiotics, a trend has been started to add algae in order to increase the functional product characteristics (Varga *et al.* 2002). Webb (1982) reported that the co-addition of microalgae and probiotics stimulates growth and increases viability and acid production of the probiotic bacteria. On the other hand, microalgae present in fermented milks will affect the sensory properties of the final product.

4.1Algae as promising source of compounds

Algae are photosynthetic organisms, which possess reproductive simple structures. These organisms contain a total of 25-30,000 species, with a great diversity of sizes and forms, and that can exist from unicellular microscopic organisms (microalgae) to multicellular of great size (macroalgae or seaweeds) (Carlsson *et al.* 2007). Algae can be a very interesting natural source of new compounds with biological activity that could be used as functional ingredients (Carlucci 1999). In addition to its natural character, other important features related to the algae are their easy cultivation, their rapid growing and the possibility of controlling the production of some bioactive compounds by manipulating the cultivation conditions. In this way, algae can be considered as genuine natural reactors being, in some cases, a good alternative to chemical synthesis for certain compounds.

Algae have been used in human and animal diets since very early times. Algae are promising source of novel biochemically active compounds like fatty acids, steroids, carotenoids, polysaccharides, lectins, vitamins and phyco-proteins, amino acids, dietary minerals, halogenated compounds, polyketides and diverse antioxidants (Kumar *et al*. 2008). Algae are characterized by its bioactive compounds, its properties like anti-viral, anti-tumor, anti-inflammatory and anti-lipedimic, and more properties (Pal *et al.* 2014).

Microalgae contain antioxidant components, amino acids, proteins, Fe and Ca, unsaturated fatty acids, many types of vitamins (A, B2, B6, B8, B12, E, and K) and known as therapeutic and functional food. They have antiviral, anti-inflammatory, and antitumor effects and reduce blood lipid profile, blood sugar, body weight, and wound healing time (Gyenis *et al*. 2005). Macroalgal extracts are very important component of most bio-stimulate product nowadays and it is best known for their richness in polysaccharide, minerals and vitamin (Holdt. and Kraan 2011). Polysaccharides have many applications like they are use in food, beverages, stabilizers, emulsifiers, thickeners, and feed. According to the nutritional perspective, macroalgae are low lipid content and having high carbohydrate most of this is dietary fibers even though they are not taken up by the human body. Algae dietary fibers composition, chemical structure, physiochemical property as well as their ability to be fermented by the colonic flora and its biological effects on human and animal cell, all is very diverse to each other (Lahaye and Kaeffer 1997). Different carbohydrates including alginates, carrageenan, and ulvansare extracted from macroalgae and are widely used in the food and pharmaceutical industries as functional ingredients (O'Sullivan *et al*. 2010).

Algal biomass is rich in carbohydrates and proteins which could be a good source for producing lactic acid. Lack of lignin in algal biomass is an additional advantage over plant biomass (Nguyen *et al.* 2012). Spirulina, Chlorella and Dunalilla are microalgae which contain high-antioxidant components, abundant amino acids, high-quality proteins, Fe and Ca, unsaturated fatty acids, and many types of vitamins including A, B2, B6, B8, B12, E,

and K. They have antiviral, anti-inflammatory, and antitumoral effects and reduce blood lipid profile, blood sugar, body weight, and wound healing time. Therefore, they are known as therapeutic and functional food (Merchant and Andre 2001, Gyenis *et al.* 2005). Algae are promising organisms for providing both novel biologically active substances and essential compounds for nutrition (Cardozo *et al*. 2007). In many countries, the food industries consume a wide range of algae, which are well known to have high contents of fiber, minerals, vitamins and different antioxidants.

4.2 Microalgae

Microalgae are source of several valuable compounds with health benefits such as protein, carbohydrates, polyunsaturated fatty acids, essential minerals, and vitamins (Wells *et al*. 2017, Caporgno and Mathys 2018), which can increase the nutritional value of food products upon incorporating. Polysaccharides and oligosaccharides are promising compounds with potential health benefits, arising attention in terms of prebiotic applications (Raposo *et al*. 2016, Jutur *et al*. 2016). This association is based on the first definition of prebiotics as "non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health," given by Moreno *et al*. (2017).

Dairy products can also be incorporated with microalgae to deliver bioactive compounds (Beheshtipour *et al*. 2013). Several authors agree that certain species such as *Spirulina* spp. can stimulate growth of desired probiotic bacteria in yogurts and fermented milk, increasing the viability of the probiotics (Varga *et al.* 2002). The availability of trace elements, vitamins, and other bioactive compounds in microalgae powders promotes the development of desired bacteria (Molnár *et al*. 2005). Previous studies suggested a synergy between microalgae and bacteria, where the former liberate exopolysaccharides into the medium that stimulate bacterial growth (Parada *et al.* 1998).

Spirulina is a filamentous blue- green algae, commonly distributed in nature. It is consumed as human food supplement for centuries because of its best known nutritional value. It contains 78% proteins, 4-7% lipids, 13.6% carbohydrates vitamins, minerals, and some natural pigments (Shekharam *et al*. 1987, Parada *et al*.1998). It contains high-quality proteins, 18 of the 20 known amino acids, vitamins A, B2, B6, E, H, and K, more vitamin B12 than cow liver, more calcium than milk, and all essential minerals, trace elements, as well as enzymes (Fox 1986). *Spirulina* contains essential amino acids; the highest values of which are leucine (10.9% of total amino acids), valine (7.5%), and isoleucine (6.8%) (Cohen 1997). Spirulina contains essential fatty acids such as linoleic acid (LA) and γ -linolenic acid (GLA) (Otles and Pire 2001). Spirulina does not have cellulose in its cell wall, a feature that makes it an appropriate and important foodstuff for patients who have poor intestinal absorption and for geriatric patients (Richmond 1984). A new high-molecular-weight polysaccharide with immunostimulatory activity has been isolated from Spirulina is called "Immulina" (Pugh *et al*. 2001).

There are data showing that Spirulina has various possible health promoting effects: the alleviation of hyperlipidemia, suppression of hypertension, hypercholesterolemia, protection against renal failure, anemia, growth promotion of intestinal *Lactobacillus*, and suppression of elevated serum glucose level (Deng and Chow 2011). Spirulina possesses some antiviral (El-Baz *et al*. 2013) and antitumor properties (Parada *et al*. 1998). One of the main concerns about the consumption of microorganisms is their high content of nucleic acids that may cause diseases such as gout. Spirulina contains 2.2% to 3.5% RNA and 0.6% to 1% DNA, which represents less than 5% of these acids, based on dry weight (Spolaore *et al.* 2006). Spirulina presents hypoglycemic (Iyer Uma *et al.* 1999), antihypertensive (Torres-Duran *et al.* 2007), and hypolipidemic (Serban *et al*. 2016) properties. Studies in rats proposed that Spirulina increases the pancreatic secretion of insulin (Muthuraman *et al*. 2009) and the lipoprotein lipase activity (Iwata *et al*. 1990). Phycocyanin is a nontoxic pigment in Spirulinaand can act as a free radical scavenger and a powerful antioxidant (Toyomizu *et al*. 2001). Due to the presence of the various phyto-nutrients, it has helpful properties against several diseases.

On the other hand, it has also been reported that extracellular products of Spirulina, obtained from a culture in late exponential stage, promote the in vitro growth of the lactic acid bacteria (*Lactobacillus bulgaricus*, *Lactococcus lactis*, *Lactobacillus acidophilus*, *Lactobacillus casei*, and *Streptococcus thermophilus*) (Parada *et al*. 1998). Probiotics, including the genera Lactobacillus and Bifidobacterium (Finamore *et al.* 2016), are largely used as starter bacteria for the production of yogurt (Mocanu *et al*. 2013), the most popular fermented diary product worldwide. Spirulina biomass has a stimulatory effect during fermentation and storage of *Lactobacillus acidophilus* (Bhowmik *et al.* 2009), *Lactobacillus casei* (Bhowmik *et al.* 2009), *Lactobacillus bulgaricus* (Malik *et al.* 2013), *Streptococcus thermophilus* (De Caire *et al*. 2000, Fadaei *et al.* 2013), and Bifidobacterium (Varga *et al*. 2002, Mocanu *et al*. 2013).

Chlorellais a single-celled green algae belonging to the phylum Chlorophyta. Chlorellais a good source

of nutrients such as valuable protein, fat, calories, and vitamins (Belasco 1997). *Chlorella* produces astaxanthin, canthaxanthin, and *β*-carotene (Mendes *et al*. 2003). *C.vulgaris* contains other antioxidants such as chlorophyll and lutein. It is a rich nutritional ingredient because it contains 61.6% proteins, 12.5% fat, 13.7% carbohydrates, elements (selenium, magnesium, phosphorus, zinc, calcium, and aluminum), and vitamins (ascorbic acid, thiamine, B1, B2, B6, D, E, and K) (Valdivia *et al.* 2011).

Polysaccharide complexes from *Chlorella pyrenoidosa* and possibly, *Chlorella ellipsoidea*, contain glucose in combination with any of the following sugars like arabinose, galactose, mannose, rhamnose, N-acetylgalactosamine and N-acetylglucosamide (Lordan *et al*. 2011). An acidic polysaccharide was isolated from *Chlorella pyrenoidosa* containing mostly rhamnose (52%) with both arabinose (12%) and galactose (13%) in about equal amounts (Mata *et al*. 2010).

Chlorellais a good source of polyunsaturated fatty acids (PUFAs) (38.94%) and has 13.32% of total lipids (Blas-Valdivia *et al.* 2011). Palmitic acid content of Chlorella was 15.41%, EPA (20:5*n*-3) content, 3.23%, and docosapentaenoic acid, 3.11%. Docosahexaenoic acid (C22:6*n*-3) content of Chlorella was extremely high (20.94%). PUFA content of Chlorella was 38.94% and the total omega-3 (*n*-3) level was 29.21%. In addition, *Chlorella* is rich in Ca (593.7 mg), P (1761.5 mg), mg (344.3 mg), Na (1346.4 mg), Fe (259.1 mg), and K (749.9 mg). Other mineral contents involved such as Se (0.07 mg), Zn (1.19 mg), Mn (2.09 mg), Cr (0.02 mg), and Cu (0.06 mg).

It has been established that Chlorella exhibits various immunological effects such as antibacterial and antiviral activity (Blas-Valdivia *et al*. 2011). *C.vulgaris* maintains the renal cytoarchitecture against HgCl2-caused oxidative stress and nephrotoxicity. Several studies on the health benefits of consuming *Chlorella* spp. have shown that their ingested extracts can increase hemoglobin concentrations, lower blood sugar levels, act as hypo-cholesterolemic and hepatoprotective agents during malnutrition, and reduce ethionine intoxication (Barrow and Shahidi 2008, Jeong *et al*. 2009).

Chlorella and Spirulina accumulate high-quality proteins, having both species well balanced amino acid profiles according to the WHO/FAO/UNU recommendations regarding human's requirements of essential amino acids (EAAs) (Chronakis and Madsen 2011, Caporgno and Mathys 2018). The amino acid profiles of both species are similar to other conventional protein sources such as eggs and soybean (Becker 2007). In general, microalgae are deficient in sulphur-containing amino acids methionine and cysteine; however, some microalgae supplements showed to be deficient in other amino acids (Misurcova *et al*. 2014). A comparison between the amino acids profiles of several algal products, including commercially available products such as *Chlorellapills* and *Spirulina flakes*, showed that some supplements can provide high amounts of EAAs. Spirulina, Chlorella and Nannochloropsi*s* are not only a good source of proteins, but have been reported as important sources of polysaccharides or oligosaccharides, being proposed as potential prebiotic candidates (Wells *et al*. 2017). Chlorella has been successfully incorporated into yogurts (Cho *et al.* 2004) and cheeses (Jeon 2006).

Dunaliella salina (*D. salina*) is a unique unicellular species of Chlorophyta with no cell wall found in saline environments (Abu Rezq *et al*. 2010). This alga has been reported to produce extracellular polysaccharides (Mishra and Jha 2009).

4.2.1 Effects of microalgae supplementation on viability of probiotic bacteria

Yogurt have been used as the most common carrier for incorporation of probiotic organisms. Unfortunately, most of the commercial products contain less probiotic bacteria than the minimum required, because these microorganisms grow slowly in milk and often show loss of viability during storage. Furthermore, the probiotic bacteria are sensitive to dissolved, pH, hydrogen peroxide, and lactic acid in fermented milk (Zhao *et al*. 2006).

Numerous compositional and process factors affect the viability of probiotic microorganisms in fermented milks significantly including molecular oxygen, pH, titratable acidity, redox potential, hydrogen peroxide, bacteriocins, short-chain fatty acids, solids nonfat content, carbonation, addition of salt, sugar and sweeteners, flavoring agents, rate and proportion of inoculation, microbial competitions, step-wise/stage-wise fermentation, microencapsulation, milk supplementation of milk with nutrients, heat treatment of milk, incubation temperature, storage temperature, cooling rate of the product, and scale of production, and packaging materials and packaging conditions, (Mortazavian *et al*. 2006; Champagne and Rastall 2009). The pH is of most critical factors decreases the viability of probiotic organisms in fermented milks (Tamime *et al*. 2005, Korbekandi *et al.* 2011).

The LAB must be viable and abundant at the time of consumption, to obtain the claimed probiotic benefits and this is called "viability" (Gomes *et al*.1995, Beheshtipour *et al.* 2013). Although no worldwide agreement has been reached on recommended levels, generally the values of 10^6 CFU/ml and 10^7 or 10^8 CFU/ml have been accepted as the minimum and satisfactory levels, respectively

(Mohammadi *et al*. 2011). Though, a major factor in the production of probiotic fermented milks is loss of viability of probiotics during the fermentation process, as well as during the refrigerated storage (Sadaghdar *et al.* 2012) and these organisms often show poor viability when marketed (Mortazavian *et al*. 2007).

Much effort has been made to improve the growth and survival of probiotic bacteria during storage. Some applications have been successful in improving survival of these bacteria in yogurt. Substances such as non-protein nitrogen, sugar sources, and oligosaccharides can improve the growth of probiotic bacteria. Vitamins, maltose, and dextrin stimulate the growth of Bifidobacteria species in milk (Zhao *et al*. 2006). A trend has been started recently, to add microalgae biomass into fermented milks in order to increase the functional product characteristics via promoting viability of probiotics as well as to enhance the nutritional attributes (Varga *et al.* 2002). They reported that microalgae can increase the viability of probiotic bacteria. The substances responsible for the stimulatory properties of algal biomass were identified as free amino acids, adenine, and hypoxanthine. The co-addition of microalgae and probiotics stimulates growth and increases viability and acid production of the probiotic bacteria (Webb 1982).

The co-culturing of microalgae and probiotics can stimulate growth and increase the viability of probiotics in the products as well as in the gastrointestinal tract due to their alkaline character and presence of effective compounds (Parada *et al*. 1998). The growth of LAB in synthetic media was promoted by *S. platensis* extracellular product (De Caire *et al.* 2000). Varga *et al.* (1999b) reported that blue green algal biomass significantly stimulated growth and acid production of thermophilic dairy starter bacteria. Consequently, it proved to be suitable for the cost-effective manufacture of novel functional fermented dairy foods.

The overgrowth of natural yogurt bacteria leads to the inhibition of probiotics in fermented milks and the consequent viability reduction (Ahmadi *et al.* 2012). Therefore, the impact and control of microalgal addition on the viability of yogurt bacteria in fermented milks is rather important during fermentation and storage. De Caire *et al*. (2000) studied the effect of a natural additive, a dry *S. platensis* biomass on the growth of LAB in milk. They grew *L. delbrueckii* YL1, *L. lactis* C2, and *S. thermophiles* TH with and without the addition of 3 mg of dry *S. platensis*/ml biomass. After 4 h, the LAB growth promotion by *S. platensis*, at pH 6.8, was 13.42% for C2, 9.29% for YL1, and 8.22% for TH4, compared with the controls. After 8 h, the increase was 3.46%, 9.73%, and 7.76% for C2, YL1, and TH4, respectively, and that is probably due to a decrease in the amount of the stimulatory factors. The 3 strains treated with Spirulina reached the stationary phase at 10 h and the counts remained the same up to 20 h, while the same strains without Spirulina addition grew more slowly and continued to grow up to 20 h, reaching the same value as the supplemented ones. The growth promotion of C2 was 27.3% after 4 h and for strain LO1, an increment of 22.8% was observed after 8 h. The tested LAB showed more growth in milk enriched with natural nutrients from the Spirulina, and they clearly responded to different extents according to the strain (De Caire *et al*.2000).

Parada *et al.* (1998) showed that addition of extracellular products obtained from a late log phase culture of *S. platensis* stimulate the growth of some LAB. Hence, it was proposed that *S. platensis* could have a stimulatory effect on LAB by acting as a prebiotic factor. The addition of Spirulina filtrate to de Man Rogosa and Sharpe agar stimulated the bacterial growth significantly for all the strains investigated. A similar effect was observed using enriched medium. The addition of Zarrouk medium, treated the same as the Spirulina culture filtrates, did not change the extent of growth observed in the media prepared without extracellular products. Changes recorded in the above parameters showed that *S. platensis* acted as a photoautotropic microorganism that consumes nitrogen from the culture medium and liberated exopolysaccharide and other compounds that could be responsible for the stimulatory effect on LAB (Parada *et al.* 1998).

Varga *et al*. (1999a) found that biomass of *S. platensis* has no influence either on fermentation activity or on growth of *B. bifidum* or *B. animalis* when the milk was inoculated with a mixed culture of *S. thermophiles*, *B. animalis*, and or *B. bifidum.* Although the viable cell counts of *L.bulgaricus* showed generally some fluctuations, in general, yogurt samples supplemented with *S. platensis*, had significantly higher viable counts of *L. bulgaricus.* So, supplementation with algal biomass significantly increased the viable counts of *L. bulgaricus* in both natural and probiotic yogurt. The stimulatory effect of the algal biomass on the survival of *L. bulgaricus* was noticeable throughout the storage period. This effect may be returned to the presence of free amino acids, adenine, peptone, and hypoxanthine in the algal biomass because these nitrogenous substances are capable of significantly stimulating the growth and acid production of *L. bulgaricus* (Molnar *et al*. 2005). In complementary research accomplished by Varga *et al.* (1999b), there were significant differences in the viability of *S. thermophilus* between the yogurt samples with or without *S. platensis*. In general, higher viable counts of *S. thermophilus* were enumerated in

yogurts containing no *S. platensis* during storage. Therefore, the addition of algal biomass significantly decreased the growth of *S. thermophilus.* The viable counts of *S. thermophilus* in all yogurt samples were enumerated above 8 log CFU/ml during 28 days (Varga *et al.* 1999b). Furthermore, the Spirulina supplemented fermented ABT milk contained significantly higher levels of viable Bifidobacteria throughout the entire storage period than did the control product (Varga *et al.* 2002).

Varga and Szigeti (1998) enumerated minimum 8 log CFU/ml for viable counts of *S. thermophilus* in both natural and algal yogurt during storage at 4^{o}C. The survival rate of *S. thermophiles* was better than that of both *L. bulgaricus* and *B. animalis*. The viable counts of *S. thermophilus* were higher by 2 to 3 log orders than those for *L. bulgaricus* in yogurt samples (Varga and Sziget 1998).

Molnar *et al.* (2005) studied the effects of Spirulina biomass on single strains of mesophilic lactic acid bacteria. Used at the rate of 3 g/dm^{3}, Spirulina significantly increased the acid production by various strains of mesophilic lactic acid bacteria. During the first and second week of refrigerated storage at 4±2^{o}C, the *Spirulina* biomass significantly increased viability of mesophilic starter bacteria in the product. Because of its alkaline character and possession of considerable buffering capacity, Spirulina significantly stimulated the acid production and increased growth rates of some LAB during the fermentation process and even during the first week of storage. However, viability percentages declined slowly thereafter.

Gyenis *et al.* (2005) studied the use of dried microalgal biomasses to stimulate acid production and growth of *L. plantarum* and *E. faecium* in milk. According to their results, acid production and growth of *E. faecium* and *L. plantarum* were stimulated significantly by *C. vulgaris* and *S. platensis*, respectively, in all culture media formulations used (Gyenis *et al*. 2005). Their findings were consistent with those of Varga *et al*. (1999b), who demonstrated that acid production and growth rates of thermophilic dairy starter cultures, such as *S. thermophilus, L. delbrueckii* ssp. *bulgaricus, L. acidophilus,* and *B. bifidum*, could be stimulated effectively by *S. platensis* biomass (Gyenis *et al*. 2005).

Beheshtipour *et al*. (2012) studied the effects of *C. vulgaris* and *S. platensis* addition on the viability of probiotic bacteria in yogurt and its biochemical properties. According to their results the viability of both probiotic bacteria (*L. acidophilus* LA-5 and *B. lactis* BB-12) was significantly and markedly greater in the treatments containing microalgae than the control. Also, the higher concentration of microalgae (from 0.25% to 1.0%) had greater viability of both probiotic bacteria at the end of fermentation and during refrigerated storage (Beheshtipour *et al*. 2012). Therefore, the impact and control of microalgal addition on the viability of yogurt bacteria in fermented milks during fermentation and storage is rather important.

4.2.2 Effects of microalgae supplementation on acidification rate in fermenting milk

Several studies have showed that the chemical characteristics (pH, acid production) of fermented products such as yogurt and probiotic fermented milk products improved due to supplementation with prebiotics such as inulin, resistant starch, fiber and calcium, date fiber, *β*-glucan, glucose, and raffinose. This could be due to the nutritional benefits of prebiotics in enhancing the growth of probiotics and promoting acid production during fermentation and storage (Zare *et al*. 2011).

In a study by Ásványi-Molnár *et al*. (2009), changes in acid production of mesophilic lactic acid bacteria grown in milk were investigated. The results showed that *Spirulina* levels were capable of effectively stimulating acid production of lactococci. The addition of *S. platensis* caused a decline in pH values of yogurt samples. This decline was probably due to the stimulatory effect produced by the *S. platensis* biomass on the growth of *L. bulgaricus*, which was also supported by the higher viable cell counts of *L. bulgaricus* in algal yogurts in the 1st day of storage (Ásványi-Molnár *et al.* 2005). A pH drop rates were observed for the treatments constituting *S. platensis*. These treatments also showed significant increase in acidity rates. In contrast, the control showed significantly lower mean acidity increase rates. Similar situations were observed for final acidity in the treatments. These characteristics can be attributed to the different buffering capacity effects of the treatments. Samples containing *S. platensis* exhibited higher buffering capacity. The greater the buffering capacity, the slower the pH drop and this stimulates acidification rate by starter bacteria because they are inhibited considerably later during fermentation (Beheshtipour *et al.* 2012).

4.2.3 Effects of microalgae supplementation on sensory attributes of fermented milks

Addition of microalgae into fermented milks can change the sensory attributes, mostly undesirably, although there is not enough related information in the literature. Beheshtipour *et al.* (2012) reported that treatments with higher amounts of microalgae possessed weaker sensory acceptability for all sensory parameters compared to the control. *S. platensis* exhibited more unpleasant flavor. Addition of microalgae into the yogurt changed the color of this product to greenish or bluish based on the type and concentration of microalgae added. This characteristic

was realized as an inappropriate sensory attribute (appearance) by the panelists. Moreover, graininess caused by insoluble microalgal particles was recognized mostly in treatments with 1% microalgae. There were no considerable differences among the treatments from numeral texture points of view. However, differences were remarkable from an oral texture standpoint. Treatments containing 1% microalgae had the lowest sensory score for oral texture and mouth feel. Some characteristics of microalgae limit their utilization in food products. Despite the antioxidant-rich nature of Chlorella and Spirulina, changes in colour and flavor in foods are usually perceived as undesirable by consumers (Becker 2007, Prakash and Kumari 2011).

Prakash and Kumari (2011) studied the preparation of high-protein and low-fat frozen yogurt enriched with Spirulina and papaya pulp with the objective to find out the optimum level of Spirulina that could be incorporated to obtain a better-quality frozen yogurt. It was observed that incorporation of *Spirulina* from 2% to 8%, before incubation with the addition of 10% papaya pulp, was the more acceptable. The frozen yogurt prepared with 6% Spirulina with 10% papaya pulp was found best on the basis of sensory attributes compared to the rest of treatments tried in the study. Higher levels of *Spirulina* adversely affected sensory characteristics of frozen yogurt. Much effort has been made to improve the growth and survival of probiotic bacteria during fermentation and storage is rather important.

4.3 Macroalgae and marine microalgae and their active compounds as prebiotics

Macroalgae (seaweeds) occur naturally (Chlorophytes, Phaeophytes, and Rhodophytes) are rich with polysaccharides (PS). Some of their PS (native or somehow modified, such as LMW-PS) were already recognized and accepted as dietary prebiotics: GOS, AGAROS, XOS, neoagaro-oligosaccharides (NAOS), alginate-derived oligosaccharides (ALGOS), arabinoxylans, galactans, Beta-glucans, although the fulfillment of the criteria still has to be proved for some of them (Raposo *et al*. 2016). However, these algal PS are not degraded by enzymes in the upper part of the GI tract. Therefore, they can be used as dietary prebiotics (fibers), as they also enhance the growth of lactic acid bacteria (LAB) (Zaporozhets *et al.* 2014).

The brown seaweeds contain mostly fucoidans, soluble homo- or heteropolymers, with L-fucose as the main sugar residue; fucoidans are irregularly branched sulphated HMW-PS, whose monomers are usually linked by (1,3)- and (1,4)- (alternating) bonds Raposo *et al.* (2015a). Alginates are the principal carbohydrates in Sargassum, Fucus, and Ascophyllum (20%–29% DW), which may also present fucoidans in lower percentages (10%–11% DW) (Doty *et al*. 1987). Laminaria, Saccahrina, Ascophyllum, Fucus and Undaria also contain laminaran, a glucan, with (1,3)- and (1,6)- glucose linkages, with some other sugar residues linked laterally. Galactofucans may appear in some brown macroalgae (Laminaria, Undaria) as well (Raposo *et al.* 2015a).

The main carbohydrates of red macroalgae are floridean starch (as reserve/storage) and S-galactans (carrageenans and agarans), as is the case of Chondrus and Kappaphycus, and Porphyra and Gracilaria, respectively. Usual linkages and principal monomers are D-galactose, and anhydrous galactose or D-galactose (alternating). Carrageenans are widely used in foods, for example, as gelling agents in plant-derived gelatins. Polysaccharides from green macroalgae may also consist of (gluco) mannans (Capsosiphon) and a rare mannan in *Codium fragile*, while ulvan is the main PS present in green macroalgae (Enteromorpha, Ulva). Rhamnans (Enteromorpha), galactans (Caulerpa) and other, more complex PS may appear as well (Raposo *et al.* 2015).

In a study of Ramnani *et al.* (2012), they subjected human feces (with respective microbiota) to native and LMW derivatives from alginate and agar, along with extracts from Ascophyllum, Gelidium, and Gracilaria and observed that LMW-PS effectively induced changes in the microbiota. Meanwhile, the effectiveness was greater with Gelidium extract, with a significant increase in the number of Bifidobacteria. In addition, a shift up in SCFAs was observed with a significant increase in acetic and propionic acids after fermentation of the oligo- and polysaccharides from those seaweeds. The highest production of total SCFAs, and acetic and propionic acids, was also noticed after the fermentation of Gelidium-extract (Ramnani 2012). Additional prebiotic properties of these oligosaccharides was shown by a significant increase in the numbers of the various species of Bifidobacterium and Lactobacillus. A positive change in the numbers of beneficial bacteria was also observed in vivo, in the feces and fecal contents of rats and mice, and the growth of bacteroides was inhibited together with other putrefactive microorganisms (Hu *et al.* 2006). They verified that the prebiotic effectiveness of NAOS, was higher than that of other known oligosaccharides (FOS and GOS) as well. AGAROS had already been proven to be able to inhibit the release of pro-inflammatory cytokines and to act against the enzyme glycosidase (Fernandez *et al.* 1989, Enoki *et al.* 2003). The decrease in the pH in vitro studies with different algal-derived oligosaccharides, following an increase of the number of beneficial bacteria (mostly Bifidobacteria and Lactobacilli), is probably due to the production of SCFAs. However, these end-products of the bacterial

fermentation of the oligosaccharides were not determined, the same happening with several animal models (Hu *et al*. 2006).

Some microalgae are also known to have prebiotic properties. For example, the biomass of *Arthrospira platensis* can promote the growth of beneficial bacteria, such as *Streptococcus thermophiles*, *Lactobacillus casei*, and *L. acidophilus* in special (Parada *et al*. 1998). Additionally, harmful pathogenic bacteria (*Bacillus subtilis*, *B. pumulis*, and *Proteus vulgaris*) were inhibited in an in vitro study (Bhowmik *et al*. 2009). When added to yogurt, the biomass from Arthrospira promoted the growth of *L. acidophilus* and Bifidobacteria as well (Beheshtipour *et al.* 2012). *Isochrysis galbana* is another marine microalga with high contents of both soluble and insoluble fibers, and it is promising as a prebiotic since the numbers of LAB increased in the feces of rats treated with *I. galbana* (Nuño *et al*. 2013).

PS from marine microalgae, a homogalactan in Gyrodinium and glucan in *C. vulgaris* are heteropolymers of several different monosaccharides. The structures for the repeating mono-, di- and oligosaccharides were already described for the PS of *Arthrospira platensis*, Porphyrium and Rhodella (Raposo *et al.* 2015b).

In another study, Liu *et al*. (2015) showed that the biomass from the microalgae *Chondrus crispus* possesses prebiotic properties. These researchers fed rats a diet supplemented with *C. crispus* and verified that the animals' microbiota was improved. The beneficial bacteria increased, as did the levels of the acetic, propionic and butyric SCFAs. An improvement of the histomorphology of the colon and an increase in the water-holding capacity of the feces were observed as well, as favorable effects provided by the biomass of the red seaweed. The immune status was also enhanced, as the levels of immunoglobulins A and G increased.

The prebiotic properties provided by seaweeds and marine microalgae should not be restricted to their PS and lignin, but should rather be extended to monosaccharides, enzymes, polyunsaturated fatty acids (PUFAs), peptides, polyphenols, and alcohols, as it was demonstrated for similar compounds from other origins (Gawronski *et al.* 1996, Yangilar 2013, Raposo *et al*. 2013). In the near future, the possibility of using PS from marine algae or oligosaccharides resultant thereof, through several degrading techniques, to modulate the microbiome, and, consequently, to prevent diseases is foreseen.

The various research studies have shown that aqueous algal extracts from *S. platensis*, *Chlorococcum*, *D. salina*, *S. magnus*, *Chlorella* are potential sources for prebiotic production. The extract of *Spirulina platensis* was regarded as the best algal source for prebiotic as it had a greater stimulatory effect on the growth of all three probiotic bacteria (*L. bulgaricus*, *L. lactis*, and *B. longum*). Galactose and xylose characterized by HPLC in algal extracts make up oligosaccharides that function as prebiotic compounds for stimulation of probiotic bacteria (Gourbeyre *et al.* 2011). Thus there is a great scope for successful production of prebiotics from algal sources.

Conclusions

There is growing indication to show that probiotics can be taken by healthy people to prevent certain diseases. Probiotics have established an ability to prevent and treat some infections, particularly GI tract. Several mechanisms, such as stimulation immune response, reduction of intestinal inflammation, reduction of mutagenic compounds, and production of SCFAs, have varying levels of supporting evidence. Antimicrobial production is an important feature of probiotic organism functioning in the gut. Prebiotics may be used as an alternative to probiotics, or as an additional support for them. The development of bio-therapeutic formulas containing both appropriate microbial strains and synergistic prebiotics may lead to the improvement of the probiotic effect in the small intestine and the colon. The concurrent administration of probiotics and pre-biotics, named symbiotics, may synergistically improve their health-promoting effects in the organisms. Microalgae have lately become widespread as new source for both nutraceutical and pharmaceutical products. They have less complex biological systems compared to higher organisms. Certainly, viability of probiotic bacteria during the fermentation process and subsequent refrigerated storage is a major concern in the production of probiotic yogurt or other milk products. Algal polysaccharides present a great potential for developing prebiotics to be used directly, in the case of microalgae, or as dried biomass or nutraceuticals, after extraction from the biomass or from the culture medium. They may be included in food and/or feed. The addition of algae could raise the viability of probiotics in fermented dairy products like yogurt. Future studies related to the addition of different types of microalgae into types of fermented milks other than yogurt, as well as improvement of sensory characteristics of the final products are needed.

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