



Overview of the role of probiotics in health foods and disease prevention

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Abstract

In the industrialized world, functional foods have become a part of an everyday diet and are demonstrated to offer potential health benefits beyond the widely accepted nutritional effects. Currently, the most important and frequently used functional food compounds are probiotics and prebiotics, or they are collectively known as 'synbiotics'. Moreover, with an already healthy image, dairy products appear to be an excellent means for inventing nutritious foods. Such probiotic dairy foods beneficially affect the host by improving survival and implantation of live microbial dietary supplements in the gastrointestinal flora, by selectively stimulating the growth or activating the catabolism of one or a limited number of health-promoting bacteria in the intestinal tract, and by improving the gastrointestinal tract's microbial balance. Probiotics are live microorganisms that live in the gastrointestinal (GI) tract and are beneficial for their hosts and prevent certain diseases. In this chapter, after a complete introduction to probiotics, definition, mechanism of action, and their classification, currently used organisms will be discussed in detail. Moreover, different kinds of nutritional synthetic products of probiotics along with their safety and drug interaction will be noticed. This chapter mentions all clinical trial studies that have been done to evaluate probiotic efficacy with a focus on gastrointestinal diseases.

Keywords: Functional food, probiotics, microorganism, gastrointestinal tract

Introduction

Probiotics, in the form of supplements or food products, have emerged as the most prominent ingredient in the era of functional foods. Probiotics have always been a vital component and commercial target for providing potential health benefits (Sanz *et al.*, 2016) ^[1]. The term "probiotic" was first presented by Werner Kollath in 1953, It is known to be a derivative of the Latin word pro and the Greek word βιο meaning "for life." Kollath defined probiotics as active bodies with essential functions for promoting various health aspects (Gasbarrini *et al.*, 2016) ^[2]. Food and Agriculture Organization (FAO) and World Health Organization (WHO) described them as "live microbes when administered in adequate quantities, confer health benefits on host organisms. Several bacteria belonging to the genera *Pediococcus*, *Lactococcus*, *Enterococcus*, *Streptococcus*, *Propionibacterium*, and *Bacillus* are considered potential microbes for probiotic status (de Brito Alves *et al.*, 2016) ^[3].

The frequently used strains belong to the divergent group of *Bifidobacterium* and *Lactobacillus* that significantly affect health with various actions. They detoxify xenobiotics and environmental pollutants (Reid, 2015) ^[4], bio-transform mycotoxins in foods, synthesize vitamin K, riboflavin, and folate (Reid, 2015) ^[4], and ferment undigested fibre in the colon. Probiotics prevent pathogenic bacteria by restricting binding sites on mucosal epithelial cells and modulating the host immune response, thus improving intestinal barrier integrity. The advantages of probiotics are related to the modulation of gut microbiota, mitigation of nutritional intolerances (lactose

intolerance), increase in bioavailability of macro and micronutrients, and alleviation of allergic incidences in susceptible individuals (Roobab *et al.*, 2020) ^[5].

Probiotics can be consumed either by incorporating them into foods or drinks in the form of dairy or non-dairy foodstuffs or as supplements (Fenster *et al.*, 2019) ^[6]. Various fermented foods have active microbes genetically similar to the strains utilized as probiotics. It has been observed that fermented foods enhance the functional and nutritional aspects by transforming substrates and producing bioactive and bioavailable end-products (Marco *et al.*, 2017) ^[7]. The approximate consumption of 10⁹ colony-forming units (CFU)/day has been revealed as an effective dose (Hill *et al.*, 2014) ^[8]. By keeping in view, the effective dosage, probiotics are being incorporated into many foods like beverages, ice cream, yogurt, bread, and many others by the food industry. The most significant barrier associated with probiotics in the food industry is their susceptibility to processing conditions and sensitivity to gastrointestinal (GI) stresses. However, regarding their health benefits, the consumer always showed an inclined interest in probiotic products (Konuray and Erginkaya, 2018) ^[9]. Now scientists have developed new and innovative methods like nanoencapsulation and genetic modification, which enable probiotics to withstand harsh conditions of both processing and GI stresses in the body (Putta *et al.*, 2018) ^[10]. This review paper provides a profound insight into the mechanistic approach and current perspective on the beneficial aspects of probiotics in preventing and treating various diseases.

The application and safe utilization of probiotics in major food industries have also been described.

The association of probiotics with well-being has a long history. More than a century has passed since Tissier observed that gut microbiota from healthy breastfed infants were dominated by rods with a bifid shape (bifidobacteria) which were absent from formula-fed infants suffering from diarrhoea, establishing the concept that they played a role in maintaining health. Since then a series of studies have supported this association but they were originally poorly designed and controlled and faced practical challenges such as strain specificity of properties and the slow growth of probiotics in substrates other than human milk. By time, they have successfully evolved with the more recent ones accumulating more substantial evidence that probiotic bacteria can contribute to human health. These data have coincided with the increasing consumer awareness about the relationship between health and nutrition creating a supporting environment for the development of the functional food concept introduced to describe foods or food ingredients exhibiting beneficial effects on the consumers' health beyond their nutritive value. The functional food market is expanding, especially in Japan - its birthplace - with further growth prospects in Europe and the United States and in most countries the largest share of its products is held by probiotics ^[1,2]. The reported beneficial effects of probiotic consumption include improvement of intestinal health, amelioration of symptoms of lactose intolerance, and reduction of the risk of various other diseases, and several well-characterized strains of *Lactobacilli* and *Bifidobacteria* are available for human use ^[3,4]. Nevertheless, despite the promising evidence, the role of probiotics in human health as well as the safety of their application should be further investigated as the current knowledge of the characteristics that are necessary for their functionality in the gut is not complete.

Mechanisms of Action

Outstanding advances have been made in the field of probiotics, but there has yet to be a key breakthrough in the documentation of their mechanism of action. Probiotics possibly exert a positive potential on the human body through these main mechanisms; competitive exclusion of pathogens, improvement in intestinal barrier functions, immunomodulation in the host's body, and production of neurotransmitters (Figure 1; Plaza-Diaz *et al.*, 2019) ^[15]. Probiotics compete with pathogens for nutrients and receptor-binding sites, making their survival difficult in the gut (Plaza-Diaz *et al.*, 2019) ^[15]. Probiotics also act as anti-microbial agents by producing substances; short chain fatty acids (SCFA), organic acids, hydrogen peroxide (Ahire *et al.*, 2021) ^[16], and bacteriocins (Fantinato *et al.*, 2019) ^[17] thus decreasing pathogenic bacteria in the gut. Moreover, probiotics improve the intestinal barrier function by stimulating the production of mucin proteins (Chang *et al.*, 2021) ^[18], regulating the expression of tight junction proteins, including occluding and claudin 1, and regulating the immune response in the gut.

Probiotics also regulate the innate and adaptive immune response modulating dendritic cells (DC), macrophages B and T lymphocytes. Probiotics also increase the production of anti-inflammatory cytokines while interacting with intestinal epithelial cells and attracting macrophages and mononuclear cells (Sajedi *et al.*, 2021) ^[19]. Furthermore, probiotics can produce neurotransmitters in the gut through the gut-brain axis. Specific probiotic strains can modulate the serotonin, gamma-aminobutyric acid (GABA), and dopamine levels, affecting mood, behaviour, gut motility, and stress-related pathways (Srivastav *et al.*, 2019) ^[20].

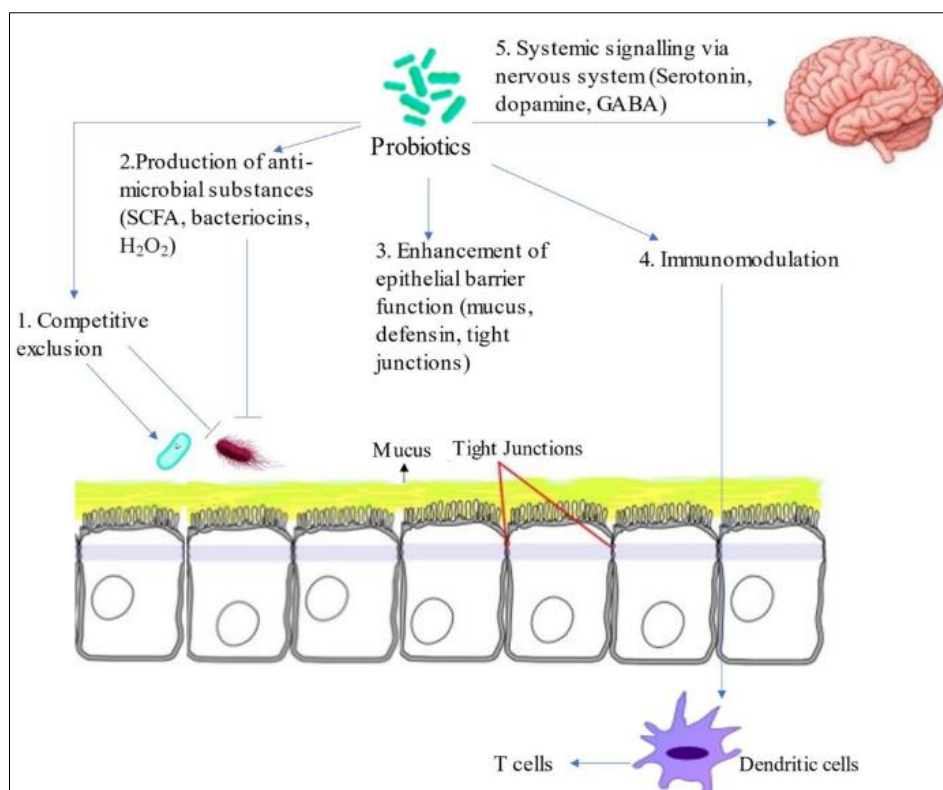


Fig 1: Mechanism of action of probiotics

Microorganisms as probiotics

Numerous studies proved lactic acid bacteria (LAB), bifidobacteria, *Bifidobacterium infantis*, *B. longum*, *B. lactis*, *Escherichia coli*, *Saccharomyces cerevisiae*, *S. boulardii*, *S. lactis*, etc. could be used as probiotics (Table 1). Most of the studies focused on the *in vitro* probiotic establishment of the isolates; very few have tested probiotic efficacy in an animal or human model. Nevertheless, the probiotic activity in most cases is strain-specific. Lactic acid group bacteria such as *Lactobacillus*, *Streptococcus*, *Enterococcus* *Lactococcus*, and *Leuconostoc* are non-sporing and non-motile and acquire their energy by sugar fermentation. Normally, these are classified as facultative anaerobes. According to Zheng *et al.* (2020), *Lactobacillus* genus was reclassified into 25 genera including two host-adapted organisms such as *Lactobacillus delbrueckii* and *Paralactobacillus*, and rest 23 of them were

as *Holzapfelia*, *Amylolactobacillus*, *Schleiferilactobacillus*, *Loigolactobacillus*, *Lacticaseibacillus*, *Latilactobacillus*, *Dellaglioia*, *Bombilactobacillus*, *Companilactobacillus*, *Lapidilactobacillus*, *Agrilactobacillus*, *Ligilactobacillus*, *Liquorilactobacillus*, *Furfurilactobacillus*, *Lactiplantibacillus*, *Limosilactobacillus*, *Paucilactobacillus*, *Fructilactobacillus*, *Apilactobacillus*, *Aceitilactobacillus*, *Secundilactobacillus*, *Levilactobacillus*, and *Lentilactobacillus*. LAB is commonly distributed as natural microbiota in the intestinal tracts and different fermented foods such as pickles, sauerkraut, cheese, yoghurt, beer, wine, juices, and sausage. Lactic acid bacteria may have several health benefits along with nutritious advantages. Probiotics improve the food's nutritional value, regulate intestinal infections, improve lactose digestion via sufficient quantity of lactase production, control some types of cancers, and reduce blood cholesterol.

Table 1: List of microorganisms that are widely used as probiotics

<i>Lactobacillus</i> sp.	<i>L. acidophilus</i> , <i>L. rhamnosus</i> <i>L. gasseri</i> , <i>L. casei</i> <i>L. reuteri</i> , <i>L. plantarum</i> , <i>L. salivarius</i> <i>L. johnsonii</i> , <i>L. gallinarum</i> , <i>L. plantarum</i> , <i>L. fermentum</i> <i>L. helveticus</i> , <i>L. brevis</i> <i>L. murinus</i> , <i>L. crispatus</i> , <i>L. amylovorus</i>
<i>Bifidobacterium</i> sp.	<i>B. infantis</i> , <i>B. longum</i> <i>B. lactis</i> , <i>B. adolascensis</i> <i>B. bifidum</i> , <i>B. animalis</i> <i>B. breve</i> , <i>B. thermophilum</i> <i>B. pseudolongum</i>
Yeast	<i>S. boulardii</i> , <i>S. lactis</i> , <i>S. carlsbergensis</i> , <i>Kluuyveromyces marxianu</i> , <i>S. cerevisiae</i>
Other micro-organisms	<i>B. subtilis</i> , <i>B. licheniformis</i> , <i>Enterococcus faecalis</i> , <i>E. faecium</i> , <i>Leuconostoc mesenteroides</i> <i>L. lactis</i> , <i>L. citreum</i> , <i>Pediococcus acidilactici</i> , <i>P. pentosaceus</i> , <i>Propionibacterium freudenreichii</i> , <i>Streptococcus salivarius</i> subsp. <i>Thermophilus</i> , <i>S. infantarius</i>

Prospective applications of probiotics in developing healthful foods

A growing public awareness of diet-related health issues and mounting evidence regarding the health benefits of probiotics have increased consumers' demand for probiotic foods. Many food products including yoghurt, frozen fermented dairy desserts, spray-dried milk powder, cheeses, ice cream, freeze-dried yoghurt (Nagpal *et al.*, 2007; Kumar *et al.*, 2009; Nagpal & Kaur, 2011), and fruit juices (Nagpal *et al.*, 2012) ^[60-63] have been suggested as delivery vehicles for probiotic to the consumer. It has been suggested that approximately 10⁹CFU per day of probiotic microorganisms is necessary to elicit health effects. Based on the daily consumption of 100 g or mL of probiotic food, it has been suggested that a product should contain at least 10⁷ cells per g or mL of food, a level that was also recommended in Japan (Ross *et al.*, 2002) ^[64]. The most popular food delivery systems for probiotics have been fermented milk and yoghurt. A few studies have shown that many commercial yoghurt products have failed to successfully deliver the required level of viable cells of probiotic bacteria (Dave & Shah, 1997) ^[65]. Cheeses have several advantages over fresh fermented products (such as yoghurt) as a delivery system for viable probiotics to the GI tract. Cheeses tend to have a higher pH and more solid consistency where the matrix of the cheese and its relatively high fat content may offer protection to probiotic bacteria during passage through the GI tract. Cheese also has a higher buffering capacity than yoghurt (Gardiner *et al.*, 1998) ^[66]. Overall, the major points to be addressed while incorporating probiotics into foods are the selection of a compatible probiotic strain/food type combination; using food processing conditions that are compatible with probiotic survival; ensuring that the food matrix supports probiotic growth (if fermentation is required); selecting a product matrix, packaging, and environmental conditions to ensure adequate probiotic survival over the product's supply chain and during

shelf storage; and finally ensuring that addition of the probiotic does not adversely impact on the taste and texture of the product.

Probiotics and their use in different health products

There is increasing evidence in favour of the claims of beneficial effects attributed to probiotics, including improvement of intestinal health, enhancement of the immune response, reduction of serum cholesterol, and cancer prevention. These health properties are strain-specific and are impacted by the various mechanisms mentioned above. While some of the health benefits are well documented others require additional studies to be established. There is substantial evidence to support probiotic use in the treatment of acute diarrhoeal diseases, prevention of antibiotic-associated diarrhoea, and improvement of lactose metabolism, but there is insufficient evidence to recommend them for use in other clinical conditions.

The use of probiotics in the form of live bacteria for health promotion in animals and human beings is emerging daily. Today, a vast array of fermented food items and beverages is available, accounting for approximately one-third of worldwide human diets (Borresen, *et al.* 2012) ^[21]. The level of probiotics in foods ranges from 2 to 20 g/day depending on the component and desired effect and can be added to different food products, including cereals, biscuits, bread, sauces, yoghurts, and drinks (Dekumpitiya., *et al.*, 2016) ^[22]. Curd is considered the most preferred source of probiotics, as it is globally consumed (Granato., *et al.*, 2010) ^[12]. Interest in and development of functional foods consisting of both probiotics and prebiotics have increased due to increased awareness of their health-promoting properties. They positively affect gut health and decrease the risk of diseases, which is why they are used as therapy (Sullivan., *et al.*, 2020) ^[24].

All probiotic products have different nutritional and therapeutic characteristics, due to various conditions, such as the genetic makeup of the strain, the amount of the probiotics used in the

product, the purpose it is used for, and its shelf life.

The selection of a probiotic strain depends on its production, impact, and health benefits in the host (Ghishan., *et al.*, 2011) [25]. A probiotic food must have 10⁶ CFU/g of probiotic microorganisms to achieve a health benefit. The dosage recommended for human consumption is 10⁷–10⁹ CFU/mg/day. It is known that the effect of probiotic food consumption depends on the specific strain used in that product (Islam, *et al.*, 2016) [26]. To get the beneficial strains of probiotics, the following genera are of great importance: *Lactobacillus*, *Escherichia coli*, *Bifidobacterium*, *Enterococcus*, *Saccharomyces*, *Pediococcus*, *Streptococcus*, and *Leuconostoc*. The most common micro-organisms used as probiotics are lactic acid bacteria (LAB) and *Bifidobacteria* (Harneet Singh, *et al.*, 2014) [27].

Strains of *Lactobacillus* species that are commonly found in saliva samples include *L. paracasei*, *L. plantarum*, and *L.*

rhamnosus. The *bifidobacterial* species are the anaerobes that are also found in the oral cavity, and both species are found in breast milk and are generally regarded as safe (Salveti., *et al.*, 2012) [28]. Several elements, such as nutrition, age, environmental difficulties, incompatibilities, illnesses, and treatment routes, strongly impact gut microbiota growth, maintenance, and functionality (Zommiti., *et al.*, 2020) [29]. When selecting the strain it must be kept in mind that it should be originated from target and natural microflora as it is vital for its survival in an acidic environment during its travel to the intestine (Shokryazdan., *et al.*, 2017) [30] (Shewale, *et al.*, 2014) [31]. Probiotics have a positive effect on the immune system of the host and it was proven that they influence the healthy bacteria present in the gut or intestine (Jiang, *et al.*, 2017) [32]. Probiotics improve the immunity system by modifying the humoral and cellular immune response (Dhama, *et al.*, 2011) [33]. Figure 2 summarizes the benefits of different probiotics on health.

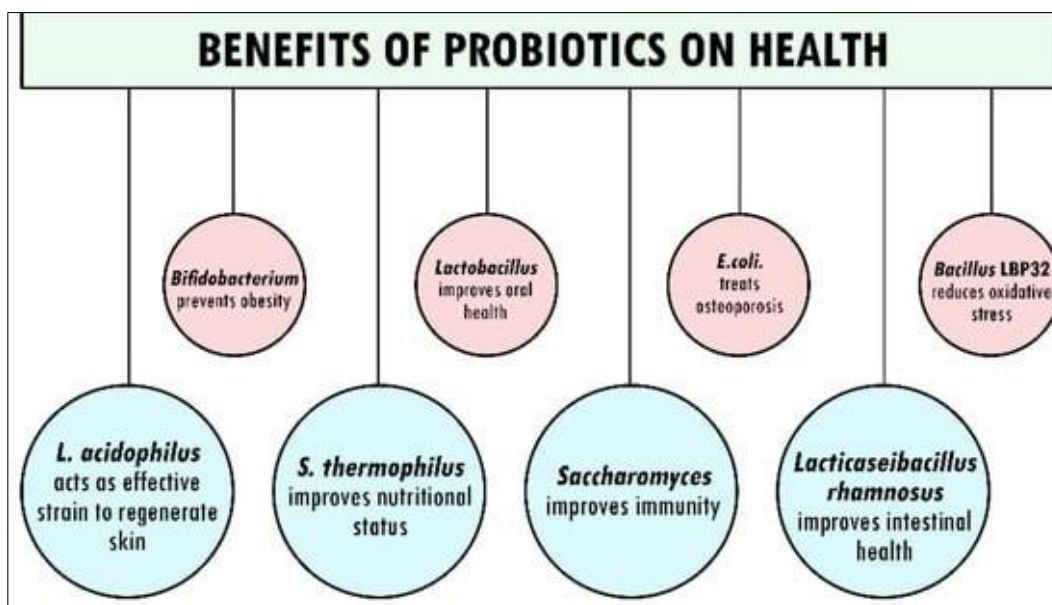


Fig 2: Benefits of probiotics on health (Kechagia, *et al.*, 2013) [34]

The strains that are being selected also depend on the biosafety level, which means they should not be toxic or pathogenic (Venugopalan, *et al.*, 2010) [35]. They should be tested for safety parameters, including antibiotic susceptibility, antibiotic resistance genes, and hemolytic activity. Antimicrobial production is an important feature of probiotics against pathogens, but non-optimal antimicrobial activity will disrupt the healthy microbiota in the intestines and pose harmful effects (Santacroce, *et al.*, 2019) [36]. Bile present in higher concentrations resulted in the lower growth of strains (Sivamaruthi, *et al.*, 2020) [37]. Probiotics can alter the pH of the surrounding environment, and hence they can compete with the pathogens present there.

In the same way, probiotics adhere to the adhesion sites on the mucosa, which decreases the chances of adhesion of pathogens and decreases the cases of probiotics being washed out (Chaucheyras-Durand, *et al.*, 2001) [38]. Different tests are performed to identify the strain of bacteria, such as biochemical and molecular tests, and then further techniques are used to differentiate between the strains of the same species, such as polymerase chain reaction (PCR) and gene sequencing tests

(Galanis., *et al.*, 2015) [39] (Sattler., *et al.*, 2014) [40]. Other tests are performed, such as hemolytic tests to determine whether the organisms are destroying red blood cells or not and platelet aggregation tests, which are crucial factors for pathogen activity (Collins, *et al.*, 2012) [41]. The recommended storage temperature for probiotic foods is 4–5 °C, and the product must be used according to the information noted on the label, which should be clear (Fenster, *et al.*, 2019) [6].

Association of Probiotics in Prevention of Diseases

Probiotics are very helpful in preventing chronic diseases by mediating their effects. They show positive effects on gut health and help in skin-related problems such as burns, scars, infections, and wounds. They increase the skin's innate immunity and help to regenerate healthy skin (Delgado, *et al.*, 2017) [43]. The action of *Saccharomyces cerevisiae* dressing improved burn skin healing significantly as demonstrated by (Oryan, *et al.*, 2018) [44], whereas a hypothetical model of intestinal microbiota influencing wound healing through gut-brain-skin axes explains damaged tissue repair (Lukic, *et al.*, 2017) [45].

The distinction in gut microbiota constitution and decreased

levels of *Bifidobacteria* and *Lactobacillus* in infants' guts leads to the onset of allergic symptoms. Both the reports of specific probiotic strains and their results indicate that they can be used in the prevention of eczema. Dysbiosis, also known as dysbacteriosis, is a term used for imbalance in microbes inside the body, such as impaired microbiota, which is often related to inflammatory bowel disease, colonic cancer, metabolic syndrome, and allergic reactions. Improving the gut microbiota balance by different nutritional concepts or by ingesting specific micro-organisms led to significant improvement in health and decreased the risk of diseases or changing treatment mode (Salonen, *et al.*, 2010) ^[46].

The development of irritable bowel syndrome is associated with deviation in intestinal homeostasis, whose outcome is the uncontrolled immune response to gut microbiota by intestinal immune cells and epithelial cells, which results in complications including ulcers and fibrosis. A prebiotic is a valuable food substance that can be used to facilitate the growth of beneficial bacteria that modifies intestinal microbiota. Both probiotics and prebiotics are helpful for irritable bowel syndrome (Lukic, *et al.*, 2017) ^[45].

Probiotics have been involved in the healing process of intestinal ulcers and infected cutaneous wounds. Skin microbiota acts as a defensive barrier and can regulate the skin's inflammatory response to minor epidermal injury by decreasing and promoting cytokine production to maintain healthy skin (Iacono, *et al.*, 2011) ^[47]. The process through which probiotics show positive effects includes directly killing the pathogen, increasing the epithelial barrier, competitive displacement of pathogenic bacteria, and induction of fibroblasts (Nole, *et al.*, 2014) ^[48].

Probiotics are also very beneficial for burn patients; they can reduce the bacterial load on the ulcer area (Holmes, *et al.*, 2014) ^[49]. Skin injuries cause disturbance in microbiota levels and increase the prevalence of bacteria that exert adverse effects on wounds. Additionally, having a wound causes stress, which results in alterations of neuro-endocrinal responses and impairs wound healing (Tsiouri, 2017) ^[50]. Chronic wounds are those that are difficult to heal and can exert a burden not only on the patient but also on the health care system, for example, diabetic foot ulcers (DFU), venous leg ulcers (VLU), and decubitus ulcers (DU). In chronic wounds, polymicrobial biofilms that promote pathogenic microbial growth and interfere in the process of wound healing are abundant and play an important role in the development of impaired wounds (Moratalla, *et al.*, 2021) ^[51].

Probiotics play an important role in the treatment of autism by affecting the microbiome, which is present in the gut and responsible for imbalanced neuro-developmental conditions, like autism. If gene *Shank3* is disturbed by gut microbes, it affects a person's behavior and can lead to autism (Navarro, *et al.*, 2016) ^[52]. There are numerous medicines available for treatment, but they have side effects; to avoid these side effects, probiotics are used as an alternative therapy. Probiotics alter the gene that is responsible for neurodevelopment and maintains the gut environment to treat this disease (Daulatzai, *et al.*, 2014) ^[53]. This bacterial disorder promotes different pathophysiological gastrointestinal syndromes like bowel syndrome, obesity, diarrhea, and food allergies (Roman, *et al.*, 2018) ^[54].

Dietary biotic aid is used to maintain the GIT flora and relieve pain, vomiting, nausea, and bowel syndrome. The most potent

probiotic strains used to treat GIT disorder are *L. rhamnosus* GG, *L. reuteri* 17938, VSL #3, and *Bifidobacteria* species (Larroya-García, *et al.*, 2019) ^[55]. With probiotic intake, stool PCR tests of autistic children indicated increased colony count of *Bifidobacteria* and *Lactobacilli* with a major bodyweight loss and great progress in the severity of autism and gastrointestinal disorders (Hori, *et al.*, 2020) ^[56]. In pregnancy, Interleukin-6, 17a cytokines prompt autism spectrum disorder. Probiotics play an important role in inhibiting the production of cytokines and preventing the autism spectrum disorder induced by maternal immune activation (Liu, *et al.*, 2016) ^[57].

Osteoporosis is a disease that affects the skeletal system, manifesting as low bone mass density, deterioration of the skeletal system, and greater bone brittleness and sensitivity to cracks. Most cracks are in the distal forearm, femur, and back. These cracks especially occur in postmenopausal women (Collins, *et al.*, 2017) ^[58]. The cause of bone loss is due to the low level of the estrogen hormone because estrogen performs a significant role in developing and sustaining bones (Svensson, 2018) ^[59].

Colorectal cancer

Colorectal cancer (CRC) is the most frequent neoplastic form of the gastrointestinal tract; its incidence is experiencing a progressive increase, due to a gradual ageing of the population, the adoption of a sedentary lifestyle, and unbalanced diets (Ponz de Leon, *et al.*, 2007) ^[67] as also suggested by the higher incidence rates in Australia and New Zealand, North America, and Europe (Dionigi, *et al.*, 2019) ^[68]. Although it is a multi-etiological condition, it should be considered the genetic susceptibility of each individual, as well as some environmental factors connected to carcinogenesis, like caloric intake, obesity, alcohol or smoking. Focusing on gut microbiota, CRC patients often develop dysbiosis due to the use of antibiotics, radiation therapy, and chemotherapy, and their gut microbiota is characterized by an increased pathogenic bacteria abundance, decreased SCFA-producing bacteria and SCFA levels (Wang, *et al.*, 2012) ^[69], and butyrate seems the most affected compound, as it could be successfully used as a potential biomarker of CRC risk or as an early warning signal of the disease onset. Conversely, high levels of SCFA have antineoplastic properties, due to a combination of several mechanisms, like the downregulation of the canonical Wnt signalling pathway linked to colonic carcinogenesis, the limitation of proliferation and migration of neoplastic cells, the suppression of tumour angiogenesis, the induction of apoptosis and the promotion of neoplastic colonocytes differentiation (Wong, *et al.*, 2017) ^[69].

Neuro-psychiatric diseases

Many human and animal studies support the idea that gut microbiota plays an important role in cognitive functions, in the regulation of mood and emotions, and interpersonal interactions and communications (Sarkar, *et al.*, 2018) ^[71]. Gut microbiota can modulate brain activity and behaviour; therefore, its manipulation can be applied in the treatment of neuropsychiatric disorders such as autism spectrum disorders, depression, etc. (Kelly, *et al.*, 2016) ^[72], (Accettulli, *et al.*, 2022) ^[73]. The idea that probiotics could positively affect the clinical outcomes of depression was first postulated in 1910 when Hubert J. Norman and Georges Porter Philipps found an improvement in the symptoms after taking lactobacilli. Later then, this idea was

confirmed by several studies and clinical trials, although the mode of action of probiotics on behaviour and neuro-psychiatric diseases is still unclear, as in some cases symptom improvement and amelioration are not related to a modification in gut microbiota.

Intestinal diseases

Generally, probiotics could positively impact gastrointestinal disorders (GI) (abdominal pain or discomfort, swelling and flatulence) through metabolic effects resulting from the enzymatic activity and the crosstalk with the central nervous system, by improving gut function (Eales, *et al.*, 2017) [75]. In addition, there are several evidence of positive effects on Inflammatory Bowel Disease (IBD) and Irritable Bowel Syndrome (IBS).

Obesity

Gut microbiota is involved in the control of body weight, energy homeostasis and inflammation states; therefore, it plays an important role in the pathophysiology of obesity. Firmicutes and Bacteroidetes are the two phyla involved in microbial dysbiosis and in the development of obesity. The ratio between these phyla is very important; in fact, (Bervoets, *et al.* 2013) [76] studied the gut microbiota of 26 overweight and obese children and 27 skinny children and found that obese children have a higher ratio of Firmicutes to Bacteroidetes.

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