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REVIEW FOR HEALTH BENEFITS OF PROBIOTICS IN DISEASE PREVENTION

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ABSTRACT

The health benefits imparted by probiotics and prebiotics as well as synbiotics have been the subject of extensive research in the past few decades. Probiotics, live cells with different beneficiary characteristics, have been extensively studied and explored commercially in many different products in the world.Probiotics used in humans are most of ten of the Lactobacillus and Bifidobacterium species. However, as more research is conducted, new species with beneficial, probiotic properties are being discovered. This paper provides a review of available information about the influence of probiotics on human health. Few treatments for human diseases have received as much investigation in the past 20 years as probiotics. In 2017, English-language meta-analyses totaling 52 studies determined the effect for various probiotics include cardiovascular disease, colon cancer, acute diarrhea, antibiotic-associated diarrhea & radiation associated diarrhea, *H. pylori* infection, allergic conditions, hepatic encephalopathies, inflammatory bowel diseases, irritable bowel syndrome common infectious disease, necrotizing enterocolitis, lactose malabsorption, nonalcoholic fatty liver disease,upper respiratory tract infections, prevention of systemic infections, boosting immune response, Anti-diabetic and Anti-obesity activity etc. The literature on the health benefits of probiotics has often focused on disease states using either animal models of such diseases or studies in human populations.

INTRODUCTION

Probiotic is a relatively new word meaning 'for life', which is used to name microorganisms that are associated with the beneficial effects for humans and animals' health [1]Research in probiotic has progressed considerably in the past two decades and significant advances have been made in the selection and characterization of specific probiotic cultures along with substantial health benefits upon consumption. An ecological consideration of the gut flora is necessary to understand their relevance in human health, as well as the probiotic food concept. Each individual has a unique signature of more than 100-1000 microbial species in gastrointestinal tract (GIT) [2].Bacterial cells comprise half of the wet weight of colonic material and their numbers exceed by 10-fold the number of tissue cells forming the human body. Normally, the stomach contains 10^3 different bacterial species, the total microbial population of colon comprises of about 10^{11}-10^{12} cfu/g[3].

The United Nations Food and Agricultural Organization and the World Health Organization define probiotics as "live microorganisms such as bacteria or yeast that are similar to beneficial microorganisms found in the human gut, which when administered in adequate amounts confer a health benefit on the host [4,5] and are included in a number of fermentable foods, pills, powders, and liquid drops. Common probiotics are available in pharmacies, groceries, and online in the United States. They include but are not limited to *Lactobacillus rhamnosus GG, Lactobacillus reuteri, Lactobacillus casei, Lactobacillus paracasei, Bacillus coagulans, Bacillus clausii, Bifidobacterium infantis, Bifidobacterium longum, Bifidobacterium infantis, Streptococcus thermophilus, Escherichia coli strain Nissle1917,* and yeasts, including *Saccharomyces boulardii and Saccharomyces cerevisiae*. Many probiotics contain mixtures of two or more individual species. Prebiotics are defined as metabolic substrates that promote the growth and/or activity of beneficial microorganisms, usually in the gastrointestinal tract[6].

Although their definition has been debated and modified, the general consensus is that prebiotics are nondigestible by human gastrointestinal cells. Prebiotics include oligosaccharides, resistant starch, and soluble or insoluble fibers. Synbiotics are defined as mixtures of probiotics and prebiotics that beneficially affect the host by impacting the microbiome within the gastrointestinal tract[7]. Probiotics are able to regenerate our digestive system with good microbes that will neutralize the harmful ones. Useful microbes will ferment our food correctly and improve our health. During our lives, we are exposed to different types of microbes, which are unsuitable for our health. Antibiotic treatment could destroy our useful microflora. In such cases, Probiotics should be used to regenerate our microflora. If

our daily food contains Probiotics, that will be the best and the cheapest way to recover any losses in our digestive system microflora and to improve our health. In olden civilizations, the public used to include food-containing Probiotics in their daily food [8]. However, when our microflora has been affected severely due to any reasons, Probiotics should be given in large dosage as tablets or in any other suitable forms [9].

Meaning of probiotics

Probiotics are live microbes that can be formulated into many different types of products, including foods, drugs, and dietary supplements. Species of Lactobacillus and Bifidobacterium are most commonly used as probiotics, but the yeast *Saccharomyces cerevisiae* and some *E. coli* and Bacillus species are also used as probiotics. Lactic acid bacteria, including Lactobacillus species, which have been used for preservation of food by fermentation for thousands of years, can serve a dual function by acting as agents for food fermentation and, in addition, potentially imparting health benefits. Strictly speaking, however, the term "probiotic" should be reserved for live microbes that have been shown in controlled human studies to impart a health benefit. Fermentation of food provides characteristic taste profiles and lowers the pH, which prevents contamination by potential pathogens. Fermentation is globally applied inpreservation of a range of raw agricultural materials (cereals, roots, tubers, fruit and vegetables, milk, meat, fish etc.) [10].

The genus Bifidobacterium

Bifidobacteria were first isolated and described in 1899–1900 by Tissier, who described rod-shaped, non-gas-producing, anaerobic microorganisms with bifidobacterial morphology, present in the faeces of breast-fed infants, which he termed Bacillus bifidus. Bifidobacteria are generally characterized as Gram-positive, non-spore-forming, non-motile and catalase-negative anaerobes [11]. They have various shapes including short, curved rods, club-shaped rods and bifurcated Y-shaped rods. Presently, 30 species are included in the genus Bifidobacterium, 10 of which are from human sources (dental caries, faeces and vagina), from animal intestinal tracts or rumen, two from wastewater and one from fermented milk [12]. Bifidobacteria are microorganisms of paramount importance in the active and complex ecosystem of the intestinal tract of humans and other warm-blooded animals, as well as of honeybees [11].They are distributed in various ecological niches in the human gastrointestinal and genitourinary tracts, the exact ratio of which is determined mainly by the age and diet. The indigenous microflora of infants is dominated by bifidobacteria, which are established shortly after birth. Their proliferation is stimulated by the glycoprotein components of k-casein in human colostrum and, to a lesser extent, human milk. The

number of bifidobacteria decreases with increasing age of an individual and eventually becomes the third most abundant genus (accounting for approx. 25 %of the total adult gut flora) after the genera Bacteroides and Eubacterium [13].

The genus Lactobacillus

In 1990, Moro was the first researcher to isolate a strain which he typified as Bacillus acidophilus, a generic name for intestinal lactobacilli. Lactobacilli are in general characterized as Gram-positive, non-spore-forming and non-flagellated rods or coccobacilli [14]. They are either aerotolerant or anaerobic and strictly fermentative. Glucose is fermented predominantly to lactic acid in the homofermentative case, or equimolar amounts of lactic acid, CO2 and ethanol (and/or acetic acid) in the heterofermentative counterpart. Gomes and Malcata [13] reported that 56 species of the genus Lactobacillus have been recognized. Lactobacilli are distributed in various ecological niches throughout the gastrointestinal and genital tracts and constitute an important part of the indigenous microflora of man and higher animals. Their distribution is affected by several environmental factors, which include pH, oxygen availability, level of specific substrates, presence of secretions and bacterial interactions. They are rarely associated with cases of gastrointestinal and extraintestinal infection, and strains employed technologically are regarded as non-pathogenic and safe microorganisms. Furthermore, they have the reputation of health promoters, especially in the human gastrointestinal and genitourinary tracts [15].

Health benefits of probioticsand symbiotic

The most important and documented beneficial effects of probiotics include the prevention of diarrhea, constipation, changes in bile salt conjugation, enhancement of antibacterial activity, anti-inflammatory. Furthermore, they also contribute to the synthesis of nutrients and improve their bioavailability; some probiotics are known to exert anti-oxidative activity in the form of intact cells or lysates. Probiotics have also demonstrated their inherent effects in alleviating symptoms of allergy, cancer, AIDS, respiratory and urinary tract infections. There are stray reports on their beneficial effects on aging, fatigue, autism, osteoporosis, obesity and type2diabetes [16]. As shown below a number of mechanisms are thought toassociated with probiotic beneficial effects:

- Production of inhibitory substances like H_2O_2, bacteriocins, organic acids, etc.,
- Competition with the pathogenic bacteria for nutrients,
- Blocking of adhesion sites for pathogenic bacteria.
- Modulation of immune responses.
- Degradation of toxins as well as the blocking of toxin receptors,

Probiotics in Food and Beverages

As it was reported by Chow [17], the notion that food could serve as medicine was first conceived thousands of years ago by the Greek philosopher and father of medicine, Hippocrates, who once wrote: 'Let food be thy medicine, and let medicine be thy food'. However, during recent times, the concept of food having medicinal value has been reborn as 'functional foods'. A probiotic may also be a functional food [18]. Functional foods are defined as: 'foods that contain some health-promoting component(s) beyond traditional nutrients'. Functional foods are also known as designer foods, medicinal foods, nutraceuticals, therapeutic foods, superfoods, foodiceuticals, and medifoods. In general, the term refers to a food that has been modified in some way to become 'functional'. One way in which foods can be modified to become functional is by the addition of probiotics [19]. New food products have been formulated with the addition of probiotic cultures. Different types of food matrices have been used such as various types of cheese, ice creams, milk-based desserts, powdered milk for newborn infants, butter, mayonnaise, powder products or capsules and fermented food of vegetable origin [20].

Nowadays, consumers are aware of the link among lifestyle, diet and good health, which explains the emerging demand for products that are able to enhance health beyond providing basic nutrition. The list of health benefits accredited to functional food continues to increase and the probiotics are one of the fastest growing categories within food for which scientific researches have demonstrated therapeutic evidence. Among several therapeutic applications of the probiotics can be cited the prevention of urogenital diseases, alleviation of constipation, protection against traveller's diarrhoea, reduction of hypercholesterolemia, protection against colon and bladder cancer, prevention of osteoporosis and food allergy [21]. One of the most studied strains, *Bifidobacterium lactis*, has been used in several types of studies to demonstrate its probiotic ability, and scientific evidence for this strain has been cited in many reviews [22–26]. Ingestion of LAB has been suggested to confer a range of health benefits including immune system modulation [27,28], increased resistance to malignancy [29] and infectious illness [30, 31].

Allergic Diseases

Allergic diseases have become a serious health concern in recent decades. The number of cases of atopic dermatitis, food allergies, or asthma is constantly increasing, especially in Western societies.More favorable results were obtained by examining the effectiveness of probiotics in the prevention and treatment of eczema and atopic dermatitis. Kukkonen et al. proved that giving pregnant women complex probiotics (*Lactobacillus rhamnosus*, *Bifidobacterium breve*, and *Propionibacterium freudenreichii*)

significantly reduces the risk of atopic dermatitis in children up to the age of two [32]. The preventive effect of LG Ghas also been demonstrated in another clinical study conducted on pregnant women in New Zealand [33]. A meta-analysis of 21 clinical trials in which prenatal and postnatal women were given probiotics showed that they are effective in preventing but not treating atopic dermatitis. The results of another meta-analysis showed the preventive effect of probiotics on the development of eczema, but the effectiveness of the use of probiotics for other allergic diseases has not been confirmed [34].

Heart and Circulatory System

Cardiovascular disease (CVD) is a leading cause of death worldwide. There are numerous reports on the beneficial properties of certain probiotic strains used in treatments aimed at lowering cholesterol and treating hypertension.[35]Hypertension is closely related to hypercholesterolemia. It has been proven that selected strains of the genera Lactobacillus and Bifidobacterium are effective in lowering blood pressure because they produce peptides that act similarly to drugs from the group of angiotensin converting enzyme (ACE) inhibitors [36]. The cardioprotective effect of probiotics on the heart muscle has been proven in animal model studies. Inhibition of proinflammatory cytokine production and reduction of oxidative stress have also been exhibited by B. breve, *L. casei*, *L. bulgaricus*, and *L. acidophilus*. Therefore, probiotic supplements may find use as an additional prophylactic option in patients at risk of coronary heart disease [37, 38]. High cholesterol, especially the LDL fraction, is a major precursor of hypertension, hyperlipidemia, and coronary heart disease and also causes plaque buildup in the arteries. The serum LDL fraction maintained within the optimal range reduces the chances of these diseases occurring. In a study in which a meta-analysis of randomized clinical trials was conducted on 1971 patients, it was shown that probiotic strains, i.e., *L. acidophilus*, *L. Lactis*, and *L. plantarum*, significantly reduce the level of total serum cholesterol [39]. Lowering the total cholesterol and LDL fraction in all groups compared to the control group was observed in a study involving 485 patients with high, borderline, and normal cholesterol [40].hence more randomized multicenter studies should be conducted to broaden the knowledge about the possibility of using probiotics in the treatment of cardiovascular diseases.

Neurodegenerative Diseases

Neuropsychiatric diseases have various causes. The emerging evidence of the interaction between the brain, intestines, and microbiome can help explain the mechanisms underlying these complex interactions. A two-way information exchange takes place on the gut-brainaxis. Direct and indirect exchange mechanisms include nerve (vagus, intestinal

nerves), hormonal (serotonin, monoamines, GABA, neutrophilic brain factor), and immune pathways. It is believed that changes in the intestinal microbiome are a possible cause of some brain diseases, including Parkinson's disease (PD), Alzheimer's disease(AD), and multiple sclerosis (MS).A study by Akbari et al. showed that a probiotic supplement consisting of *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum*, and Lactobacillus fermentum administered for 3 months improves the cognitive functions of patients with AD [41].One of the latest review articles discusses microbiological therapy as a novel treatment for Parkinson's disease. This analysis also contains data on the effects of stool transplantation in patients with Parkinson's disease [42].Patients with MS also have a reduced amount of Lactobacillus bacteria. The administration of these probiotic strains resulted in increased bacterial diversity in the microbiome. At the immune level, the administration of probiotics induced an anti-inflammatory peripheral immune response. In addition, in the control group with the MS risk gene (HLA-DQA1), a reduced expression of this gene was observed. These results suggest that probiotic treatment may have a synergistic effect [43].In addition, future research probiotics in patients with neurodegenerative diseases, as well as hormonal, immunological, neurochemical, and metabolic changes induced by probiotics or prebiotics. Therefore, further investment in large-scale clinical trials is needed to prove the efficacy of probiotics in neurodegenerative diseases [44].

Diarrhea

Diarrhea is defined by the World Health Organization as three or more loose or watery stools during 24-hour period. In the last 2 decades, several investigations on probiotic microorganisms by *in vitro* studies, animal experiments and appropriate well-designed clinical studies have validated the positive effects of probiotic consumption in arresting diarrhea of different types [45].

- **Acute infantile diarrhea**

Acute infantile diarrhea caused by rotaviruses is most studied gastrointestinal condition and rapid oral rehydration is the primary treatment. Probiotics have been found to be useful as adjunct to rehydration therapy. Although limited data is available, it suggests the minimal effective dose in children is 10 billion CFU within the first 48 hours [46].

- **Antibiotic associated diarrhea**

Probiotics including various bacterial species like *L. acidophilus*, *L. rhamnosus* GG, *L.delbruckii*, *L.fermentum* etc. and the yeast *S. boulardii* are effective in reducing the incidence of antibiotic-induced diarrhea [47]. However, it remains to be established by controlled clinical studies which probiotic is more effective and what dosage(s) are to be used. [48].

- **Traveller's diarrhea**

It is estimated that 20–60% of travellers around the world are affected by traveller's diarrhea. It particularly affects people who travel from industrialized to developing countries, especially tropical and semi-tropical regions. The most common causes are bacteria (60–85 % of cases) and most responsible bacterial pathogen is *Escherichia coli* followed by *Campylobacter jejuni*, Shigella spp.AndSalmonellaspp.Parasitesaccountforabo ut10%and viruses for balance 5 % of infections [49]. It was observed that S.boulardii was found to be more effective on bacterial diarrhea and Lactobacillus GG showed effectiveness against viral and idiopathic diarrhea. Lactobacilli, Bifidobacteria, Enterococci and Streptococci have been used prophylactically to prevent traveller's diarrhea [50].

Irritable bowel syndrome (IBS)

IBS is one of the most common functional gastrointestinal disorders and is a chronic condition characterized by recurrent bouts of abdominal discomfort and pain, bloating and a changeable bowel habit with an absence of anyovert mucosal abnormality and flatulence. The multi-factorial pathophysiological factors for inducing IBS are:a) Psychological factors like stress and emotional status b) Social factors like upbringing and support systems and c) Biological factors like gut motility and visceral sensitivity, which interact in a complex way to exacerbate the symptoms [51].Probiotic *Escherichia coli* Nissle 1917 has also been proved effective in IBS treatment, especially in patients with altered enteric microflora, e.g., aftergastro-enterocolitis or administration of antibiotics [52].

Inflammatory bowel disorder: (IBD)

IBD is chronic, relapsing, multi-factorial disorder causing inflammation of the gastro-intestinal tract that causes severe watery, bloody diarrhea accompanied by abdominal pain. IBD affects bothcolon, small intestine and includes Ulcerative colitis (UC), Crohn's Disease (CD) and pouchitis [53].

- **Ulcerative colitis**

(UC) UC like IBD mainly affects the lining of the large intestine and rectum. Long-standing UCisa risk factor for colon cancer. Use of various probiotic species like *S. boulardii*, *Lactobacillus casei* and *Bifidobacterium bifidum* has shown promising results [54].

- **Crohn's disease**

Crohn's disease is a form of IBD which usually affects the intestine, but may occur anywhere. Body's ability to absorb nutrients and eliminate waste in a healthy way. Salmonella, *Campylobacter jejuni*, *Clostridium difficile*, Adenovirus, and Mycoplasma have been identified as some of the common causative agents. There are reports suggesting the effectiveness of probiotics in countering the problems of CD (e.g., *E. coli* Nissel1917, *S. boulardii*, *Lactobacillus rhamnosus* strain GG, VSL#3, L. GG) in humans [55].Probiotics also prevent IBD by restoring integrity of the

Bprotectiveintestinal mucosa [56].In another study, 10 Crohn's Disease patients receiving 15 g of FOS demonstrated a reduced disease activity index [57].

- **Pouchitis**

Pouchitis is another type of IBD where ileal pouch gets inflamed especially after colectomy and ileal pouch canal anastomosis. In different studies the VSL#3 probiotic mixture was found to be highly effective for maintaining remission of chronic pouchitis [58]. Prebiotics also have been reported to play a beneficial role in controlling the IBD. A significant reduction in the number of bacteriodetes in faeces was reported in patients with chronic pouchitis treated with 24 g per day of inulin [59]. Several studies on both acute and chronic intestinal inflammation suggest that probiotics, prebiotics and/or synbiotics may be helpful in the management of inflammatory bowel disorder [56].

Upper Respiratory Infections

All probiotics induce an immune response, and probiotics increase immunoglobulin A (IgA)-secreting cells in respiratory and gastrointestinal mucosae [60]. Day care center studies showed that consuming a daily probiotic by healthy children resulted in an approximately 25% reduction in the number of days of school missed [61]. Systematic reviews of probiotics have shown that there is a reduction of the severity of symptoms associated with probiotics and a shorter duration of respiratory tract infection by approximately 1 day [62].

Infant Colic

Colic may be a factor in child abuse and infanticide [63,64]. In one investigation of 112 cases of abusive head trauma to infants, forensic interrogation revealed that shaking of the infant was violent and repetitive in most cases. The parent, usually a father, reported that he shook the infant in order to stop the baby from crying in 63% of cases, not intending to hurt the baby [65]. With these considerations in mind, at least 5 published studies have now investigated the role of a single probiotic, L. reuteri to alter the course in infants with colic. The preparation was originally isolated from a Peruvian mother's breast milk, cured of an antibiotic-resistant plasmid, and is now provided as liquid drops in sunflower oil. Two meta-analyses concluded that in breastfed infants with colic, quantified "crying + fussing time" was reduced byapproximately 1 hour per day within 2 weeks of administering the probiotic [66,67].

Netrotizing Enterocolitis (NEC)

NEC is the scourge of premature infants and neonatologists. It affects 5% to 10% of infants with birth weight between 500 and 1500 g, and approximately 50% of these infants require surgery [68]. Mortality rates range from 20% to 30%, and NEC is the leading cause of short bowel syndrome in children.They found that during the first 60 days of life, infants not

developing NEC experienced an expansion of fecal Negativicutes,whereas those developing NEC saw a reduction in Negativicutes and a more than doubling of the composition of Gammaproteobacteria Thus, NEC would appear to be a classical disease associated with gastrointestinal dysbiosis.There have been at least 3 meta-analyses showing that probiotics prevent NEC. In 2012, and also reported on meta-analysis of 20 RCTs in which probiotics were given individually to prevent NEC in very preterm infants [69].

***Helicobacter pylori* infections**

Lactobacillus salivarius capable of producing high amounts of lactic acid, which can inhibit the growth of *H. pylori in vitro*. There is some preliminary evidence that Probiotic bacteria may inhibit the gastric colonization and activity of *H. pylori*, which is associated with gastritis, peptic ulcers and gastric cancer. L. salivarius was found to inhibit *H. pylori* colonization in the *in vitro* studies as well as in mice [70,71]. The use of Probiotics in the field of *H. pylori* infection has been proposed for improving the eradication rate and tolerability and for the compliance of multiple antibiotic regimens used for the infection [72,73].

Anti-diabetic activities

Management of type-2 diabetes by modulating gut hormones, such as gastric inhibitory polypeptide and glucagonlike peptide-1, via probiotic and prebiotic interventions is another convincing strategy. In this context, hormones play an implicated role in glucose homeostasis, which results in neutralizing the disorder caused by peripheral insulin resistance or failure of b-cells to produce insulin. Currently,research is focused on generating new prebiotics, such as arabinoxylan and arabinoxylan oligosaccharides, which show promising results in counteracting related metabolic disorders, becausecarbohydrates have been linked to adiposity reduction [74].

Anti-obesity activity

Probiotics possess physiological functions that contribute to the health of host environment regulating microbes. In most instances, weight loss is facilitated by thermogenic and lipolytic responses through stimulating the sympathetic nervous system. Probiotic strains, Lactobacillus gasseri BNR17 have shown properties of inhibiting the increase in adipocyte tissue that are the main source of leptin and adiponectin and thereby, limiting leptin secretion. Other probiotic microbes such as *L. casei*, *Lactobacillus acidophilus* and *Bifidobacterium longum* have also been reported to have hypocholesterolemic effects [75,76].

Canceractivity

L. acidophilus is known to prolong the induction of colon tumors. It was demonstrated that feeding milk and colostrum fermented with *L. acidophilus* resulted in 16–41 % reduction in tumor proliferation [77]. The other probiotic *L. bulgaricus* has also been reported to induce antitumor activity against sarcoma-180 and

solid Ehrlich ascites tumors.Beta-glucosidase and urease convert pro-carcinogens in to proximate carcinogens. *Propionibacterium freudenreichii* was shown to induce cell death of human colon and gastric cancer cell lines through secretion of SCFAs in to culture media [78].GOS consumption in humans resulted in reduced activity of nitro reductase which is involved in producing genotoxic metabolites, indicating the potential of prebiotics and probiotics to reduce or prevent carcinogenesis [79].

CONCLUSION

Overall in this review probiotics, prebiotics and synbiotics have been discussed with respect to the systemic effects they exert on the host's health, metabolism and immune system. Probiotics, probiotics and synbiotics have systemic effects on the host's health metabolism and immune system. Utilization of prebiotics by probiotics should be a pre-requisite for symbiotic selection, in order to maintain a good synergy between the two and maximize the beneficial effects. The evidence-based, mechanistic research on probiotics reveals that cultured microorganisms, when given in adequate quantities for sufficient periods of time, are beneficial in many human disease conditions and safer than most pharmaceuticals. These conditions includeAllergic Diseases, Heart and Circulatory System, Neurodegenerative Diseases, Acute infantile diarrhea, Antibiotic associated diarrhea, Traveller's diarrhea, Irritable bowel syndrome (IBS), Upper Respiratory Infections, Infant Colic, Netrotizing Enterocolitis (NEC), *Helicobacter pylori* infections, Anti-diabetic, Anti-obesity, Cancer activity etc.Dietary probiotic supplementation generally involves dairy products but probiotics can also be incorporated into non-dairy fermented food products, presenting an alternative and more advantageous source in the process of evaluating new probiotic strains. Moreover, present clinical and nutritional evaluations have been successful in exposing someprobiotic strainsand their applicability in biomedical/clinical research, paving a new direction for exploration and exploitation of probiotics aimed at improving human health.

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