مروری بر کاربرد پروبیوتیک ها ومتابولیت های آن در درمان بیماریها

محدثه لاری پور[1]*، حمیده کربلایی حیدر[2]، کیمیا بسیجی[3]، مائده ابراهیمی[4]

*[1]دانشیار قارچ شناسی ، دانشکده علوم زیستی ، گروه میکروبیولوژی ، دانشگاه آزاد اسلامی، واحد تهران شمال ،تهران، ایران

[2و4] دانش آموخته ارشد بیوتکنولوژی، دانشکده علوم زیستی، گروه بیوتکنولوژی،دانشگاه آزاد اسلامی ،واحدتهران شمال، تهران، ایران

[3] دانش آموخته ارشد میکروبیولوژی، دانشکده علوم زیستی، گروه بیوتکنولوژی،دانشگاه آزاد اسلامی ،واحدتهران شمال، تهران، ایران

*نویسنده مسئول: ایمیل: *m.larypoor@iau-tnb.ac.ir* ، تلفن: ۰۹۱۲۲۸۸۵۳٤٦، *Orcid:0000-0002-2003-8343*

چکیده

مقدمه: دستگاه گوارش انسان حاوی میکروبیوتای غنی و پیچیده ای است که در عملکرد دستگاه گوارشی، فرایندهای ایمونولوژیک و درمسیر برخی از بیماری ها از جمله دیس بیوز نقش مهمی را ایفا می کند. بر طبق تحقیقات مجموعه میکروبیوتای دستگاه گوارش می تواند، بر روی کاهش یا افزایش جمعیت میکروبیوم پوست، دستگاه عصبی و قسمتهای دیگر بدن انسان تأثیر گذار باشد. مصرف مکملهای غذایی فراسودمند به عنوان یک استراتژی بالقوه و امیدوارکننده برای تنظیم میکروبیوتای روده وبهبود بیماری های تحت تأثیر آن در حال ظهور است. انواع مکمل های پروبیوتیک می تواند شامل مخمرها، باکتری ها و انواع پری بیوتیک شامل پلی ساکارید های غیر قابل هضم با منشاء گیاهی، میکروبی، قارچهای کلاهدارو جلبکها باشند. همراه شدن پروبیوتیک ها و پری بیوتیکها منجر به تولید فراورده های سینبیوتیک با اثرات قوی تر در ارتقاء سلامت انسان می شود. علاوه بر این موارد، پست بیوتیک ها محصولات جانبی متابولیک آزاد شده از پروبیوتیک ها می باشند و پس از تجزیه باکتری با اثرات سلامتی زیادی مانند تنظیم سلامت روده و تقویت سیستم ایمنی، مانند پروبیوتیک‌ها مورد استفاده قرار گرفته اند.

بحث: تا به امروز در مطالعات انجام شده، اثرات افزایش پروبیوتیک های روده و کاهش میکروارگانیسم های بیماریزا پری بیوتیک و اثرات ضد سرطانی ، التهابی و ایمونومدولاتوری پست بیوتیک ها و سین بیوتیک ها بر روی میکروبیوم دستگاه گوارشی اثبات شده لذا تهیه مکمل های فراسودمند ومصرف آنها افزایش پیدا کرده است.

کلمات کلیدی: پروبیوتیک، سین بیوتیک، پری بیوتیک، پست بیوتیک

An overview of the use of probiotics and their metabolites in the treatment of diseases

Mohaddeseh Larypoor[1*], Hamideh Karbalaeiheidar[2], Kimia Basiji[3], Maede Ebrahimi[4]

[* 1]Associate Professor of Mycology, Department of Microbiology, Faculty of Biological Sciences, Islamic Azad University, Tehran North Branch, Tehran, Iran

[2,4] Master's degree of biotechnology, Department of Biotechnology, Faculty of Biological Sciences, Islamic Azad University, Tehran North Branch, Tehran, Iran

[3]Master's degree of Microbiology, Department of Microbiology, Faculty of Biological Sciences, Islamic Azad University, Tehran North Branch, Tehran, Iran

* Corresponding author: Email: m.larypoor@iau-tnb.ac.ir , Tel: 09122885346, Orcid:0000-0002-2003-8343

Abstract

Introduction: The human gastrointestinal tract includes a rich and complex microbiota that plays an essential role in the functioning of the gastrointestinal tract, immunological processes and the path of some diseases, including dysbiosis. According to research, the gastrointestinal microbiota can increase or decrease the microbiome population of the skin, nervous system, and other human body parts. Consumption of beneficial dietary supplements is emerging as a potential and promising strategy for regulating the intestinal microbiota and improving its effects. Probiotic supplements can include yeasts, bacteria, and prebiotics, including indigestible polysaccharides of plant, microbial, fungal, and algal origin. The combination of probiotics and prebiotics leads to the production of synbiotic products with stronger effects in improving human health. In addition, postbiotics are metabolic byproducts released from probiotics and, after bacterial degradation, has several beneficial impacts such as regulating intestinal health and strengthening the immune system, like probiotics.

Conclusion: To date, studies have proven the effects of increasing intestinal probiotics, the use of prebiotics and the anticancer, anti-inflammatory and immunomodulatory effects of postbiotics and synbiotics on the gastrointestinal microbiome. Therefore, the preparation of beneficial supplements and their consumption has increased.

keywords: Probiotics, Prebiotics, Synbiotics, Postbiotics

Introduction

Recently, with increasing concerns about human health, the physiological functions of food have received much attention[1]. Researchers are also looking for natural growth promoters such as organic acids, probiotics, prebiotics and phytobiotics[2]. The human gastrointestinal tract (GIT) has diverse microorganisms that play a crucial role in health and disease[3]. The human gut consists of trillions of microorganisms, including bacteria, protozoa, fungi and viruses, also known as gut microbiota and comprise about 5% of the bodyweight[4, 5].Dysbiosis, or imbalance in the gut microbiota, can lead to various diseases, including cancer and gastrointestinal disorders. New strategies for treating this deficiency include dietary intervention, intake of probiotics, and faecal microbiota transplantation. It seems that some natural products can modulate the gut microbiota and are also used to help treat diseases[3].

Bacteroidetes and *firmicutes*, *Rominococcus*, *Lactobacillus* and *Clostridium*, make up more than 90% of known phylogenetic groups and affect healthy intestinal microbiota[5]. Yeast in the stomach and colon are good candidates as probiotics, as probiotics entering the gastrointestinal tract must resist local stresses, such as the presence of digestive enzymes, bile salts, organic acids, and significant changes in pH and Temperature resistance. The natural resistance of yeasts to antibacterial antibiotics is the main reason for their use in patients treated with antibiotics[6]. Probiotics and fungal yeasts have the potential as food additives; however, they have long been ignored. Fungal additives in animal feed can increase the growth and health of livestock[7].

An article in 2000 stated that many drugs with powerful and unique health-boosting properties have recently been isolated from fungi with medicinal properties and distributed worldwide. Many are not pharmaceutical products but represent a new class of dietary supplements or nutrients[8].In addition, instead of using synthetic materials, people have turned to boosters with natural food sources such as plants. Increasing consumer demand has led to the emergence of various health products, called dietary supplements, designer foods, special foods, nutritious and functional foods. These terms refer to foods that have beneficial effects, primarily on humans[9].

1.Probiotics

The concept of probiotics is first derived from Elie Metchnikoff's theory that swallowing certain selected bacteria beneficially affects the human gastrointestinal tract. He said that because of the dependence of intestinal microbes on food, it is possible to change the body's microflora and replace harmful microorganisms with beneficial microorganisms; this idea has been further developed over the decades. The word “probiotics” is originated from Greek and means “prolife.” Lilly and Stillwell used the word for substances produced by microorganisms that promote the growth of other microorganisms. Parker also defined probiotics as "organisms and substances that provide colonic microbial balance”. Several scientists and researchers have discussed new definitions of probiotics until the World Health Organization and the Food and Agriculture Organization explain probiotics as "living microorganisms that have health benefits for the host if consumed in sufficient amounts". The last update on the definition of probiotics was in 2013, assembled by the International Scientific Association for Probiotics and Prebiotics, in which the definition of probiotics by FAO/WHO. Eventually, in partial grammatical changes, it was thought

of as "living microorganisms that, when adequately administered, contribute to the host's health".This definition includes three main aspects of probiotics: microbial, viable, and beneficial to health[10].

The term probiotics refer to products such as probiotic drugs (including pharmaceutical products, live biotherapy products for humans), medical equipment, probiotic foods (such as food, dietary supplements or foods for specific medical purposes), directly fed microorganisms (For animal use) and genetically modified probiotics. Human related probiotics are mainly: *Lactobacillus*, *Bifidobacterium* and *lactococcus*, *Streptococcus*, *Enterococcus*[11]. The most commonly applied are lactic acid bacteria, particularly *Lactobacillus* and *Bifidobacterium* species. Plus, the yeast Saccharomyces boulardii seems to have health benefits.

Probiotic bacteria reduce the intestinal pH by producing lactic acid, acetic acid, and propionic acid, suppressing the growth of various pathogenic bacteria, and adjusting the intestinal flora[12].

1.1 Criteria for the selection of probiotic

according to the opinions of WHO, FAO and EFSA (European Food Safety Organization), in selecting probiotic strains, what should consider both safety and performance criteria and issues related to technological usefulness[11].In evaluating the safety of probiotic products, topics such as infection, pathogenicity, excessive immunosuppression in susceptible individuals, risk factors (toxicity, metabolic activity and essential properties of microbes) should be considered[13].Criteria such as competitiveness for the microbiota inhabiting the intestinal ecosystem, ability to survive and manage metabolic activity and grow in the target site, and antagonistic activity against pathogens and bacteriocin resistance are criteria for selecting the appropriate strain[11].

1.2 The consumption of probiotics

Bacterial probiotic products involve dairy products, especially probiotic yoghurt, non-dairy foods such as probiotic sweets, and non-food supplements such as powders and capsules[14]. Probiotics are used to prevent and treat various medical conditions and to support general health. The impacts of probiotics are particular, and their products might be varied. The common purpose of most probiotics are gastrointestinal diseases include acute rotavirus infection in children, Crohn's disease, ulcerative colitis (UC), Irritable Bowel Syndrome (IBS), Helicobacter pylori infection and others due to their ability to restore the gut microbiota[11, 12].Other significant applications of probiotic supplements are in the poultry industry; for instance, in laying hens, consumption of probiotic supplements (such as *Clostridium* butyricum or a combination of Pediococcus acidilactici and *S.boulardii*) could improve Ovulation function, dietary change, egg quality, eggshell strength and intestinal health of laying hens[15]. In poultry feeding, probiotic species such as *Lactobacillus*, *Candida*, *Aspergillus*, *Streptococcus* and *Bifidobacterium* are used; they have potentially beneficial effects on modulating the gastrointestinal microflora and at the same time inhibiting pathogenic bacteria[16].

Conditions	Probiotics impacts	Reference
Digestive disease	• Accelerate the healing of stomach ulcers by *L. rhamnosus* • Treatment and prevention of constipation • Decreased pH • Increased muscle contractions and smoky bowel movements • Increased mucus secretion • Reduction of intestinal inflammation by *B. infantis* strain 35624 • Improves bloating and pain • Fix intestinal movement problems	[14]
H. pylori infection	• Inhibitory activity against *H. pylori* • Reduce the side effects of antibiotics • Decrease in *H. pylori* count • Reduction of bacterial load in specific doses by *S. bouladii* and *L. johnsonii La1*	[14]
Urinary and vaginal infections	• The effect of *L. rhamnosus* in people with *Gardnerella vaginalis* and *C. albicans* infections	[14]
Liver disease	• Decreased bacterial urease activity reduces ammonia in the portal system • Decreased ammonia absorption by lowering intestinal pH and permeability • Prevent the absorption of toxins • Reduce inflammation and oxidative	[14]
COVID-19	• E. faecium Inhibits the replication of enteropathogenic coronavirus transmissible gastroenteritis virus in pig testicular cells. • Fight against *COVID 19* as a result of modulating the immune system. • Reduce secondary risks of disease • Reduce disease severity and mortality by manipulating the immune system	[17]
Mental disorders	• Decreased Hamilton Depression Rating Scale • Decreased C-reactive protein (CRP), interleukin 10 (IL-10) and malondialdehyde (MDA) levels • No significant change in Beck Depression Inventory score, tumour necrosis factor-α (TNF-α), interleukin 6 (IL-6), nitric oxide (NO), Glutathione (GSH) and Total Antioxidant Capacity (TAC) Levels	[18]
Gut inflammation	• Improves intestinal microbial population • Increased mucus secretion • Prevent the degradation of tightly bound proteins by reducing the number of Lipopolysaccharides (LPS)	[19]

	• Increased inflammatory markers as a result of binding of endothelial LPS to the Toll like2 receptor (TLR-2) and dendritic activation of cells and macrophages • Reduction of dysbiosis and thus minimizes the development of inflammatory biomarkers and unnecessary activation of the immune system. • Differentiation of Tcell to T helper 2 (Th2) and development of cytokines including IL- 4 and IL-10	
Antibiotic-associated diarrhoea	• Reduce diarrhoea caused by antibiotics • Not all probiotic strains are effective under any circumstances. No reduction in the number of diarrhoea cases in adults hospitalized with *Lactobacillus GG* • Reduction of additional cases of diarrhoea using *L. casei*, L. bulgaricus and S. thermophilus • Reduction of *C. difficile* infection using *S. boulardii* with metronidazole or vancomycin	[20-22]
Infection diarrhoea in children	• Reduced diarrhoea time by 0.7 in studies • Short-term duration of diarrhoea • Decreased stool frequency • Beneficial effects on the treatment of acute diarrhoea	[23-25]
IBS	• Improve some symptoms • Reduction of pain caused by IBS	[26-28]
IBD	• Possibility of modulating intestinal microflora and creating an immune response in the gut	[29,26,31]
Atopic disease	• Regulatory effects of the immune system • Mothers who use *Lactobacillus GGT*, their infants are less likely to develop atopic dermatitis in the first two years.	[32]
Celiac disease	• Hydrolysis of toxic gliadin peptides in BALB / c mice with an improvement of enteropathy and reduction of histological damage and production of proinflammatory cytokines by *Saccharomyces* and boulardii *KK1* • Reducing the toxic and inflammatory effects of gliadin-derived peptides by *Bifidobacterium longum CECT 7347* • Helps proteolysis of intact gluten proteins, gliadins and glutenins and reduces cytotoxicity and proinflammatory response in intestinal epithelial cells by *Bacterium* species like B. *bifidum BB-G90*, *B. longum BLG301*, *B. breve BB-G 95* and *B. animals L-G101*	[33-35]
Crohn's disease	• Improves gut microbiome	[36]

Colorectal cancer	• anti cancer effects on the immune system of rats.	[37]
Weakness in the immune system	• *Lactobacillus* Increased host immune response. • *Lactobacillus reuteri* Induces the secretion of apoptotic agents in myeloid leukaemia cells. • Increased levels of cytokines and immunoglobulins • Activate macrophages and increase the activity of autoimmune modulation and stimulation of Natural killer cells (NK)	[14]
Respiratory disease	• *Lactobacillus rhamnosus GG* Reduce respiratory infections	[11]

Table1.The impression of probiotics on various diseases

1.3 Fungi and yeasts as probiotics

The discovery of several fungal strains as probiotics have started a new era in the probiotic family. Fungi are significant candidates for probiotics due to their unique cellular structure and better ability to survive in the challenging environment of the gastrointestinal tract. A group of fungal have been reported as new candidates in the probiotic family, including:

Candida humilis, Debaryomyces hansenii, Debaryomyces occidentalis, Kluyveromyces lactis, Kluyveromyces lodderae, Kluyveromyces marxiamus, Saccharomyces cerevisiae var. boulardii, Pichia kluyveri, Issatchenkia orientalis, Pichia kudriavzevii, Candida tropicalis, Meyerozyma caribbica, Candida saitoana, Candida pintolopesii, Cryptococcus albidus and Torulaspora delbrueckii

One of the most promising commercial probiotic yeasts is *Saccharomyces boulardii* because it has favourable effects both in the natural state and in the unfavourable physiological conditions of the host body. Yeasts have been reported to affect the gastrointestinal tract alone or in combination with other types of probiotics[38].

Yeast	Beneficial and probiotic effects	Reference
Saccharomyces cerevisiae	• Increased bacterial cells in the rumen of ruminants • Beneficial effect on milk and meat production • Different responses in animal performance • Responses range from low effect to positive effect. • It does not alter dry matter intake consumption and weight gain for livestock.	[39]
Saccharomyces boulardii	• Preventive and therapeutic agent for antibiotic-related diarrhoea and *C. difficile* • Used as an immunobiotic	[6,40,41]

	• Not affected by antibacterial agents • Increased intestinal enzyme activity such as disaccharides, α-glucosidases, alkaline phosphatases and aminopeptidases • Secretion of leucine aminopeptidase against pathogens • Reduce the time of diarrhoea in infants and rapid return of lost weight • Increase the absorption of D-glucose in the intestine and finally the absorption of water and electrolytes during diarrhoea • The therapeutic agent in several acute and chronic gastrointestinal diseases • Immune regulatory properties	
Pichia kudriavzevii	• Increase food folate content with folate production and high phytase activity • Improves taste with proteolytic activity • The secretory metabolites of *Pichia kudriavzevii AS 12* have anticancer activity on colon cancer cells by inhibiting their growth and inducing apoptosis	[42 ,43]

Table2. Beneficial and probiotic effects of yeast

1.4 The role of plants as probiotics

The concept of plant probiotics includes all the microorganisms, especially fungi and bacteria recognised as plant growth promoters according to their valuable role in the general growth of plants and their faster adaptation to environmental changes, such as drought, heat or salinity[44]. Herbal and dietary supplements (HDS) have been used for health purposes for over 5,000 years and are used in all communities worldwide. HDS are complementary and alternative medicine usually used as a health tonic or to prevent or treat diseases. Some of these supplements are applied to lose weight or to increase physical fitness. There is almost no scientific evidence of their beneficial effects, and most of them have no medicinal value, and their use has long been based on belief[45]. Although many modern medicines are derived from herbal sources, they can have beneficial and side effects. However, herbal supplements may be safer than Chemical medicine[46]. Complementary and alternative medicines (CAM) are popularly used by people in the United States and other countries to treat conditions such as hypertension (HTN), cardiovascular disease (CVD), heart failure, hyperlipidemia, and other conditions[47]. Among the plants used for this purpose, we can mention *Echinacea*[48].The study of the effect of probiotics and herbal products on histomorphological and immunological growth showed that probiotics increase the number of *Lactobacillus spp* in small and large intestines, and consumption of plant powder shows a dual effect on CD3+ cell distribution and in the large intestine. Plants also increase CD3 + cells in the lamina propria[7].

However, the medical community is concerned that herbs that stimulate the immune system may interfere with the immunosuppressive effects of corticosteroids and cyclosporine and exacerbate autoimmune diseases; despite this, no report on this theory is available[48]. The use of phytobiotics and natural products such as herbs as food additives in the poultry industry may also be successful.

The use of phytobiotics and natural products such as herbs as food additives in the poultry industry may also be successful[2].

Plant	Description	Reference
Plane trees	• Contains flavonoids, alkaloids, terpenoids, iridoids, fatty acids, phenolic acids and vitamins • Significant role in wound management, bacterial and viral infections, pain, inflammation and diarrhoea	[49]
Nettles	• Rich in bioactive compounds and nutrients • Inhibition of proinflammatory cytokine production • Decreased levels of CRP • Increased superoxide dismutase • High anti-inflammatory and antioxidant effects	[50]
Milk thistle	• Hypericin and hyperforin are bioactive components with an antidepressant role. • Has antibacterial, antiviral and anti-inflammatory properties	[51]
Hemp	• No psychoactive effect • In the food industry, as raw materials • Cholesterol-free seeds, rich in protein, vitamins and minerals, high in fibre and biologically active substances • Rich in terpene with antioxidant activity	[52]

Table3. Plants as probiotics

1.5 Disadvantages of probiotics

According to reports, the mortality of healthy people due to the consumption of probiotic bacteria are infrequent, and the percentage of fatal infections caused by *Lactobacillus* is deficient. Nonetheless, even if probiotic bacterial strains are considered safe, they may rarely cause bacteremia or endocarditis as opportunistic bacteria[53, 54].

The most critical risk factor in using probiotic microorganisms is the lack of awareness of their activity. Given that the side effects of probiotics have been recorded, it is necessary to fully understand the mechanisms of activity of probiotic bacteria[55]. Rare cases of sepsis, endocarditis and liver abscess have been observed while using *Lactobacillus*. In addition, some cases of fungal diseases have also been reported in patients with severe disease after using *S. boulardii*. Most probiotics are safe. However, safety precautions should be considered when prescribing probiotics to patients with severe disease or immunodeficiency[56, 57]

2- Prebiotics

Prebiotics are indigestible oligosaccharides and polysaccharides that promote the growth of beneficial bacteria in the GIT and exert antagonistic effects on opportunistic and pathogenic bacteria. The concept and definition of prebiotic were expressed in 1995 by Gibson et al with the following criteria: resistance to gastric acidity, improved gastrointestinal absorption and selective stimulation of the growth of beneficial bacteria residing in the gastrointestinal tract. It remained

unchanged for 15 years[58, 59]. The researchers found that the description of prebiotic is more or less coincident with the description of dietary fibre, except for its selectivity for certain species. Cummings, Macfarlane, and Englyst, on the other hand, classified prebiotics in 2001 as relatively short-chain carbohydrates[9].In 2008, the Sixth Session of the International Scientific Association of Probiotics and Prebiotics (ISAPP) identified "dietary prebiotics" as a "selective fermented component leading to specific changes in the composition and/or activity of the GIT microbiota".As a result, it provides benefits to the health of the host. The word "selectivity", or prebiotic power to stimulate specific gut microbiota, was another critical element of the original definition; however, the concept has recently been questioned[59].Prebiotics are naturally present in various foods, including asparagus, sugar beet, garlic, chicory, onions, leeks, wheat and honey, bananas, barley, tomatoes, rye, soy, human and cow milk, peas, beans and more. They have also recently been found in seaweed and microalgae [11, 59]. Lactic acid-producing bacteria use these substances, and the short-chain fatty acids (SCFAs) produced in this process are used as an energy source for epithelial cells. Ultimately, prebiotics modulate intestinal immunity and prevent the adhesion of pathogenic bacteria[60].

2.1 Types of prebiotics

Most prebiotics are a subset of carbohydrate groups, and most are oligosaccharides carbohydrate. There are also some evidences that prebiotics are not just carbohydrates.

Prebiotics	Types and Description	Reference
Fructan	• consists of inulin and fructo-oligosaccharide or oligofructose • a linear chain of fructose with β (2→1) linkage • Fructan chain length is a significant criterion for determining which bacteria can ferment them. As a result, other bacterial species can be promoted directly or indirectly by fructans.	[59]
Galacto-oligosaccharides (GOS)	• the product of the lactose branch, are classified into two subgroups: o GOS with addition galactose at C3, C4 or C6 o GOS made from lactose within enzymatic trans-glycosylation(trans-galacto-oligosaccharides) • Some galacto oligosaccharides are derived from lactulose are also considered prebiotics.	[59]

	• The other sorts are based on sucrose called raffinose family oligosaccharides (RFO)that, their effect on gut microbiota has not been clarified yet.	
Starch and Glucose-Derived Oligosaccharides	• Resistant starch (RS) promotes health by producing high butyrate levels and is resistant to upper gut digestion. • Polydextrose, a glucose-derived oligosaccharide that can stimulate *Bifidobacteria* (not yet confirmed)	[59]
Other oligosaccharides	• Oligosaccharides originated from pectin and are based on the extension of galacturonic acid or rhamnose. • inulin is also included in this group and is used in many probiotic groups.	[11,59]
Non-carbohydrate oligosaccharides	• Flavonol is derived from cocoa is not in the carbohydrate group but is classified as a prebiotic.	[59]

Table4. Prebiotics, types and characteristics

2.2 Criteria for classifying a compound as a prebiotic

There are different criteria for classifying food compounds as prebiotics, such as:
Prebiotics are resistant to acidic stomach pH and indigestible in the upper gastrointestinal tract. Therefore, they not be hydrolyzed by mammalian enzymes and will effectively stimulate the growth of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*.
Another criterion is the ability of the intestinal microbiota to ferment prebiotics. Prebiotics should selectively stimulate the growth and/or activity of intestinal bacteria, thereby improving host health. It is also advantageous for the health of the host and is consistent in food processing.
In addition, two criteria distinguish fibre from carbohydrate-derived prebiotics:(1) Fibres are carbohydrates with a degree of polymerization equivalent to or greater than 3. (2)Small intestine enzymes cannot hydrolyze them[9, 59].

2.3 Profits of prebiotics

1. increase the growth of beneficial bacteria and slow down the overgrowth of pathogenic bacteria.
2. Reduces glucose adsorption and insulin resistance and improves blood sugar.
3. diminish LDL cholesterol and triglycerides and raise the risk of coronary heart disease while increasing HDL cholesterol.
4. Prevents inflammation of the intestinal epithelium and leaky gut syndrome and promotes or prevents chronic inflammation.

5. Helps to regulate the immune system and inhibits infections, some autoimmune diseases such as allergies, asthma and eczema[58].

2.4 Fungi as a prebiotic source

Medicinal fungi have been used as a dietary supplement or medicinal food in China for more than 2,000 years, and their extractable components have been shown to enhance the biological function of the human body. Fungi are rich in indigestible dietary fibre, including glucan, chitin, and heteropolysaccharides. As a result, these fungi are potential candidates for prebiotic compounds. Various fungi produce different types of polysaccharides that can be soluble or insoluble in water[9, 58].In 2009 Synytsya et al. Reported that *oyster mushroom* contains soluble fibre compounds, especially non-starch glucans, and small amounts of other glucans such as chitin and galactomannan, which benefit the *Lactobacillus* population[2]. Some studies have shown that polysaccharides in fungi may act as immune boosters or immune modulators and exhibit antibacterial, antiviral, and antiparasitic biological activities. Some studies have shown that polysaccharides in fungi may act as immune boosters or immune modulators and exhibit antibacterial, antiviral, and antiparasitic biological activities. Phenolic compounds in them may also act as antioxidants and etcetera[61]. Edible mushrooms are also considered a good food because they contain a high portion of protein, carbohydrates, fibre and vitamins[9]. Common fungi used in nutritional programs include *Saccharomyces cerevisiae, Antrodia cinnamomea, Pleurotus spp, Aspergillus oryzae, Cordyceps militarist* and *Flammulina spp*. Moreover, *Cordyceps spp* and *Antrodia spp* are among the medicinal fungi[62, 63]. Species that can be extensively used for prebiotic purposes include:
Agaricus Bisporus, Agaricus bitorquis, Agaricus Blazei, Auricularia auricular-judae, Boletuserythropus, Calocybe indica, Flammulina Velutipes, Ganoderma Lucidium, Geastrums saccatum, Hericium erianaceus, Lentinus edodes, Phellinus linteus, Pleurotuseryngii, Pleurotus florida, Pleurotusostreatus[58].

Among these fungi, *Ganoderma lucidum*, also known as “Ling Zhi”, “Rishi” and “Mannentake”, has been used for thousands of years as a traditional medicine to prevent and treat various human diseases in Asia[64, 65], and it plays a prebiotic role in many strains of probiotics. *Ganoderma lucidum*, as the 'king of herbs', contains polysaccharides, flavonoids and alkaloids, amino acids, steroids, oligosaccharides, proteins, mannitol, vitamins B1, B2, B6, choline and inositol. Among amino acids, glutamic acid, aspartic acid, glycine and alanine have the highest relative abundance, and methionine has the lowest relative abundance. This fungus is rich in leucine and lysine, and it also has a type of high oxygen triterpenoids and the main bioactive components to inhibit cancer growth called ganoderic acids[64]. Ganoderic acids have potential applications such as antitumour activity, anti-HIV activity, antihypertensive effects, antihepatotoxic, antihypertensive, prevents histamine release, and affects blood cholesterol and platelet aggregation. In addition, as a prebiotic,

they affect the growth of intestinal probiotic bacteria and are used as an analgesic, anti-ageing supplement, and in cosmetic formulations[65].

Ganoderma lucidum polysaccharides enhance gut *Lactobacillus* and its probiotic features to a large extent and modulate intestinal microbiota compounds[64].In 2012, Yamin S et al. researched to discover the ability of oligosaccharides from *Ganoderma lucidum* polysaccharide extract (GLCP) and the second fraction of polysaccharide fractions (2PF) to selectively increase the growth of *Bifidobacterium* strains and expose the effect of GLCP and PF-2 as prebiotic towards the bacterial microflora in human faeces. They discovered that these polysaccharides could increase the growth of three selected strains of *Bifidobacterium* and ultimately enhance the health of the host gut. Moreover, increasing the growth of *Bifidobacterium* due to GLCP and 2 PF causes the generation of acetic acid and lactic acid, which repress the growth of pathogenic bacteria[66]. Studies in obesity have proved that a high-fat diet can degrade the number of *Bifidobacterium* and *Lactobacillus* and cause chronic systemic endotoxemia, which eventually leads to metabolic diseases[5]. The discovery of *Ganoderma lucidum* as a prebiotic led to studies on the effects of this fungus in the treatment of obesity. In one of these studies, the effect of this fungus on mice fed a high-fat diet was investigated. With the use of *Ganoderma lucidum*, fat mass, glucose homeostasis, inflammation of adipose tissue and liver in mice improved and serum lipopolysaccharide levels decreased, and as a result, the hepatic activity of the Toll4 receptor pathway was repressed. In the meantime, the abundance of several species of bacteria also changed[67].

Chitin extracted from *Trametes versicolor* is also a type of polysaccharide used to produce chitosan and glucosamine. In a study conducted in 2020, the production of chitosan from the medicinal fungus Trametes versicolor, native to Iran, was performed by the Taguchi method, and the antibacterial properties of this valuable substance were investigated. Chitosan antibacterial activity for *Staphylococcus aureus* was higher than in *E. coli* and more efficient than gram-positive bacteria[68]. Another producer of chitin in the forests of northern Iran is *Schizophyllum commune*, one of the most important food and medicinal fungi in the world, which is widely used in industry and medicine, and one of the significant polysaccharides of this fungus is the chitin-glucan complex[69].

Fungal polysaccharides	**Fungal origin**	**Description**
D-Glucan	*Agaricus bitorquis* *Agaricus blazei* *Auricularia auricula-judae* *Calocybe indica* *Ganoderma lucidum*	• It is the main and the most polysaccharide extracted from Ganoderma lucidum. • Contains beta-glucans with a backbone of β-(1→3)-linked D-glucopyranosyl residues, with branches of mono-, di- and oligosaccharide side chains replacing at the C-6 of the glucosyl residues in the main chain. • Ability to regulate the immune system

	Geastrum saccatum *Phellinus linteus* *Pleurotus eryngii* *Sparassis crispa* *Termitomyces eurhizus* *Termitomyces microcapus*	• Activators of *Lactobacillus rhamnosus, Bifidobacterium bifidum* and *Enterococcus* • Merging of β -1,3glucan to innate immune cells such as NK and macrophages • Merging of β- 1,6 glucan to proteins or other parts of sugar molecules and use in antitumour activity • Reduced cholesterol and LDL levels in patients with hypercholesterolemia
Lentinan	*Lentinus edodes*	• 3-strand polysaccharides • Activate *E. coli* and inhibit *Salmonella* • According to some research in 1989, these polysaccharides increase macrophages and thus increase phagocytic action.
Grifloan	*Grifola frondose*	• Glucose molecule with β bond • Has a triple helical structure • Activate *Bifidobacterium* and *Lactobacillus* • Inhibitory effect on *Salmonella* • Has activities like Lentinan • Stimulation of Interleukin (IL) and Tumour necrosis factor (TNF-α) production
Glycoprotein	*Ganoderma lucidum*	• Protein-bound polysaccharides • Includes compounds such as β-glucan with protein, α-glucan with protein and heteropolysaccharide with protein

Table5. Types of fungal polysaccharides[58, 70, 71]

2.5 Algae as a source of prebiotics

Algae are a group of ancient photosynthetic organisms that extend from prokaryotic *cyanobacteria* to eukaryotic microalgae[11]. They grow in dry and aquatic environments as well as in fresh and saltwater. Algae are mainly classified according to their colour, shape and life cycle. They are divided into micro-and macroalgae based on size and can generally be classified into three groups: green (*Chlorophyta*), red (*Rhodophyta*) and brown-kelp (*Phaeophyta*). *Arthrospira*, *Chlorella*, *Dunaliella*, *Nostoc* and *Aphanizomenon* are the representative species of microalgae[59].

Cyanobacteria, as prokaryotic microalgae, perform a significant role in the natural ecosystem, especially in plant and microbial interactions71]. Algae generate an extensive range of valuable bioactive secondary metabolites, including proteins, carbohydrates, lipids, polyunsaturated fatty acids (PUFAs), omega-3 fatty acids, polysaccharides, polyphenols, sterols, and pigments.

Chlorophylls, carotenoids, phycobilins. Plus, the quality of the resulting protein is lower than other plant protein sources. They are a good source of dietary fibre and contain vitamins A, B1, B12, C, D and E, riboflavin, niacin and pantothenic acid. These organisms are rich sources of calcium, sodium, magnesium, phosphorus, potassium, iron, zinc, and iodine. They can also absorb heavy metals such as cadmium, zinc, lead, nickel and copper; therefore, they are a good source of dietary and pharmaceutical supplements[73]. These compounds have antibacterial, antifungal, antioxidant, anti-inflammatory, antitumour and antiviral properties[72].

Carotenoid, first produced by *D. salina* algae, is a pigment with antiviral, antibacterial, antifungal, antioxidant, anti-inflammatory and antitumour properties and protects cells against oxidative stress. The *Dictyotacae* family can produce diterpenes such as Dictyodial, Dictyol C and Dictyol H with antimicrobial, antiseptic and cytotoxic activity. *Spirulina* microalgae produce an attractive group of Phycobiliprotein (water-soluble proteins in *Cyanobacteria*, *Rhodophyta* and *Cryptomonad*, et cetera), which have hepatoprotective, anti-inflammatory and antioxidant activities. Seaweeds also contain sufficient amounts of structural polysaccharides, monosaccharides and storage polysaccharides, the main of which are sulfated polysaccharides, which have numerous properties and potential applications in medicine, food and pharmaceutical industries[74]. Sulfated polysaccharides from seaweed can repress the proliferation of enveloped viruses such as HIV, Dengue, herpes simplex virus (HSV), respiratory syncytial virus and human cytomegalovirus[11]. Research has shown that polysaccharides derived from green algae, Fucoidan, Laminarin, alginate from brown algae, Carrageenan derived from red algae, and oligosaccharides derived from algae can stimulate the immune response and protection against plant pathogens[59].

Prebiotics	Algae origin	Impacts	Reference
Alginate	Brown algae (*Laminaria japonica*)	• Increase in acetate and propionate concentrations • Stimulate bacterial growth	[11]
	Brown algae	• No change in bacterial population • SCFA, acetate and propionate with high molecular weight were seen.	[59]
Laminarin	Brown algae	• No reduction in *Bifidobacterium* and *Lactobacillus* populations • Decreased pH in the gut • Increased expression of neutral mucin in the rat clone	[71 ,72]

	Brown algae	• higher expression of SGLT1, GLUT1 and GLUT2 in the piglets' ileum • increasing the populations of *Bifidobacterium* and *Lactobacillus spp* • increase in average daily gain • the lower proportion of propionic acid	[11]
	Brown algae	• Increase of Total Short Chain Fatty Acids (Total SCFA) and Acetate in Cecum • Decreased colonic expression of precursor cytokines	[59]
Fucoidan	Brown algae (*Ascophyllum nodosum*)	• No production of SCFA and gases was found.	[71]
	Brown algae (*Lonicera japonica*)	• Increase production of acetate, butyrate and lactate • More *Bifidobacterium*, *Lactobacillus* and *Enterobacteria*	[72]
Agar and Carrageenan	Red algae	• Alginate oligosaccharides (AlgO) inhibit the growth of pathogenic bacteria such as Escherichia, Shigella and Peptoniphilus and modify gut microbiota composition. • Agarose oligosaccharides (AO)can modulate the gut to a healthier model. • κ-carrageenan oligosaccharides (KCO) increased abundance of butyric acid-producing bacteria	[74]
	Red algae	• κ-carrageenan oligosaccharides increased the growth of *Prevotella* and repressed the growth of *Bacteroides* and *Parabacteroides*	[11]
Ulvan	Green algae	• They are poorly destroyed by intestinal bacteria.	[71]
Polyphenols	Brown algae (*Ascophyllum nodosum*)	• Promotes the binding of polyphenols to methyl, glucuronidated or sulfated forms instead of hydrolysis to aglycons	[72]
	Brown algae (*Ecklonia radiata*)	• Increased *Bacteroidetes*،*Clostridium coccoides* ،*E. coli a*nd Faecalibacterium *Prausnitziii* but Communities of *Bifidobacterium* and *Lactobacillus* reduced after 24 hours.	[73]
Carotenoid	Green and Red algae	• Increased abundance of Bifidobacterium in the cecum of astaxanthin-fed mice	[59]

	Green and Red algae	• Increased population of Bifidobacterium, *Lachnospiraceae*	[11]
Polyunsaturated fatty acids	Seaweed	• Eicosapentaenoic acid *(*EPA)and Docosahexaenoic acid (DHA) have anti-inflammatory properties. • Decreased ratio of Firmicutes to Bacteroidetes, • Reduction of LPS -producing bacteria • Increase population of *Bifidobacterium, Lachnospiraceae*	[72]

Table6. Algal prebiotics and their impacts

Type of algae	**The name of algae**	**Potential as a prebiotic supplement**
Macroalgae	*Ascophyllum nodosum*	• Increased the amount of *Bacteroidetes* and *Firmicutes* • Reduced the risk of obesity • Reduced the total amount of SCFAs after fermentation • Improving human gut health
	Ecklonia radiat	• Decreased levels of toxic protein fermentation products • Increasing the number of butyrate-producing bacteria such as *Faecalibacterium prausnitzii* • Decreased number of potentially pathogenic *Enterococcus*
	Enteromorpha polifera Laminaria japonica	• Regulation of enteroendocrine secretion (secretory cells in the gut), blood glucose and lipid metabolism • Reducing the symptoms of metabolic syndrome
	Porphyra yezoensis	• It contains exciting amounts of glycerol galactoside fermented by *Bifidobacterium*
microalgae	*Chlorella*	• It contains fats, carbohydrates, vitamins and pantothenic acid • Increased the blood pressure and cholesterol levels • Increased the immune system • Relief of fibromyalgia (chronic musculoskeletal pain syndrome) • Relief of high blood pressure • Relief of UC

		• Stimulate beneficial flora such as *Lactobacillus* and *Bifidobacterium* • resolving constipation, IBS and other problems
	Dunaliella	• It contains large amounts of beta carotene, glycerol and protein • Excellent liver protection effects • Reduction of the liver lesion incidence
	Chlorella pyrenoidosa *Chlorella ellipsoidea*	• Immune stimulating qualities • Reproduction of *Listeria Monocytogenes* • Inhibition of *Candida albicans*
	Haematococcus pluvialis	• Anti-inflammatory and anticancer agent for cardiovascular diseases • Prevention of diabetes and neurological disorders • Stimulation of immunization
	Aphanizomenon	• It contains C-phycocyanin • It has antioxidant and anti-inflammatory properties • Decreased cholesterol and triglyceride levels • Production of SCFAs
	Spirulina	• It Contains C-Phycocyanin • Has antioxidant and anti-inflammatory qualities • It has a positive effect on the bioavailability of probiotics • Elimination of harmful bacteria *E. coli* and *Candida* yeast • Stimulation of *Bifidobacterium* and *Lactobacillus* • Promote digestion • Increased the number of *Lactobacillus* beneficial to the gastrointestinal tract and excellent absorption of vitamins • Strengthen and support beneficial gut microorganisms to contend against gastrointestinal diseases • Treatment of gastric ulcer, chronic gastritis and duodenal ulcer • Regulate the function of the immune system

	Arthrospira platensis	• In patients with HIV 1:
		  ○ Increased haemoglobin levels
		  ○ Significant reduction in released viral levels
		  ○ Stimulate the immune system
		  ○ Inhibit virus replication
		• In bees that used it as a food source:
		  ○ Significant increase in body fat
		  ○ Improve bee health

		○ Increased bacterial count of intestinal microbiota ○ Stimulation of growth of *Lactobacillus* and other lactic acid bacteria ○ Removal of pathogenic bacteria

Table7. Potential of seaweed, macroalgae and microalgae as prebiotics and food and drug supplements[11,59-72]

2.6 The consumption of prebiotics

The effect of prebiotics on organisms is indirect because host metabolic enzymes do not digest prebiotics, but microorganisms in the gastrointestinal tract digest them and eventually help to increase the number of beneficial microorganisms[58]. Inulin and oligofructose as prebiotics in the diet can bring many health benefits. Benefits include reducing blood LDL levels, stimulating the immune system, enhancing calcium absorption, maintaining proper intestinal pH, and diminishing the symptoms of gastric ulcers and vaginal fungus. Other effects include preventing cancer and supporting lactose intolerance, or treating tooth decay[11]. Prebiotics have an apparent effect on the immune system by modulating the normal microflora; therefore, several factors affect the composition of the gut microbial flora from birth. According to research, the intestinal microbiota of breastfed infants is commonly dominated by *Bifidobacterium* and lactic acid bacteria. Colonization with these bacterias may directly inhibit the growth of pathogenic microorganisms or indirectly induce an effective immune response[76].

The effects of prebiotics can be seen not only in humans but also in poultry. Prebiotics may improve the performance and health of poultry by altering biological processes in the digestive tract of chickens. They potentially affect the breakdown of indigestible nutrients, the synthesis of nitrogen components and vitamins, and the digestion of undesirable elements in the diet. With rising antibiotic resistance, the use of most antimicrobial growth promoters (AGPs) was banned in the EU, which increased the desire for alternative growth stimulants and dietary supplements in poultry production[102]. Hence, prebiotics were added to the poultry diet to prevent intestinal diseases[103].

Diseases	Impact of prebiotics	Reference
Gut microbiota deficiency	• Modification of gut microbiota • The energy supply of microbiota and finally modulation of its composition and function • The reduction of acidic fermentation products improves the intestinal environment. • The release of gases increases the volume of the gut and reduces the time of food transfer. • Anti-constipation • Maintain gut health by changing its microflora	[77,,78 79,80]

Hepatic encephalopathy (HE)	• Decreased blood ammonia levels by prebiotic lactulose	[80]
Atopic dermatitis	• Reduction of dermatitis (skin sensitivity) • Consumption of Galacto-oligosaccharides reduces dehydration, pruritus and increases CD44, Collagen type I and skin expression of cell adhesion.	[80]
Kidney disease	• Consumption of Galactooligosaccharides alone or combined with *Bifidobacterium* by women decreases dehydration and creatine formation due to phenols.	[80]
Cardiovascular disease (CVD)	• Reduction of inflammatory components • Reducing the risk of CVD • decreasing cholesterol and apolipoprotein levels	[80]

Table8. The impact of prebiotics on several diseases

3.Synbiotics

Synbiotic is a dietary supplement that combines probiotic and prebiotic to enhance the level and activity of beneficial microorganisms in the gut[81]. Since the word refers to synergy, the definition should be allocated to products in which the prebiotic compound selectively supports the probiotic compound. For example, a product including oligofructose and *Bifidobacterium* could meet the definition, whereas a product containing oligofructose and a probiotic *Lactobacillus casei* strain could not[82]. The mechanism of action of synbiotic supplements is still unknown and needs further investigation.

The crucial point about choosing the correct synbiotic is choosing the appropriate probiotic and prebiotic when combining the synbiotic formula because the functional mechanism of synbiotic will be based on the synergistic effect of prebiotic and probiotic in the large intestine. Two types of synbiotic formulations are introduced, complementary and synergistic[82]. A mixture of *Bifidobacterium* or Lactobacillus with fructooligosaccharides in synbiotic products appears to be the most common mixture. Two styles of synbiotic operation are acknowledged (1) Action by enhancing the sustainability of probiotic microorganisms;(2) Action by providing specific health impacts[11].

3.1 The consumption of synbiotics

The application of synbiotics leads to a significant increase in SCFAs, ketones, carbon disulfides, and methyl acetate, which ultimately positively affects the host's health and have antibacterial and anti-allergic effects. They prevent the decay processes in the gut and inhibit constipation and diarrhoea. They also seem to be very efficient in preventing osteoporosis, reducing fat and blood

sugar, regulating the immune system, and treating brain disorders associated with abnormal liver function. Advantageous effects of synbiotics on humans include:

Increase in the number of *Lactobacillus, Bifidobacterium* bacteria and maintain the stability of gut microbiota;

Improving liver function in patients with cirrhosis;

Improve complementary safety capabilities

Restrict bacterial transmission and reduce nosocomial infections in patients after surgery and similar interventions[11].

Experimental evidence suggests that synbiotic supplementation may be a valid strategy for improving IBD. As shown by reducing inflammatory markers and improving clinical outcomes, SCFA is produced by providing selected probiotic strains and prebiotic fibres[108]. The effects of synbiotics on other diseases, including autism spectrum disorder (ASD), atopic dermatitis, chronic kidney disease (CKD), diabetes, UC, necrotizing enterocolitis (NEC) and others, have also been studied.

There are also several studies on the effect of synbiotic supplements on livestock and poultry and the quality of their products. For example, in 2015, Tang et al. Investigated the influences of prebiotics, isomaltooligosaccharide (IMO), PrimaLac probiotics, and their combination as synbiotics on the chemical composition of egg yolk and the egg quality of laying hens. The results showed that IMO and PrimaLac supplements alone or in combination might help improve cholesterol content and modify the composition of egg yolk fatty acids without affecting the egg quality of laying hens between 24 and 36 weeks. They also significantly increase eggs' total unsaturated fatty acids, total omega-6, and polyunsaturated fatty acid (PUFA), including linoleic acid and alpha-linolenic acid levels[83].

Disorders	Synbiotic	Effect of Synbiotic Resources	Resources
Ulcerative colitis	*Enterococcus faecium,* *L. plantarum* *S. thermophilus* *B. lactis,* *L. acidophilus,* *B. longum* + fructooligosaccharide	• Selective stimulation of intestinal bacteria • Reduced CRP • Decreased disease activity	[83]
Necrotizing enterocolitis (NEC)	*Bifidobacterium lactis* + inulin	• Less occurrence of NEC • Limited mortality rate	[84]
	L. acidophilus *B. longum*	• Diminished the incidence and severity of NEC	[85]

	B. bifidum *S. thermophiles* + fructooligosaccharide		
Obesity	*L.plantarum* *S. thermophilous* *B. bifidum* + fructooligosaccharide	• Decreased appetite and fasting blood sugar during consumption	[5]
Autism spectrum disorder	*B. infantis Bi-26* *L. rhamnosus HN001* *B. lactis BL-04* *L.paracasei LPC37* + fructooligosaccharide	• Decreased total score and ATEC subdomain (Autism treatment evaluation checklist) • Decreased GSI (gastrointestinal severity index)	[85]
Atopic dermatitis	*B. breve* *Bifidobacterium animalis subsp. Lacti s* *L.casei* *L. gasseri* *L. plantarum* *L.rhamnosus* + maltodextrin + inulin + apple pectin	• Atopic dermatological scoring decreases over time in patients after synbiotic bathing. • Improves pruritus and dry skin significantly improves • Improvement of microbiome	[86]
Chronic kidney disease	*L.casei* *L.acidophilus* *L.bulgarigus* *L .rhamnosus* *B. breve* *B .longum* *S. thermophilus* + fructooligosaccharide	• Decreased levels of blood urea nitrogen, creatinine, uric acid • Other serum renal function indices did not show significant changes	[87]
Diabetes	*B. lactis BB-12* *L. acidophilus LA-5* +inulin + Monk Fruit extract	• Improve blood glucose regulation. • Decreased resistance to insulin and glycosylated haemoglobin. • Improve SCFA levels and gut microbiota status • Improve liver and kidneys	[87]

Table9. The impact of synbiotics on several disorder

4. Postbiotics

The concept of postbiotics is based on the observation that the secretion of various metabolites mediates the beneficial effects of the microbiota. Still, its accurate description remains under discussion[88]. They are functional fermentation compounds, which can be used in combination with nutrients to promote health[89].

According to Tsilingiri et al., In 2013, postbiotics contain any substance released due to the metabolic activity of microorganisms and has beneficial effects on the host. They create these effects directly and indirectly[90]. Postbiotics are not considered synbiotics and may not only have a positive effect on the gut microbiota but may also enhance the gut microbiome. Therefore, Zółkiewicz et al. Believe that the term synbiotics should be further explored and include the concept of postbiotics. Postbiotics display beneficial health impacts through similar mechanisms that characterize probiotics. At the same time, since they are not live microorganisms, it would minimize the risks of using probiotics. Postbiotics like prebiotics appear to have fewer side effects while having similar efficacy to probiotics[91].

4.1 The consumption of postbiotics

Directly available groups of postbiotic drugs include: supernatants (without cell or cell), exopolysaccharides, enzymes, vitamins, amino acids, peptides, cell wall fragments, SCFAs, bacterial lysates and metabolites Are produced by the gut microbiota. Supernatants help prevent cancer through the reduction of oxidative stress and antitumour activity. Cell-free supernatants contain biologically active metabolites secreted by bacteria and yeast in the fluid around them in cell culture medium, obtained directly from these media. Biopolymers secreted outside the cell wall during growth create a heterogeneous group of substances called exopolysaccharides (ESPs). These substances are applied as stabilizers in the food industry[91]. ESPs modulate the immune response by interacting with dendritic cells (DCs) and macrophages and increasing the proliferation of T lymphocytes and NKs[92].

Enzymes produced by microorganisms have created defence mechanisms against the harmful effects of reactive oxygen species (ROS), which can damage lipids, proteins, carbohydrates, and nucleic acids. Some enzymes controlling ROS include Glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase, and NADH-oxidase.

Bacterial lipoteichoic acid (LTA) is found in the cell wall of gram-positive bacteria and can be released spontaneously into the environment, showing the effects of immune stimulation. Some believe that it stimulates the production of cytokines by regulating immune activity, while others believe that it does not decrease inflammatory processes and creates damage to gut tissues. Its topical application enhances nonspecific defence mechanisms and finally releases disinfectant peptides, including human beta-defensin and colchicine. Therefore, it may be more widely used to treat many skin infections, anti-inflammatory and anticancer activities. However, it can create side effects and cause allergic and inflammatory reactions.

SCFAs result from the fermentation of plant polysaccharides by gut microbiota, and their known types include acetic acids, propionic acids and butyric acids. Of these three types, butyrate is one of the most significant energy sources for enterocytes, which assists in regenerating the intestinal epithelium and modulates gene expression. Acetate directly regulates appetite in the central nervous system and can be used to prevent cardiovascular disease.

Bacterial lysates result from chemical or mechanical degradation of gram-positive and gram-negative bacteria; by stimulating the intestinal DCs, they activate T and B lymphocytes and finally exert their effect on the immune system. Bacterial lysates mimic the presence of bacteria in the body[93].

The effect of postbiotics on diseases and health states is directly on the body's signalling pathways or indirectly on the metabolism and composition of the intestinal microbial flora[94].

Lactobacillus plantarum strains are the main species of lactic acid bacteria that can produce postbiotic metabolites with anticancer properties[94]. Due to their anti-inflammatory, immunomodulatory and antimicrobial activities against pathogenic strains, postbiotics are most commonly used in children due to their susceptibility to intestinal disorders. Their positive effects on microbiota growth, intestinal maturity and various immunomodulatory actions are significant and interesting, especially in children[95].

Postbiotic	**Microorganism's source**	**Effects**	**Resources**
Cell-free supernatants	*Lactobacillus acidophilus, Lactobacillus casei*	• Anti-inflammatory and antioxidant influence on gut epithelial cells, macrophages and neutrophils	[95]
Cell-free supernatants	*Lactobacillus casei Lactobacillus rhamnosus GG*	• Ability to prevent the invasion of colorectal cancer cells	[96]
Cell-free supernatants	*Lactobacillus Bifidobacterium*	• Defend enterocyte cells from enteroinvasive *Escherichia coli* invasion	[97]
Cell-free supernatants	*Lactobacillus plantarum*	• Positive effect on maturity and morphological structure of intestinal barrier • prevented tumour development in mice with a high-fat diet	[98]
Cell-free supernatants	*Saccharomyces cerevisiae, Saccharomyces boulardii*	• Reversed the state of intestinal peristalsis caused by stress stimuli.	[99]

		• *Boulardii* exhibits anti-inflammatory and antioxidant activity similar to bacterial cell supernatant. • Accelerate wound healing and intestinal barrier repair.	
Cell-free supernatants	*Lactobacillus rhamnosus SHA111, SHA112, and SHA113*	• Induction of apoptosis plays an anticancer role by upregulating BAD, Bax, Caspase-3, Caspase-8, Caspase-9 and down-regulating BCL-2 genes.	[11]
Cell-free supernatants	*Lactobacillus fermentum sp*	• Induction of apoptosis by upregulation of Caspase-3, Bax, BAK, and Noxa and BID gene mRNA expression	[14]
Cell-free supernatants	*Bifidobacterium bifidum*	• Decreased growth of cancer cells in human colon cancer	[11]
Cell-free supernatants	*Bifidobacterium adolescentis SPM0212*	• Inhibit the growth of cancer cells in three colon cancer cell lines	[14]
Supernatant	*Bifidobacterium breve*	• Induces maturation and survival of DCs, increases IL-10 secretion, and represses TNF-α secretion. • Influence on the immune system	[51]
Supernatant	*Bacillus coagulans*	• Increased anti-inflammatory cytokine production and Th2-dependent immune responses	14] [
Supernatant	*Lactobacillus rhamnosus*	• Defending human intestinal smooth muscle cells from damage	[11]
Exopolysaccharide (Tofu)	*Lactobacillus plantarum*	• Induction of NO secretion • Increased phagocytic ability of macrophages • Increased IgA concentration in the intestinal mucosa • Stimulation of lymphocyte proliferation	[97]

Exopolysaccharide	*Lactobacillus casei*	• As an adjuvant, the effect of the foot-and-mouth disease vaccine increased.	[98]
Exopolysaccharide	*Lactobacillus strains isolated from fermented Dorian fruit*	• Antimicrobial and antioxidant properties	[99]
Exopolysaccharide	*Lactobacillus helveticus*	• Capability to bind iron ions • Responsible for the antioxidant features of green tea	[14]
Exopolysaccharide (Kefir)	*Lactobacillus kefiranofaciens*	• Delayed the spread of atherosclerosis in a preclinical animal model (rabbit) • Preventing high blood pressure and maintaining blood glucose levels in mice that consumed too much cholesterol • Has antiatherogenic properties	[92]
Exopolysaccharide	*Peanibacillus mucilaginosus TKU032*	• Incidence of antioxidant properties	[93]
Exopolysaccharide	*Lactobacillus plantarum 70810*	• As antitumour agents in vitro • Repression of tumour cell proliferation	[93]
Enzyme (GPx)	*2 strains of Lactobacillus fermentum*	• Strong antioxidant qualities	[95]
Enzyme (SOD) or catalase	*Lactobacillus*	• Altered strains provided symptom relief in the mouse model of Crohn's disease compared to unchanged counterparts. • *Lactobacillus* strains with dismutase like activity are more effective in relieving gut inflammation than strains producing catalase. • Genetically modified strains expressing catalase have been suggested to prevent chemical colon cancer in mice.	[96]

Bacterial (LTA) cell wall fragments	*Lactobacillus Bifidobacteria Strains*	• Stimulation of the Mast Cell response of the skin toward some bacterial and viral infections	[91]
Bacterial (LTA) cell wall fragments	*Lactobacillus plantarum JCM1149 and Lactobacillus plantarum L-137*	• Anti-allergic, antitumor and antiviral effects that lead to the T helper 1 (Th1) immune response.	[92]
Bacterial cell wall fragments	*Bacillus coagulans*	• Increase anti-inflammatory cytokine production and immune responses dependent Th2	[11]
Bacterial cell wall fragments	*Lactobacillus paracasei sp*	• It reduces cell proliferation and induces apoptosis and thus has anticancer effects.	[14]
Peptide	*Lactococcus lactis*	• Showed an antimicrobial effect.	[65]
Protein	*Staphylococcus hominis MANF2*	• Anti-*Mycobacterium tuberculosis*	[66]
SCFA Butyrate	*Roseburia intestinalis*	• Repression of atherogenesis in the rat model of atherosclerosis • Significant reduction in endotoxemia and inflammatory markers in serum and aorta	[67]
SCFA Propionate	*Propionibacterium freudenreichii*	• Selectively induces apoptosis in gastric cancer cells. • Antitumour activity.	[98]
SCFA Propionate	*Clostridium butyricum sp*	• It suppresses the Wnt / β-catenin signalling pathway and modulates intestinal microbiota composition, thus having an anticancer effect.	[99]
Bacterial lysates Folate	*Lactobacillus paracasei killed by heat*	• Decrease the symptoms of dry eye syndrome	[11]
Bacterial lysates Folate	*Lactobacillus helveticus CD*	• Displayed antioxidant activity	[99]

Table10. Effects of postbiotics consumption

4.2 Safety of using postbiotics

Fortunately, postbiotics eliminate the problem of access to antibiotic resistance genes and virulence factors and the need for exposure to living microorganisms, which is especially important in children with immature immune systems and leaky gut barriers[14]. In order to investigate the safety of postbiotics, the role of postbiotics in a systematic and randomized controlled study in the prevention and treatment of common infectious diseases among children under five was evaluated. In this study, only in 3 cases, side effects such as high vomiting and severe dehydration were reported, and in the remaining cases, no unfavourable effects of postbiotics were reported. However, there are few studies on the potentially harmful effects of the use of postbiotics. Due to their structure, shelf life, stability, non-toxic impacts and market conditions, postbiotics can be a safe alternative to probiotics and used in the food and pharmaceutical industries[19].

5.Dysbiosis

Our body's microbiome performs a variety of vital functions for us. Without the presence of microbes, human anatomy and physiology would be completely different. The disorder in this cooperative relationship will be called dysbiosis. Any dysbiosis in the microbial communities that make up the microbiome can be controlled by probiotics, prebiotics or synbiotics[19]. A wide range of intestinal microorganisms, typically common, can become a potential threat to the host in one step[10]. Dysbiosis in the intestine is related to differences in the composition and activity of intestinal microbiota, damaging effects on host health through qualitative and quantitative changes in intestinal bacteria, changes in their metabolic activity or changes in their location[25]. Some commensal bacteria inhibit the growth of opportunistic pathogens. For example, during lactose fermentation, *Bifidobacterium* decreases the intestinal pH, thus preventing the colonization of pathogenic E. coli; therefore, they prevent the growth of opportunistic pathogens[40]. Intestinal dysbiosis reduces the mucosal barrier's stability, disrupts the immune system, and causes oxidative stress and inflammation. Over time, intestinal dysbiosis and bacterial transmission can increase the incidence of a variety of diseases[19]. Impairment of intestinal mucosal homeostasis, influenced by genetic factors, intestinal microbiome, immune system and environmental contacts, predisposes to IBD[19]. In 2016, a study investigated the mechanical link between acute cerebral ischemia, microbiota changes, and the immune response after brain trauma. Decreased species diversity and bacterial overgrowth of bacteroids were identified as signs of dysbiosis after stroke, which was associated with dysfunction of the intestinal barrier and decreased intestinal motility, which was detected by detecting intestinal bolus in the body[19].

6.Tumour necrosis factor (TNF- α)

It is one of the main inflammatory cytokines and is responsible for creating strong inflammatory processes in patients with IBD. Thus, reducing or inhibiting TNF-α release has been the focus of IBD-guided treatments for many years. Regulating TNF-α production may prevent severe and persistent inflammation, which is crucial in inflammatory diseases. Probiotics reduce

inflammatory cytokines, such as TNF-α, especially in chronic diseases, to perform their anti-inflammatory activities. The major regulators of TNF-α expression include nuclear factor kappa B (NF kB) and members of the mitogen-activated protein kinase (MAPK) family[14].

Conclusion

As mentioned, previous, one of the best ways to help people stay healthy is through natural products such as probiotics, prebiotics, synbiotics and postbiotics. Due to their particular structure, these products can be beneficial and used as a therapeutic or preventive agent. They can also diminish the duration of symptoms. They have revealed beneficial impacts in studies in the prevention and treatment of disease, but the application of prebiotics and postbiotics seems to be safer in sensitive individuals due to the absence of living microorganisms. Although, probiotic supplements show a high ability to heal gastric ulcers faster with other drugs and prevent and treat constipation and Helicobacter pylori disease, one of the most annoying diseases of the gastrointestinal tract. Even during the recent coronavirus pandemic, probiotics were used to decrease symptoms in COVID-19, with successful results. All four of these supplements are effective in treating cancer, especially colorectal cancer.

Using different sources of probiotics and prebiotics, such as fungi and algae, will be more economical and less harmful. In addition, these sources alone have many benefits for human, livestock and poultry health. Probiotic, postbiotic, prebiotic and synbiotic supplements can be used to treat and prevent apoptotic dermatitis, kidney problems, lactose intolerance, prevent osteoporosis and help improve some symptoms, especially gastrointestinal symptoms in patients and especially used for children with autism and others.

Nevertheless, this topic still requires more extensive research and investigation on the effects of probiotics, prebiotics, synbiotics and postbiotics supplements in the inhibition and treatment of other conditions and the development of these supplements.

Resources

1. Arihara, K., *Strategies for designing novel functional meat products.* Meat science, 2006. **74**(1): p. 219-229.
2. Daneshmand, A., et al., *Effect of oyster mushroom (Pleurotus ostreatus) with and without probiotic on growth performance and some blood parameters of male broilers.* Animal feed science and technology, 2011. **170**(1-2): p. 91-96.
3. Cheung, M.K., et al., *A Review of the Effects of Natural Compounds, Medicinal Plants, and Mushrooms on the Gut Microbiota in Colitis and Cancer.* Front Pharmacol, 2020. **11**: p. 744.
4. Valdes, A.M., et al., *Role of the gut microbiota in nutrition and health.* Bmj, 2018. **361**.
5. Anggeraini, A.S., et al., *Effects of synbiotic supplement on body weight and fasting blood glucose levels in obesity: A randomized placebo-controlled trial.* Annals of Medicine and Surgery, 2021. **68**: p. 102548.
6. Czerucka, D., T. Piche, and P. Rampal, *yeast as probiotics–Saccharomyces boulardii.* Alimentary pharmacology & therapeutics, 2007. **26**(6): p. 767-778.

7. Gāliņa, D., L. Ansonska, and A. Valdovska, *Effect of probiotics and herbal products on intestinal histomorphological and immunological development in piglets.* Veterinary medicine international, 2020. **2020**.
8. Wasser, S.P., et al., *Dietary supplements from medicinal mushrooms: diversity of types and variety of regulations.* International Journal of Medicinal Mushrooms, 2000. **2**(1).
9. Aida, F., et al., *Mushroom as a potential source of prebiotics: a review.* Trends in Food Science & Technology, 2009. **20**(11-12): p. 567-575.
10. Shokryazdan, P., et al., *Probiotics: from isolation to application.* Journal of the American College of Nutrition, 2017. **36**(8): p. 666-676.
11. Markowiak, P. and K. Śliżewska, *Effects of Probiotics, Prebiotics, and Synbiotics on Human Health.* Nutrients, 2017. **9**(9).
12. Williams, N.T., *Probiotics.* American Journal of Health-System Pharmacy, 2010. **67**(6): p. 449-458.
13. Ishibashi, N., *Yamazaki S.* Probiotics and safety. Am J Clin Nutr, 2001. **73**: p. 465S-470S.
14. Hessari, H., et al., Probiotics and therapeutic applications. Laboratory and Diagnosis, 2019. 10(42): p. 61-66.
15. Xiang, Q., et al., *Effects of different probiotics on laying performance, egg quality, oxidative status, and gut health in laying hens.* Animals, 2019. **9**(12): p. 1110.
16. Higgins, J., et al., *Temporal effects of lactic acid bacteria probiotic culture on Salmonella in neonatal broilers.* Poultry Science, 2007. **86**(8): p. 1662-1666.
17. Kurian, S.J., et al., *Probiotics in Prevention and Treatment of COVID-19: Current Perspective and Future Prospects.* Archives of medical research, 2021.
18. Amirani, E., et al., *The effects of probiotic supplementation on mental health, biomarkers of inflammation and oxidative stress in patients with psychiatric disorders: A systematic review and meta-analysis of randomized controlled trials.* Complementary therapies in medicine, 2020. **49**: p. 102361.
19. Cristofori, F., et al., *Anti-inflammatory and immunomodulatory effects of probiotics in gut inflammation: a door to the body.* Frontiers in Immunology, 2021. **12**: p. 178.
20. Cremonini, F., et al., *Meta-analysis: the effect of probiotic administration on antibiotic-associated diarrhoea.* Alimentary pharmacology & therapeutics, 2002. **16**(8): p. 1461-1467.
21. McFarland, L.V., *Meta-analysis of probiotics for the prevention of antibiotic associated diarrhea and the treatment of Clostridium difficile disease.* Official journal of the American College of Gastroenterology| ACG, 2006. **101**(4): p. 812-822.
22. Hickson, M., et al., *Use of probiotic Lactobacillus preparation to prevent diarrhoea associated with antibiotics: randomised double blind placebo controlled trial.* Bmj, 2007. **335**(7610): p. 80.
23. Van Niel, C.W., et al., *Lactobacillus therapy for acute infectious diarrhea in children: a meta-analysis.* Pediatrics, 2002. **109**(4): p. 678-684.
24. Allen, S.J., et al., *Probiotics for treating acute infectious diarrhoea.* Cochrane Database of Systematic Reviews, 2010(11).
25. Guandalini, S., et al., *Lactobacillus GG administered in oral rehydration solution to children with acute diarrhea: a multicenter European trial.* Journal of pediatric gastroenterology and nutrition, 2000. **30**(1): p. 54-60.
26. Islam, S.U., *Clinical uses of probiotics.* Medicine, 2016. **95**(5).

27. McFarland, L.V. and S. Dublin, *Meta-analysis of probiotics for the treatment of irritable bowel syndrome.* World journal of gastroenterology: WJG, 2008. **14**(17): p. 2650.
28. Choung, R.S. and G. Locke 3rd, *Epidemiology of IBS.* Gastroenterology Clinics of North America, 2011. **40**(1): p. 1-10.
29. Mulder, D.J., et al., *A tale of two diseases: the history of inflammatory bowel disease.* Journal of Crohn's and Colitis, 2014. **8**(5): p. 341-348.
30. Kirsner, J.B., *Historical origins of current IBD concepts.* World journal of gastroenterology, 2001. **7**(2): p. 175.
31. Jakubczyk, D., K. Leszczyńska, and S. Górska, *The effectiveness of probiotics in the treatment of inflammatory bowel disease (IBD)—a critical review*. Nutrients, 2020. **12**(7): p. 1973.
32. Rautava, S., M. Kalliomäki, and E. Isolauri, *Probiotics during pregnancy and breast-feeding might confer immunomodulatory protection against atopic disease in the infant.* Journal of allergy and clinical immunology, 2002. **109**(1): p. 119-121.
33. Papista, C., et al., *Gluten induces coeliac-like disease in sensitised mice involving IgA, CD71 and transglutaminase 2 interactions that are prevented by probiotics.* Laboratory investigation, 2012. **92**(4): p. 625-635.
34. Olivares, M., M. Laparra, and Y. Sanz, *Oral administration of Bifidobacterium longum CECT 7347 modulates jejunal proteome in an in vivo gliadin-induced enteropathy animal model.* Journal of proteomics, 2012. **77**: p. 310-320.
35. de Almeida, N.E.C., et al., *Digestion of Intact Gluten Proteins by Bifidobacterium Species: Reduction of Cytotoxicity and Proinflammatory Responses.* Journal of Agricultural and Food Chemistry, 2020. **68**(15): p. 4485-4492.
36. Limketkai, B.N., et al., *Probiotics for induction of remission in Crohn's disease.* Cochrane Database of Systematic Reviews, 2020(7).
37. Shams, K., M. Larypoor, and J. Salimian, *The immunomodulatory effects of Candida albicans isolated from the normal gastrointestinal microbiome of the elderly on colorectal cancer.* Medical Oncology, 2021. **38**(12): p. 1-12.
38. Banik, A., et al., *Fungal probiotics: Opportunity, challenge, and prospects*, in *Recent Advancement in White Biotechnology Through Fungi*. 2019, Springer. p. 101-117.
39. Mahyuddin, P. and M. Winugroho, *Effect of combination of yeast (Saccharomyces cerevisae+ Candida utilis) and herbs supplementation in finishing diet on carcass characteristics of beef cattle.* Journal of the Indonesian Tropical Animal Agriculture, 2010. **35**(4): p. 251-256.
40. Oak, S.J. and R. Jha, *The effects of probiotics in lactose intolerance: A systematic review.* Crit Rev Food Sci Nutr, 2019. **59**(11): p. 1675-1683.
41. Luyer, B.l., G. Makhoul, and J. Duhamel, *A multicentric study of a lactose free formula supplemented with Saccharomyces boulardii in children with acute diarrhea.* Archives de Pédiatrie, 2010. **17**(5): p. 459-465.
42. Saber, A., et al., *Secretion metabolites of probiotic yeast, Pichia kudriavzevii AS-12, induces apoptosis pathways in human colorectal cancer cell lines.* Nutrition research, 2017. **41**: p. 36-46.
43. Greppi, A., et al., *Potential probiotic Pichia kudriavzevii strains and their ability to enhance folate content of traditional cereal-based African fermented food.* Food microbiology, 2017. **62**: p. 169-177.

44. Carro, L. and I. Nouioui, *Taxonomy and systematics of plant probiotic bacteria in the genomic era.* AIMS microbiology, 2017. **3**(3): p. 383.
45. Stickel, F. and D. Shouval, *Hepatotoxicity of herbal and dietary supplements: an update.* Arch Toxicol, 2015. **89**(6): p. 851-65.
46. Cohen, P.A. and E. Ernst, *Safety of herbal supplements: a guide for cardiologists.* Cardiovascular therapeutics, 2010. **28**(4): p. 246-253.
47. Chrysant, S., *The clinical significance and costs of herbs and food supplements used by complementary and alternative medicine for the treatment of cardiovascular diseases and hypertension.* Journal of human hypertension, 2016. **30**(1): p. 1-6.
48. Lee, A.N. and V.P. Werth, *Activation of autoimmunity following use of immunostimulatory herbal supplements.* Archives of Dermatology, 2004. **140**(6): p. 723-727.
49. Adom, M.B., et al., *Chemical constituents and medical benefits of Plantago major.* Biomedicine & Pharmacotherapy, 2017. **96**: p. 348-360.
50. Nematgorgani, S., et al., *Effects of Urtica dioica leaf extract on inflammation, oxidative stress, ESR, blood cell count and quality of life in patients with inflammatory bowel disease.* Journal of Herbal Medicine, 2017. **9**: p. 32-41.
51. Saddiqe, Z., I. Naeem, and A. Maimoona, *A review of the antibacterial activity of Hypericum perforatum L.* Journal of ethnopharmacology, 2010. **131**(3): p. 511-521.
52. Nissen, L., et al., *Prebiotic potential and bioactive volatiles of hemp byproduct fermented by lactobacilli.* LWT, 2021: p. 112201.
53. Doron, S. and D.R. Snydman, *Risk and safety of probiotics.* Clinical Infectious Diseases, 2015. **60**(suppl_2): p. S129-S134.
54. Van den Nieuwboer, M., et al., *Probiotic and synbiotic safety in infants under two years of age.* Beneficial microbes, 2014. **5**(1): p. 45-60.
55. Sanders, M.E., et al., *Safety assessment of probiotics for human use.* Gut microbes, 2010. **1**(3): p. 164-185.
56. Snydman, D.R., *The safety of probiotics.* Clinical infectious diseases, 2008. **46**(Supplement_2): p. S104-S111.
57. Horwitch, C.A., et al., *Lactobacillemia in three patients with AIDS.* Clinical infectious diseases, 1995. **21**(6): p. 1460-1462.
58. Bhakta, M. and P. Kumar, *Mushroom polysaccharides as a potential prebiotics.* Int. J. Health Sci. Res, 2013. **3**(8): p. 77-84.
59. Davani-Davari, D., et al., *Prebiotics: definition, types, sources, mechanisms, and clinical applications.* Foods, 2019. **8**(3): p. 92.
60. Johnson-Henry, K.C., et al., *Probiotics, prebiotics, and synbiotics for the prevention of necrotizing enterocolitis.* Advances in nutrition, 2016. **7**(5): p. 928-937.
61. Khan, S.H., N. Mukhtar, and J. Iqbal, *Role of Mushroom as Dietary Supplement on Performance of Poultry.* J Diet Suppl, 2019. **16**(5): p. 611-624.
62. Chuang, W.Y., Y.C. Hsieh, and T.T. Lee, *The Effects of Fungal Feed Additives in Animals: A Review.* Animals (Basel), 2020. **10**(5).
63. Wu, L., et al., *Chemical structure and inhibition on α-glucosidase of the polysaccharides from Cordyceps militaris with different developmental stages.* International journal of biological macromolecules, 2020. **148**: p. 722-736.
64. Bulam, S., N.Ş. Üstün, and A. Pekşen, *Health benefits of Ganoderma lucidum as a medicinal mushroom.* Turkish Journal of Agriculture-Food Science and Technology, 2019. **7**(sp1): p. 84-93.

65. Xu, J.-W., W. Zhao, and J.-J. Zhong, *Biotechnological production and application of ganoderic acids.* Applied microbiology and biotechnology, 2010. **87**(2): p. 457-466.
66. Yamin, S., et al., *Effect of Ganoderma lucidum polysaccharides on the growth of Bifidobacterium spp. as assessed using Real-time PCR.* International Food Research Journal, 2012. **19**(3): p. 1199.
67. Delzenne, N.M. and L.B. Bindels, *Ganoderma lucidum, a new prebiotic agent to treat obesity?* Nature reviews Gastroenterology & hepatology, 2015. **12**(10): p. 553-554.
68. Yasrebi, N., A.S. Hatamian Zarmi, and M. Larypoor, *Optimization of Chitosan Production from Iranian Medicinal Fungus Trametes-Versicolor by Taguchi Method and Evaluation of Antibacterial Properties.* Iranian Journal of Medical Microbiology, 2020. **14**(3): p. 186-200.
69. Zeynali, M., A. Hatamian-Zarmi, and M. Larypoor, *Evaluation of Chitin-Glucan Complex Production in Submerged Culture of Medicinal Mushroom of Schizophilum commune: Optimization and Growth Kinetic.* Iranian Journal of Medical Microbiology, 2019. **13**(5): p. 406-424.
70. Benkeblia, N., *Ganoderma lucidum polysaccharides and Terpenoids: profile and health benefits.* J Food Nutr Diet, 2015. **1**: p. 1-6.
71. Ferreira, I.C., et al., *Chemical features of Ganoderma polysaccharides with antioxidant, antitumor and antimicrobial activities.* Phytochemistry, 2015. **114**: p. 38-55.
72. Lee, S.-M. and C.-M. Ryu, *Algae as New Kids in the Beneficial Plant Microbiome.* Frontiers in Plant Science, 2021. **12**: p. 91.
73. Ścieszka, S. and E. Klewicka, *Algae in food: A general review.* Critical reviews in food science and nutrition, 2019. **59**(21): p. 3538-3547.
74. Cherry, P., et al., *Prebiotics from seaweeds: An ocean of opportunity?* Marine drugs, 2019. **17**(6): p. 327.
75. Ricigliano, V.A. and M. Simone-Finstrom, *Nutritional and prebiotic efficacy of the microalga Arthrospira platensis (spirulina) in honey bees.* Apidologie, 2020. **51**(5): p. 898-910.
76. Bruzzese, E., et al., *Impact of prebiotics on human health.* Digestive and Liver Disease, 2006. **38**: p. S283-S287.
77. Yaqoob, M., et al., *The potential mechanistic insights and future implications for the effect of prebiotics on poultry performance, gut microbiome, and intestinal morphology.* Poultry Science, 2021: p. 101143.
78. Elgeddawy, S.A., et al., *Effects of the dietary inclusion of a probiotic or prebiotic on florfenicol pharmacokinetic profile in broiler chicken.* Journal of animal physiology and animal nutrition, 2020. **104**(2): p. 549-557.
79. Gowrishankar, S., A. Kamaladevi, and S.K. Pandian, *Prebiotics Mechanism of Action: An Over View*, in *Advances in Probiotics*. 2021, Elsevier. p. 137-148.
80. Khalil, N.A., et al., *Prospective evaluation of probiotic and prebiotic supplementation on diabetic health associated with gut microbiota.* Food Bioscience, 2021: p. 101149.
81. Currò, D., et al., *Probiotics, fibre and herbal medicinal products for functional and inflammatory bowel disorders.* British journal of pharmacology, 2017. **174**(11): p. 1426-1449.
82. Schrezenmeir, J. and M. de Vrese, *Probiotics, prebiotics, and synbiotics—approaching a definition.* The American journal of clinical nutrition, 2001. **73**(2): p. 361s-364s.

83. Roselli, M. and A. Finamore, *Use of synbiotics for ulcerative colitis treatment.* Current clinical pharmacology, 2020. **15**(3): p. 174-182.
84. Tang, S.G.H., et al., *Chemical compositions of egg yolks and egg quality of laying hens fed prebiotic, probiotic, and synbiotic diets.* Journal of food science, 2015. **80**(8): p. C1686-C1695.
85. Altun, H.K., E.A. Yıldız, and M. Akın, *Effects of synbiotic therapy in mild-to-moderately active ulcerative colitis: A randomized placebo-controlled study.* The Turkish Journal of Gastroenterology, 2019. **30**(4): p. 313.
88. Dilli, D., et al., *The propre-save study: effects of probiotics and prebiotics alone or combined on necrotizing enterocolitis in very low birth weight infants.* The Journal of pediatrics, 2015. **166**(3): p. 545-551. e1.
87. Sreenivasa, B., et al., *Role of synbiotics in the prevention of necrotizing enterocolitis in preterm neonates: a randomized controlled trial.* Int J Contemp Pediatr, 2015. **2**(2): p. 127-30.
88. Wang, Y., et al., *Probiotics and fructo-oligosaccharide intervention modulate the microbiota-gut brain axis to improve autism spectrum reducing also the hyper-serotonergic state and the dopamine metabolism disorder.* Pharmacological Research, 2020. **157**: p. 104784.
89. Noll, M., et al., *Improvement of Atopic Dermatitis by Synbiotic Baths.* Microorganisms, 2021. **9**(3): p. 527.
90. Dehghani, H., et al., *Synbiotic supplementations for azotemia in patients with chronic kidney disease: a randomized controlled trial.* Iranian journal of kidney diseases, 2016. **10**(6): p. 351.
91. Ban, Q., et al., *Effects of a synbiotic yogurt using monk fruit extract as sweetener on glucose regulation and gut microbiota in rats with type 2 diabetes mellitus.* Journal of dairy science, 2020. **103**(4): p. 2956-2968.
92. Żółkiewicz, J., et al., *Postbiotics—a step beyond pre-and probiotics.* Nutrients, 2020. **12**(8): p. 2189.
93. Wegh, C.A., et al., *Postbiotics and their potential applications in early life nutrition and beyond.* International journal of molecular sciences, 2019. **20**(19): p. 4673.
94. Tsilingiri, K. and M. Rescigno, *Postbiotics: what else?* Beneficial microbes, 2013. **4**(1): p. 101-107.
95. Makino, S., et al., *Enhanced natural killer cell activation by exopolysaccharides derived from yogurt fermented with Lactobacillus delbrueckii ssp. bulgaricus OLL1073R-1.* Journal of dairy science, 2016. **99**(2): p. 915-923.
96. Vrzáčková, N., T. Ruml, and J. Zelenka, *Postbiotics, Metabolic Signaling, and Cancer.* Molecules, 2021. **26**(6): p. 1528.
97. Chuah, L.-O., et al., *Postbiotic metabolites produced by Lactobacillus plantarum strains exert selective cytotoxicity effects on cancer cells.* BMC complementary and alternative medicine, 2019. **19**(1): p. 1-12.
98. Morniroli, D., et al., *Postbiotic Supplementation for Children and Newborn's Health.* Nutrients, 2021. **13**(3): p. 781.
99. De Marco, S., et al., *Probiotic cell-free supernatants exhibited anti-inflammatory and antioxidant activity on human gut epithelial cells and macrophages stimulated with LPS.* Evidence-Based Complementary and Alternative Medicine, 2018. **2018**.