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# Probiotics, Prebiotics, Synbiotics, and Fermented Foods as Potential Biotics in Nutrition Improving Health via Microbiome-Gut-Brain Axis

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**Abstract:** Biological, social, and psychological practices greatly affect the dietary intake of people; as a result, health-related complexities occur. Functional food and supplements have become popular due to their nutraceutical benefits, which make different choices of fermented food and beverages available to people. This review describes the characteristics of probiotics, prebiotics, post- and paraprobiotics, and their role in nutrition and in the sustainability of health. Currently, several synbiotic supplements have attracted consumers in the nutraceutical market to offer a number of health benefits, which are complementary mixtures of selected characterized probiotic cultures and prebiotic substrates. Traditional fermented foods consumed in different cultures are different than probiotics and symbiotic preparations, though these could be considered potential biotics in nutrition. Fermented foods are part of a staple diet in several countries and are cost-effective due to their preparation using seasonal raw materials available from local agriculture practices. Intake of all biotics discussed in this article is intended to improve the population of beneficial microbiota in the gut, which has proved important for the microbiome–gut–brain axis, influencing the activity of vagus nerve.

**Keywords:** probiotics; prebiotics; synbiotics; postbiotics; nutrition; gut; brain; health; microbiota

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## 1. Introduction

Our everyday usual dietary intakes are mostly comprised of a variety of food items, nutrients from plant and animal sources, and diet supplements. In general, components of food altogether influence cellular processes collectively in the metabolic system. The chemistry between the nutrient components in diets and human physiology establishes the status of our well-being in everyday life. Food components in a balanced nutritive diet should normally include those essential substances that can be absorbed in the alimentary system and in return can impose a physiological effect on the human body. The gut microbiota affected by nutrition can have an impact on metabolic disease [1,2]. This can include dietary compounds and metabolites, dietary fibers, and active ingredients from different agricultural resources. Since the constituents of food intake positively affect gastrointestinal tract (GIT) function and its health, they consequently affect our metabolism [3,4].

The research challenges relevant to this area include the understanding of dietary compounds, dietary fibers, and the impact on their absorption and the assimilation of nutrients. This influence on our ability to digest the ingredients in our diets has a profound effect on metabolism and energy balance. The highly important role of food components influencing the essential balance in the composition of nutrition remains a key factor in improving immune function. Researchers have investigated the effects of manipulation on food composition, including the supplements of probiotics on sustaining health and alleviating certain diseases, such as gut inflammation, inflammatory bowel disease, and other health issues [5].

### 1.1. Nutrition and Health through Nutraceuticals

Inclusion of fermented food and beverages in diets can deliver improved nutrition across the course of one's life. Nutraceuticals and functional food can provide additional or enhanced benefits over and above their basic nutritional importance [6]. These are produced using vital functional ingredients, including probiotics, prebiotics, sterols from plants, and a variety of agriculture-sourced foods. A variety of recipes for healthy and functional food have been prepared and consumed worldwide by communities residing in different geographical and cultural environments [7,8], including cereals and fermented wheat grain products such as fermented milk, kefir, and sour bread [9–11].

The study of challenges in this area includes the understanding of prebiotics, probiotics, and nutraceuticals for delivering benefits to human health. Conventional and novel food components affect biological and physiological processes across the course of one's life. The importance of the study of nutraceuticals not only includes the sustainability of well-being's impact on muscle and bone metabolism; the study also helps our understanding of improved recovery from diseases and infections, particularly related to gastrointestinal system pathology [1–4].

### 1.2. Biological, Social, and Psychological Practices Affecting Nutrition and Health

The main contributing factors of food choices and eating behavior are influenced geographically by biological, social, and psychological practices. Investigation into gut microbiota has been a focus of biological and biomedical sciences over the last few decades. Human traits are considered to be determined by the combination of individual genetic background and environmental factors. However, the recent findings have shown that the gut microbiota contributes to the traits of humans as much as our genes, especially in the case of health issues and long-term problems such as atherosclerosis, hypertension, obesity, diabetes, metabolic syndrome, inflammatory bowel disease (IBD), gastrointestinal tract malignancies, hepatic encephalopathy, allergies, behavior, intelligence, autism, neurological diseases, and psychological diseases [5].

Alteration of the composition of the gut microbiota even affects the behavior, intelligence, mood, autism, and psychology of its host, as well as the prevalence of migraines, through the gut-brain axis. Nutrients determine the growth of individual intestinal bacteria in the gut. Therefore, it is reasonable to speculate that nutrients are the main determinants of gut microbiota composition, which means that their effects on human traits result from modification of the gut microbiota by nutrient uptake as well as from the types and composition of nutrients themselves. Considering the dependency on specific nutritional components of microbes, gut microbiota could be the missing link between nutrients and human traits.

Recently, there has been tremendous research interest in gut microbiota composition and health. Studies have included interventions by probiotics and prebiotics for their multifaceted health advantages in various systemic disorders such as in the gastrointestinal, cardiovascular, neurological, inflammatory, oncological, and endocrine systems [12]. Beneficial gut microbiota (probiotics) in the host's GIT system selectively utilize prebiotics as substrates for increasing and sustaining their population [13,14]. Thus, prebiotics enhance the growth and number of beneficial gut bacteria, which not only exclude various pathogenic bacteria, but also provide a variety of other health benefits. Furthermore, the short-chain fatty acids (SCFAs) generated in prebiotic fermentation enhance the integrity of the gut barrier and immunomodulatory properties [12].

## 2. Biotics Related to Nutrition and Health

Terms included under biotics, i.e., those that affect health through nutrition, are probiotics, prebiotics, postbiotics, and synbiotics. These have been discussed in the following subsections.

### 2.1. Probiotics

These are beneficial microorganisms commonly categorized as lactic acid bacteria and are important for our gut health. Probiotics are defined according to the definition given by the Food and Agriculture Organization/World Health Organization as "Live microorganisms which when administered in adequate amounts, confer a health benefit on the host" [15,16]. Probiotics not only comprise bacterial cultures, mainly Lactobacillus, Bacillus, and Bifidobacterium, but also some yeast strains of Saccharomyces genera. According to the International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus panel, the probiotic mechanisms can be delivered by only a few strains of a particular class of bacteria; for example, Lactobacillus casei or Bifidobacterium bifidum [5]. Probiotic microorganisms are generally lactic acid bacteria (LAB), which are included under the "Generally Recognized As Safe (GRAS)" category by the US Food and Drug Administration (FDA) [17]. LAB belong to the phylum Firmicutes, class Bacilli, and order Lactobacillales, which include over 50 genera placed in six families, (including Lacto-bacillus, Levilactobacillus, Lacticaseibacillus, Limosilactobacillus, Lactococcus, Pediococcus, Enterococcus, Leuconostoc, Oenococcus, Streptococcus, Tetragenococcus, Aerococcus, Carnobacterium, Weissella, Alloiococcus, Symbiobacterium, and Vagococcus) and are comprised of more than 300 species [18–20].

Moreover, to be considered efficient probiotics, the microbial strains used in food preparation or supplements must have demonstrated their benefit in the host. Probiotics help the immune system function properly by training it to identify the difference between good and pathogenic microorganisms. They also help with the digestion of certain fibers, resulting in the production of health-enhancing fragments, and SCFAs. In addition, they produce certain vitamins that humans cannot produce through their metabolism. Probiotics are a good way of administering a defined amount and diversity of beneficial microorganisms in the GIT, consisting of mainly bacteria and some useful yeast strains.

The well-known specific benefit of probiotics is their aid in restocking lost intestinal microbiota after a period of antibiotic therapy. Probiotic foods are of specific interest in preventing some common intestinal infections and improving digestive disorders caused due to long travel and disturbed routines. Their uses are also suggested in infants' cases of eczema or colic by helping with lactose digestion in milk-based diets. The beneficial health effects, as supported by results from clinical trials, include the prevention and treatment of intestinal diseases such as infection- and antibiotic-associated diarrhea, inflammatory bowel disease, irritable bowel syndrome, Helicobacter pylori infection, lactose intolerance, allergies, and atopic diseases in children [5,21].

A probiotic can only fulfill its purpose if it is capable of surviving the severe conditions in the stomach environment. It is important to choose a probiotic supplement that contains strains proven to reach the gut alive. It is commonly believed that probiotics need to be taken in enteric-coated capsules to protect the probiotic cultures as they pass through the stomach before being released into the gut. This is not necessary for probiotic strains which are resilient and able to reach the gut without damage to their activity; evidence comes from probiotic cultures contained in the fermented products, such as kefir and probiotic yogurts, which do not have an enteric coating.

The probiotics take up short-term residence in either the small or large intestine depending on the conditions in these areas. Once in situ, the probiotics can dominate over any harmful bacteria by competing for their food sources and space for their colonization. During their residence in the GIT, probiotics produce certain vitamins and SCFAs known to be beneficial for hosts' health.

### 2.2. Postbiotics and Paraprobiotics

Researchers have also pointed out those compounds that are produced as metabolites by probiotics, and those released from food elements or microbial components, including non-viable cells. Such compounds termed postbiotics have the potential to promote health and well-being when dispensed in adequate amounts. According to the definition, a probiotic must be viable cells of microbial cultures; therefore, the term probiotics does not apply to dead microbial cells or the components obtained from a microbial cell.

Subsequently, other two terms—postbiotic and paraprobiotic were created to denote the health benefits beyond the inherent viability of live beneficial microbial cells of probiotics. Post- and paraprobiotics provide a wider viewpoint of the probiotic concept [22]. Post- and paraprobiotics have been used to describe nonviable microorganisms or bacterial cell-free culture supernatants that might provide benefits to hosts by offering bioactivities additional to probiotics. These terms, although having emerged recently, have been adopted rapidly in the area of food science and technology, as well as in human nutrition and health. Specific interest has emerged in the food, biotechnology, and pharmaceutical industries due to post- and paraprobiotics' potential application as functional foods, nutraceuticals, and alternative medications [23].

The difference between these two biotics has been explained thus: postbiotics can be referred to as metabiotics, biogenics, metabolites, cell-free culture supernatants, and cell extracts. On the contrary, paraprobiotics are inactivated (nonviable) microbial (probiotic or nonprobiotic) intact cells [24]. Postbiotics and paraprobiotics represent the health benefits beyond probiotic viability and possess a protective effect in cell lines and animal models. The concepts and applications of both have been discussed in detail by Cuevas-González [25].

Studies performed in vitro and in vivo have demonstrated that postbiotics and paraprobiotics demonstrate several bioactivities, such as anti-inflammatory, immunomodulatory, antiproliferative, antioxidant, and antimicrobial bioactivities. Paraprobiotics are labeled as dead cells of probiotics or nonviable inactivated probiotics and therefore are also termed ghost probiotics. Considering the characteristics of paraprobiotics and postbiotics, these are considered as biotics (Table 1) to represent new categories of biological response modifier agents [26–28].

**Table 1.** Description of terms related to nutrition and health (source of information compiled in the table from references [5,24–28].

| Term | Description | Elements |
|---|---|---|
| Probiotics | Live microorganisms,<br>intact whole cells of probiotic microbes | Selected probiotic strains<br>*Lactobacillus casei*,<br>*L. acidophilus*<br>*L. bulgaricus*, *Lactococcus lactis*<br>*Bifidobacterium bifidum*, *B. lactis (Bifidus actiregularis (R)* ** |
| Postbiotics | Components of lysed probiotic cells.<br>Microbial cell wall fragmented compounds,<br>microbial primary and secondary metabolites<br>secreted by probiotics | Metabiotics, biogenics, metabolites, cell-free supernatants, and extracted fractions e.g.,<br>*Saccharomyces boulardii* (a variety of *S. cerevisiae*) |
| Paraprobiotics | Dead, nonviable, intact (non-lysed) cells | Inactivated cells of probiotics, or nonprobiotic cells |
| Prebiotics | Fruits, legumes, root vegetables, whole grains,<br>seeds, and nuts | Fermentable Oligosaccharides (OS), dietary fibers |
| Potential Biotics | Fermented foods and fermented beverages | Products containing fermented substrates,<br>microbes and their metabolites |

** Probiotic strains in commercial products: information taken from the labels on pots of Probiotic yogurts bought May–June 2022 and from www.Danoneactivia.co.uk; www.activia.ie.

### *2.3. Prebiotics*

All those materials and substrates, which act as nourishment for our gut microbes and foster good growth for their long-term survival in the GIT, are considered prebiotics. The approved definition of a prebiotic is "A substrate that is selectively utilized by host microorganisms in the gut, conferring a health benefit" [29]. Prebiotics are found naturally in some foods and encourage the growth of good bacteria in the gut, fibers in prebiotics can support our gut and overall health. Prebiotic supplements are available to be taken with or without probiotics. FOS, GOS, and Inulin are the most recognized and researched prebiotics.

Therefore, the ideal way to nourish our gut microbiota is the inclusion of different plant-based foods, such as fruits, legumes, root vegetables, tubers, whole grains, seeds, and nuts—which are loaded with naturally occurring prebiotics—in our diet [30]. The quality of a regular diet with a diversity of food components is more important than the calorie intake, which is even more important in the balanced nutrition of elderly and sick people of advanced age [27]. A nutritious meal with probiotics and prebiotics is important for people with a less physically active lifestyle who need fewer calories.

## **3. Functioning of Prebiotics and Fibers Affecting Gut Microbiota**

The similarities between prebiotics and fibers often lead to arguments on how to differentiate between the two terms. The information from the International Scientific Association for Probiotics and Prebiotics suggests a useful comparison between prebiotics and fibers [29]. That enables us to understand the magnitude of each, which affects the survival and propagation of gut microbiota contributing to the host's health. Fiber is a significant but unknowingly neglected nutrient in the regular diets of some people. Although some fibers cannot be digested by humans, these can be broken down by the microbes resident in the gut, which collectively constitute a complex community of several groups of microorganisms. Similar to prebiotics, fibers also may act as food for microbes either resident in the gut or taken through intake of probiotic supplements [27–29].

Soluble dietary fibers are understood to be a form of numerous prebiotics in current use. Most fibers are nondigestible carbohydrates derived from plants, supporting regular bowel movements. For example, apples, black beans, and broccoli are all excellent sources of fiber. Fibers and prebiotics both have been shown to stimulate gut health and may control the immune system by regulating bowel movements, and through this mechanism, they may be beneficial for the alleviation of disorders such as gut inflammation, and irritable bowel syndrome [5], and Crohn's Disease [31]. Some of these effects are mediated by SCFAs produced by probiotics after metabolizing the prebiotics. The positive effects of prebiotics on human health are associated with their capacity to modulate gut microbiota and consequently regulate the production of metabolites, extracellular polysaccharides (EPS), and SCFA. Compared to fiber, prebiotics have a much more compelling effect on gut microbiota and the maintenance of good health [27–29].

### *3.1. Fermentable Oligosaccharides*

Some prebiotics are nondigestible materials but are useful fermentable oligosaccharides which may boost the vitality, growth, and metabolic capacity of some beneficial microflora present in the GIT [32]. Prebiotics that are resistant to acidic conditions in the gut and unaffected by digestive enzymes can safely travel through the GIT and be fermented by the resident bacteria in the colon. Such materials can effectively modulate the composition and activity of intestinal microbiota [27]. Digestive enzymes necessary for the hydrolysis of polymer bonds in the molecules of prebiotics are absent in the human intestine. Hence, prebiotics can surpass the digestion process in the small intestine and reach the colon unaffected, where they are used in fermentation by beneficial probiotic bacteria, Lactobacilli, and Bifidobacteria [33].

Consumption of oligosaccharides, which can escape the action of host digestive enzymes but can be selectively taken up by the populations of microbes resident in the host colon, improves gut health through various mechanisms. There are several functional compounds sold as mixer ingredients in commercial formulations and that also available as individual products. Commonly used prebiotics include inulin, fructo-oligosaccharides (FOSs), galacto-oligosaccharides (GOSs), lactulose, polydextrose, isomalto-oligosaccharides (IMOSs), xylo-oligosaccharides (XOSs), lactitol, etc. [34]. These compounds, if incorporated into a diet in modest quantities (about 5 to 20 gm per day), stimulate the growth of bifidobacteria and lactobacilli, which are not the most abundant microorganisms in the intestine of adults [35].

XOSs are oligosaccharides composed of 2–10 xylose residues that are linked through β-(1,4) bonds. They can be produced via the enzymatic hydrolysis of xylan [36]. After their identification as important dietary fibers, XOSs have shown the potential to be used as a prebiotic food ingredient. Hence, XOSs have been studied for their ability to boost the growth of beneficial microflora in the intestine, specifically *Bifidobacterium* spp. [37]. In addition, various species of Lactobacillus have been extensively examined for their ability to ferment XOSs, such as *acidophilus*, *casei*, *crispatus*, *delbrueckii*, *johnsonii*, *sakei*, *Levilactobacillus brevis* (previously known as *Lactobacillus brevis*), *Limosilactobacillus fermentum* (previously known as *Lactobacillus fermentum*), *Lactococcus lactis*, *Lactiplantibaillus plantarum* (previously known as *Lactobacillus plantarum*), *Lacticaseibacillus rhamnosus* (previously known as *Lactobacillus rhamnosus*), etc. [38].

### *3.2. Preparation of OS-Prebiotics in Microbial Process*

The substitutes for plant-sourced OSs have been studied for their production in a fermentation process, employing the fungal strain *Aspergillus ibericus*. The synthesized microbial product has shown prebiotic potential in a bacterial community representative of the gut microbiota [39]. Considering the prebiotic nature and their application, the microbial FOSs have also been produced in a coculture fermentation conducted by two microbes, *Aspergillus ibericus* and *Saccharomyces cerevisiae* [40]. The evaluation study for microbial FOSs was performed in a simulated bacterial consortium representing the healthy human gut microbiota. The bioactivity of microbial FOSs was compared with commercial nonmicrobial FOSs, including inulin-type materials *Raftilose* and *Frutalose*. The results showed the consumption of microbially sourced FOS as a substrate by a microbiota consortium; microbial FOS also stimulated the growth of *Bifidobacterium* and *Lactobacillus* as well as a higher yield of total SCFAs. The prebiotic potential of FOS produced by *A. ibericus* demonstrated a promising indication of its usability as a food ingredient with strong prebiotic features [39,40].

The production of multifunctional dietary compound IMOSs has been studied in an enzymatic process. IMOSs are synthesized for commercial usage using transglycosylating α-glucosidase (tAGs) enzyme acting on pretreated starch as the substrate. Enzyme tAGs is obtained from an *Aspergillus* strain to produce IMOS.

The XOSs for use as prebiotics have been synthesized from the xylan extracted from an industrial byproduct, sugarcane bagasse. For the enzymatic saccharification of xylan, a xylosidase-free endoxylanase enzyme was prepared in a fermentation process employing a fungal strain of *Aspergillus flavus* [41]. Similarly to other OS, the mixture of GOSs evaluated as an effective prebiotic in healthy humans has been produced by the enzymatic activity of *Bifidobacterium bifidum* [42].

## **4. The Synbiotics Concept**

The term synbiotics, less popular than probiotics or prebiotics, was first introduced in 1995. The name "synbiotics" was envisioned by Gibson and Roberfroid in 1995 to refer to a combination of a probiotic and a prebiotic [43]. Later, a group of scientists proposed a new definition at a meeting of the International Scientific Association for Probiotics and Prebiotics (ISAPP). The definition and applications of synbiotics have been revised in 2019. Researchers discussed the subject and health benefits of synbiotics and concluded that synbiotics were more than simply a combination recipe of separate sources of probiotics and prebiotics. This revised definition of synbiotics followed the previous revisions to the definitions for probiotics and prebiotics [29,44].

As a result of the ISAPP meeting, a current definition of synbiotics described them as "A mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms, that presents a health benefit on the host". Here, the host microorganisms indicate the microbiota normally resident in the host GIT, which will also include the intake of externally cultured microbes consumed through probiotic supplements. Both groups of microflora could be the target for the substrate (prebiotic) contained in the synbiotic preparations. As the outcome of scientific consideration, the statement was given that synbiotics could not be simply a preparation of combining a source of probiotics and a substrate of prebiotics. With this recommendation, the following two forms of synbiotics can be understood.

### *4.1. Complementary Synbiotics*

The two components of a mixture formulation of independently sourced probiotic cultures and prebiotic materials consumed as the synbiotic preparation work independently to achieve individual health benefits. The reason is that probiotics are live microorganisms that, when consumed in adequate numbers, confer a health benefit [5,13], whereas, the substances used as sources of prebiotics could be food for gut microbiota. For example, practically all preparations of synbiotics available commercially are complementary in type. Both components of a complementary synbiotic preparation must possess the minimum criteria of each component independently [15].

### *4.2. Synergistic Synbiotics*

This form of synbiotic preparation contains selected strains of live microbes to deliver a specific health benefit and a selectively utilized substrate for probiotic strains used in that preparation. Both components in such a mixture work together in synergy; hence, their association provides a resultant benefit to gut health and the well-being of humans and animals. Both elements of synbiotics work as a team (pro- with prebiotic) to contribute to an overall health benefit. An example of a synergistic synbiotic could be a combination of a beneficial lactic acid bacteria, such as *Lactobacillus* species, and its preferred food, lactose (the most abundant natural sugar in the milk), which selectively supports growth of *Lactobacillus* sp. rather than feeding all the resident members of the gut microbiota. Both the probiotic bacteria and its prebiotic substrate work together (not independently) to produce a specifically required benefit [6].

### *4.3. Functions of Synbiotics*

The health benefits of the intake of synbiotics are not only limited to gut health, as they can also affect other areas outside of the gut. The current definition of synbiotics explains their benefits based on the results of orally administered complementary synbiotics studied in human trials. Intervention studies have shown that the consumption of diets containing synbiotics was contributory to the alleviation of irritable bowel syndrome, metabolic syndrome, inflammatory bowel diseases, diarrhea, and skin problems such as atopic dermatitis [19,21,28].

Synbiotics are more than simply a commercial formulation containing freeze-dried cells of probiotic microorganisms mixed with a prebiotic material like inulin. Hence, for a healthy lifestyle, synbiotics can be easily incorporated into diets as delicious recipes that offer the benefits of probiotics and prebiotics in a variety of meals. For example, consuming natural biopot yogurt (made with known probiotic cultures) with added whole-grain cereals/granola, sourdough bread, fermented cheese, pickled fruits, fermented vegetables such as sauerkraut, and fermented probiotic beverage kefir with added pieces of fruit, etc., will benefit nutrition and health [6–11].

## 5. Fermented Foods as Potential Biotics

Food fermentation has been widely studied and reported to offer a variety of foods with nutritional and health benefits. Products produced following a process of slow controlled microbial cultivation and their enzymatic activities on raw substrates derived from plant or animal sources (Table 2) are usually defined as fermented foods [45]. Foods prepared using substrates from a variety of agricultural sources (Table 3) contain fibers from cereals/vegetables/grains/beans as a source of prebiotics and some strains of LAB present as fermenting microorganisms. Fermented tuber, root, and leafy vegetables have improved digestibility compared to when eaten in their raw form. Microorganisms used for fermentation also contribute to increased food safety as a form of preservation for storage by allelopathic activity towards harmful bacteria and fungal contaminants. Foods prepared using microbial cultures contribute desired and appreciated organoleptic features, imparting aromas, textures, and taste [45].

Each specific sensory profile is generated by manipulating variables in the fermentation process, including the development of specific cultures of microorganisms, selected raw material fruits or vegetables, and maintaining the optimum environmental conditions during fermentation. Substrates used in food fermentation as summarized in Tables 2 and 3 usually contain many prebiotic carbohydrates. Inulin-type fructans are present in large amounts in chicory root, Jerusalem artichoke, and cereals [46]. Other carbohydrates, such as soybean OSs, IMOSs, and XOSs [47], arabino-OSs, lactosucrose, resistant starch [48], psyllium, galactomannan, etc., have prebiotic effects [49]. IMOSs are well-established functional food in Asia and are being used as prebiotics in the American and European functional food markets [50].

Fermented foods prepared with grains, beans, lentils, and vegetables are rich in dietary fibers [51], which support the growth of fermenting microorganisms in GIT. Consumption of such materials contributes to a positive effect on the intestinal microbiota. The other benefit is that the fibers from vegetables, fruits, and legumes also sustain the growth of cultures present in fermented food in a synergistic relationship [52,53]. Probiotics, with the assimilation of prebiotics available in food during their sustained residence in the GIT, are able to produce metabolites, which act as potential protective barriers for the gut. The evidence was collected in a study in which inulin-type fructans present in fermented foods induced specific changes in the human gut microbiota [54]. Research has proved that inulin present in plant materials used in fermentation showed a nutraceutical effect on the human gut microbiota through the stimulation of *Bifidobacterium adolescentis* and *Faecalibacterium prausnitzii* [55]. Similarly, prebiotic properties of OSs from tapioca starch, widely used for food fermentation, have been confirmed in vitro experiments [56].

**Table 2.** Fermented foods prepared from substrate derived from plant and animal sources (source of information compiled in the table from references [57–61]).

| Components Used for Fermentation | Fermented Substrates * Sustaining Growth and Activity of Cultures |
|---|---|
| Milk/cheese + Cultures ** | Fermented dairy products |
| Cereals + Cultures | Fermented Cereal Foods |
| Vegetable + Cultures | Fermented Vegetable Products |
| Legumes + Cultures | Fermented Legume Foods |
| Root vegetables + Cultures | Fermented Root Crop Foods |
| Meat + Cultures | Fermented Meat Foods |
| Fish + Cultures | Fermented Fish Products |
| Fruits + Cultures | Fermented undistilled Beverages |

* Contains OSs, Dietary-fibers, metabolites, nutrients. ** Cultures added to start fermentation—Bacteria, yeast.

**Table 3.** Food products *, **, *** prepared from three main groups of plant-derived substrates (Source of information compiled in the table from references [45,62–68].

| Group 1 Substrates Cereals/Grains | Group 1 Fermented Foods | Group 2 Substrates Vegetables | Group 2 Fermented Foods | Group 3 Substrates Beans, Seeds | Group 3 Fermented Foods |
|---|---|---|---|---|---|
| Wheat and Rye flour | *Sourdough* | Cabbage | *Kimchi; Sauerkraut; Pao-cai* | Soybean | *Tempe; Bekang; Chungkokjang* |
| Cereals | *Boza* | Leafy vegetables, Boiled rice | *Pak-gard-dong* | Locust bean | *Dawadawa; Iru* |
| Pearl millet | *Ben-saalga* | Leafy vegetable | *Gundruk* | Soybean | *Douch; Doenjang* |
| Rice and Black Gram | *Dosa; Idli* | Mustard | *Burong mustala; Fu-tsai; Suan-tsai* | Leaves of legume Cassia sp. | *Kawal* |
| Sorghum | *Hussuwa; Kisra;* | Bamboo shoot | *Ekung; Eup; Jiang-sun; Naw-mai-dong; Mesu; Soibum; Soidon* | Soybean | *Meju; Miso; Natto* |
| Maize, Sorghum, Millet | *Busa; Kunu-zaki; Mbege; Ogi* | Cupers | *Cupers (fermented)* | Peanut press cake, Tapioca, soybean curd starter | *Oncom-Hitam (Black Oncom)* |
| Glutinous Rice | *Khamak (Kao-mak)* | Cucumbers | *Jiang-gua; Cucumbers* (fermented); Khalpi; Oiji | Soybean | *Thua nao; Tungrymbai* |
| Rice | *Lao-chao; Puto* | Wild vegetable | *Goyang* | African oil bean (*Pentaclethra macrophylla*) | *Ugba* |
| Maize | *Gowé; Kenkey; Koko; Mawè; Poto poto; Pozol;* | Mustard and Beetroot, eggplant (Aubergine) | *Dha muoi* | Melon-Seeds, castor oil seeds, pumpkin, sesame | *Ogiri/Ogili* |
| Maize, Sorghum | *Pito* | Bamboo shoot tips | *Hirring; Tuaithur* | Soybean | *Yandou* |
| Maize, sorghum, millet, Cassava flour | *Uji* | Olive | (fermented *Olives*) | Peanut press-cake, Tapioca, soybean curd | *Oncom-Merah (Orange Oncom)* |
| Cassava, Maize, Sorghum, Millet | *Togwa* | Red onion | *Hom-dong* | Locust bean | *Soumbala* |
| Wheat–Sheep milk | *Tarhana* | Leaves of *Gynandropis pentaphylla* | *Pak-sian-dong* | Soybean | *Hawaijar* |
| Rice–wheat flour–milk | *Selroti* | Vegetables | *Suan-cai* | Black Gram | *Vari/Bari* |
| Red rice | *Ang-kak* | Mustard leaves, cabbage, salt, coconut | *Sayur asin* | | |
| Glutinous rice, Ragi | *Tape Ketan* | Turnip | *Sunki* | | |

Contain fermented-substrates *, fermenting-cultures **, and metabolites ***. (* Dietary fibers (prebiotics); ** Bacteria/yeast used for fermentation; *** adding organoleptic features—digestibility, aromas, textures, and taste (postbiotics)).

## 6. Difference between Probiotics and Fermented Food

Probiotics and fermented foods cannot be considered the same things, and therefore, one should not be replaced by the other. Both are a valuable addition to a healthy diet.

Commercial probiotics are well-defined supplements, while fermented foods are part of a meal either as an accompaniment or as a complete meal in some traditional food items. According to the technical definition, fermented foods are different than probiotics; a probiotic is a product (food or supplement) that contains known species of beneficial microorganisms that present a health benefit conditional to its prescription when consumed in adequate amounts with a defined number of living cells of probiotic organisms (Table 4). Essentially, probiotics must be characterized and have clinical evidence of health benefits when consumed in adequate quantities [69].

**Table 4.** Main differences between probiotic supplements and fermented foods.

| Fermented Foods | Probiotic Supplements and Food |
|---|---|
| Fermented products are prepared using microorganisms without their characterization; mixed strains mostly involved in natural fermentation process | Products are prepared with characterized specifically selected strains of micro-organisms |
| Some products are fermented with known cultures; however, they could become inactivated during the preparation stages. Several fermented products contain no live or nonviable microbial cells as these are removed from the product | The product at the time of consumption contains viable cells of microbial strains in an adequate number. Commercial probiotic supplements of several types and brands are available on the market |
| Fermentations are purposely performed for the preservation, or long-term storage of seasonal fruits, cereals, and vegetables. In some cases, fermentation is used to prepare products of delicacies, and condiments | Commercial probiotic formulations have been designed with a combination of selected probiotic strains and their complementary prebiotic materials |
| No specific health benefits are clinically proven for fermented food products | Probiotic food or supplements are designed to target specific needs and proven clinical benefits for consumers |

Fermented food is a product (food or beverage) prepared in a process called lactic acid fermentation. The bacteria feed on the sugar and carbohydrate content of the substrate-synthesizing lactic acid as a microbial metabolite. This process was originally used and is still in practice for food preservation, as it saves the seasonal agricultural resource from spoiling in long-term storage. The process contributes nutritional value in some cases by adding beneficial bacteria, vitamins, and enzymes. Not all fermented foods are probiotics, and not all probiotics are fermented [45]. Some fermented foods might contain live microbes at the time of consumption; however, they may not fit the specific definition of probiotics with known organisms or clinically tested health benefits. Some products may not even contain live microbes because operation-factors during postproduction steps and downstream processing may have inactivated live bacteria. Although fermented foods or beverages make a great addition to any diet, it is difficult to know the exact probiotic strains present in these products [45,62–68].

Though it is not always known which specific strains of bacteria are present in different fermented foods, even though we know there are different broad types of bacteria in each type of fermented products. For example, yogurt or fermented milk includes a wide variety of Lactobacilli and Bifidobacteria [70]. In practice, a probiotic containing known microbial strains and clinically proven benefits is recommended; however, this doesn't represent the concept that fermented foods are ineffective. Many products are prepared using known characterized cultures in fermentation but living microbes might not be present in the final product. Though specific strains were employed to conduct the fermentation, they may have been inactivated in the final stage of processing (such as the baking of sour bread) or were separated in some products (fermented barley beer). A fermented food or drink prepared with characterized cultures can only be specified as a probiotic product if microbes are still living cells at the time of consumption.

Even if the fermented product still contains microbes that are actually beneficial to human health, no contamination should have occurred during a longer period of the process of fermentation. There is another aspect to consider what quantity of fermented food or drink would be needed to provide an adequate number (colony forming units—CFU) of probiotic cultures to contribute a health benefit [69]. Many fermented foods are known to be linked with positive effects on the health of consumers. However, these effects must be confirmed in human intervention studies, and clinical trials should be conducted to certify this correlation. Even though there are no such clinical studies conducted to provide evidence for the health benefits of fermented products, in many societies, specialty foods are still prepared in fermentation and consumed for nutrition and as food flavorings as part of family practices [71].

Fermented foods may contain healthy dietary components, but not all can be categorized as probiotics (Table 3). However, some foods may be considered as potential biotics depending on if their fermented substrate is still present and acting as a prebiotic, and on the presence of live LAB at the time of their consumption. Sourdough and pickles are processed in such a way that the microbes do not generally survive; kimchi, kombucha, and other fermented foods may in fact contain live and beneficial microbes, though the amount of product to be consumed to receive an adequate number of probiotic cultures cannot be certain [72].

Researchers have suggested that traditional food should be viewed as a source of synbiotics for developing novel functional products [73]. The science of fermented foods is complicated and complex to explain how these foods can benefit health. It is understood that lactic acid is produced during the fermentation process by lactic acid bacteria; this acid helps in the digestion of other protein-containing diets. The vegetables (leafy, tuber, and root) and animal-sourced substrates used in food fermentations (Table 3) are acted upon by the activities of microorganisms growing for a period of days and weeks and are largely predigested by bacteria and yeast, which then help with the better absorption of their nutrients which otherwise are not effectively digested in their unfermented form in the gut. During fermentation, microbes also biosynthesize certain enzymes which are vital to the digestive process. This is one of the reasons that the consumption of fermented foods is beneficial to gut microbiota.

## 7. Microbiome-Gut-Brain Axis

Diet can also significantly affect our mental health—the food we eat directly influences the type of microflora that flourish in our intestines. A diet rich in fermented foods and good bacteria is key to good brain health. Probiotics, prebiotics, and synbiotics have been reported to be safe options for next-generation therapeutics [74]. The antagonistic activity of the synbiotic containing *Lactobacillus acidophilus* and pineapple residue FOSs has been studied against pathogenic bacteria [75]. The ingested bacteria and their activities have a great impact on human gut microbiota [76]. Prebiotic, probiotic, synbiotic, paraprobiotic, and postbiotic compounds have been studied for their effect on IBD [77]. Mental health and immunity power are inherently linked to gut health. Hence, by improving gut health, many other systems in the body can be positively affected [78,79].

Studies have investigated the potential of probiotics in the support of social anxiety, other mental-health-related conditions, and central GABA receptor expression [80,81]. The effects of synbiotic administration on stress-related parameters have been studied [82]. This biochemistry establishes an essential role for gut microbiota in mental health disorders, from Parkinson's disease to depression. Altered gut microbiota and digestive issues have been associated with autism spectrum disorders (ASD), and it is believed that the gut–brain connection could have a significant role in the development of ASD condition– and the behavior of those affected [82].

The gut–brain axis is discussed as a tool to understand this mechanism. The idea of a gut–brain connection could be correlated with a commonly used phrase: "Gut Feeling", which shows a connection between the gut and the brain. It would be important to understand how the gut microbiome interacts with the brain and how nutritional intervention studies including specific diets supplemented with prebiotics, probiotics, and synbiotics can play a role as a therapeutic means of dealing with mental health disorders [83]. Studies have suggested that microbes resident in the gut release chemical messengers that influence cell responses along the vagus nerve and send communications to the brain via this nerve [84]. The longest and most complex of 10 cranial nerves, the vagus runs from the brain to the abdomen. It is a mixed nerve that contains parasympathetic fibres and acts as a modulator of the brain-gut axis in psychiatric and inflammatory disorders (graphical abstract).

The vagus nerve, being the main component of the parasympathetic nervous system, administers a considerable range of essential functions, including control of mood, immune response, heart rate, and digestion. It determines one of the connections between the brain and the gastrointestinal tract and sends information about the state of the inner organs to the brain via a network of afferent fibers. Therefore, it is understood that the activity of the vagus nerve is influenced by the nutritive components in the GIT [82,84]. The term "psychobiotics" describes a live organism that, when ingested in adequate amounts, produces a health benefit in patients suffering from psychiatric illness [82–85].

## 8. Conclusions

The use of probiotic, prebiotic, and synbiotic supplementation is a nutritionally important area in the research and development of several products. Commercial preparations sold in the health market are formulated using selected strains of probiotic microorganisms, and coatings of capsules or tablets are made of different plant-sourced materials to deliver the effects of prebiotics. Each preparation is designed using different blends of strains and plant materials to offer solutions for specific health-related issues. Products are available under different categories to suit customers' requirements and choices; some examples of supplements are digestive health, gut immunity, gut barrier integrity, probiotic blend; dermatological health probiotic blend; cardiovascular health probiotic blend; micronutrient synthesis probiotic blend, etc. Traditionally prepared fermented foods consumed in different cultures are preparations with potential biotics but cannot be classified as probiotics. Fermented foods are cost-effective, are part of a staple diet in several countries, and are prepared using seasonal raw materials available from local agriculture practices. These foods are delicacies, sources of nutrition, and natural healthy dietary fibers. Therefore, the selection of appropriate probiotic foods or supplements can be made from the choices available to sustain good gut microbiota, which contributes to the prevention of gastrointestinal inflammation. It has been proven in research that formulated psychobiotics act through the microbiota–gut–brain axis, and therefore have been successfully tried for the treatment of certain psychiatric disorders and ASD.

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