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Review

Inclusion of Dietary-Fibers in Nutrition Provides Prebiotic Substrates to Probiotics for the Synthesis of Beneficial Metabolites SCFA to Sustain Gut Health Minimizing Risk of IBS, IBD, CRC

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Abstract

Usually, everyday meals constitute materials and ingredients for food preparation derived from different agricultural sources. Although most customers are aware of the benefits of a balanced diet, they mainly focus on a diet based on the daily requirements of protein, fat, and carbohydrates in their meals. However, the vital aspect of the including dietary fibers in diets is overlooked, which is equally important as is the daily requirement of calories and protein intake for maintaining the muscle mass. Some societies consume a diet heavily based on animal-sourced materials, which is deficient in components of plant-derived beneficial fibers. In such consumers, the smooth functioning of the digestive system and the overall metabolism could be affected in due course of time. As a result, their excretion system would be adversely influenced. The long-term irregularities in the alimentary system might be a cause of the initiation of a problem, particularly in the colon. Foods are natural therapeutics to sustain the healthy functioning of the gastrointestinal tract (GIT), which is also interconnected with other systems impacting the physiology of the human body. Consumers generally select their meals according to their personal choice and taste, and their nutrition is geographically influenced. However, the dietary fibers (prebiotics) sourced from various agricultural materials can be easily included as a constituent of food for the survival and metabolism of probiotic cultures resident in consumers' GIT. This article aims to review information available on plant-derived dietary fibers and their role in the functioning of probiotic microorganisms resident in the gastrointestinal tract, which is important for managing gut health, thereby minimizing inflammatory gut issues.

Keywords
Dietary; fibers; nutrition; food; prebiotics; probiotics, gastrointestinal tract; short-chain fatty acids; IBS; IBD; CRC

1. Introduction

The dietary intakes are typically comprised of food items and nutrients sourced from plants, animals, and sometimes supplements. Generally, the food elements collectively influence the activities of the metabolic system of a person. The biochemistry between the components in nutrition and physiology establishes a balanced state of microbiota in the gastrointestinal tract (GIT). Consequently, the condition of consumers' general well-being is affected. The constituents in a balanced dietary serving of food should include those essential materials that can be effectively assimilated in the digestive system. In response, they can execute a physiological effect on consumers' health. The GIT microbiota, if adversely affected by malnutrition, will impact on the initiation of certain disease/s [1]. A functional diet can include ingredients in the form of dietary compounds and dietary fibers sourced from various agricultural resources. Since the components of regular nutrition might affect the ecology of gut microbiota and its functioning, they consequently affect, positively or negatively, the health condition of consumers [2]. The balanced gut microbiota with the intake of nutraceutical food prepared with prebiotic substrates and specific strains of probiotics can relieve hosts of gastric discomforts and allergic reactions to certain foods and their additives [3].

The objectives of research studies are relevant to this subject, which included understanding the dietary fibers and their influence on the activity of probiotics. Gut microbiota is a collective term for all microorganisms that survive in all vertebrates' GIT. The gut is the main site for the existence of microbiota. Hence, an individual's gut microbiota plays a dynamic role in maintaining health, or initiating and developing disease/s under balanced or disturbed conditions of microbiota, respectively [4, 5]. Various factors may prompt the changes in the organization and functioning of gut-microbiota, for example, more importantly, an imbalanced diet, then environmental conditions, low immunity-related health conditions, or treatment with prescribed antibiotics. Consequently, frequently imbalanced gut-microbiota may result in several gut disorders and chronic diseases [6].

In the last few decades, there has been a rise in research studies on the gut microbiota and the focus of investigations has commenced to include clinical trial studies. That would help to understand the mechanism by which the gut microbiota influence the general health of a person. There are research reports on the role and effectiveness of gut microbiota in the mitigation of several diseases, for instance, gut inflammation, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and colorectal cancer (CRC) [1-7]. Therefore, the routine intake of dietary components including prebiotics and probiotics, has been reported to be influential in sustaining health, as well as with their proven potential as psychobiotics for cognitive health issues treatment through the mechanism of gut-brain signaling [8]. In this article, we aim to discuss the important topic of dietary fibers derived from plants, their types, sources, and their role as prebiotic beneficial for the efficient functioning of probiotic strains resident or supplemented in GIT.

2. Dietary Fibers in Nutrition Act as Prebiotics

2.1 Description of Dietary Fibers

Dietary fibers (DF) are those parts of plant material ingested as the constituent of food based on plant sources. DF include oligosaccharides, cellulose, non-cellulosic polysaccharides such as hemicellulose, pectic substances, gums, mucilages and a non-carbohydrate component lignin. Biologically, DF can be defined as the edible parts of vegetation and their products that are not absorbed in the human small intestine, their digestion being resistant to gastric enzymes. However, DFs are used by gut probiotic microbiota in complete or partial fermentation, depending on their composition [9]. Natural Fibers synthesized by plants are mainly available in most agricultural provisions, such as vegetables, tuber crops, fruits, pulses, beans, legumes, grains and cereals. Consumption of such products provides necessary dietary fibers in the GIT system [10, 11]. Although these fibers contain various types of lignocellulosic structures and polymeric carbohydrates that cannot be digested by enzymes available in the human gut, they cannot be assimilated in the gut. However, these are components of the diet essential for the sustainability of microbiota residing in the gut [10]. The dietary fibers can be classified into insoluble and soluble forms (Table 1) based on their sources.

Table 1 Description of the two types of plant-derived dietary fibers.

Description of Insoluble Fibers*	Description of Soluble Fibers*
Composition: Mostly Lignocellulosic Polymeric e.g. Cellulose, Hemicellulose, Lignin	Composition: Usually Oligo Saccharides e.g. Pectin, Inulin etc.
Sources: Grains, Cereals, Cereal-Husks and Brans, Fibrous vegetables etc.	Sources: Fruits, Vegetables, Pulses, Beans, Lentils etc.
Major Benefits:	Major Benefits:

Contribute to Bulking Effect in the Gut. Act as Cleanser by sweeping effect. Help in regular bowel movements. Required in the diet for the Prevention of Constipation.	Source of Nutrition for Probiotics in Gut. Support the Maintenance of fluidity in GIT by soaking water. Required in the diet for controlling blood sugar and Cholesterol.

*Several agricultural materials are good sources of both types of fibers, which consumers can incorporate into their diets, according to their preferences and availability of items seasonally/geographically (A list of DF-food sources is presented in Table 2).

Most insoluble types of fibers, when consumed as an integral part of a meal, are beneficial for the digestive system as they contribute to faecal-bulking. Their main function is to provide a gut-cleaning effect for a regular bowel movement. Contributing to another vital aspect, most soluble dietary fibers give rise to the formation of viscous gels in the GIT system [10]. The presence of both types of fibers in meals has key impacts on the diversity and population of beneficial gut microbiota. Due to the fact that the physicochemical properties of various dietary fibers differ greatly depending on their source, it is essential to screen novel plant-derived fibers, aiming at the sustainability of gut microbiome and understanding their potential mechanism on gut microbiota-associated human diseases [11].

Microbiota in the host's gut forms a composite community of microbial species that regulate (in the presence of prebiotics) many key biological activities essential for good health [12]. In recent decades, epidemiological evidence demonstrated the increased consumption of industrially-processed ready-meal diets, which are low in dietary fibers but rich in fat and sugar. This dietary change may cause a partial diminution of some beneficial bacterial species, disturbing the balance in the ecology of normal gut microbiota. Consequently, dysbiosis may result in dysfunctions of microbiota, leading to an increase in the development of recurring inflammatory illnesses, for instance, conditions related to cardiovascular, obesity, type 2 diabetes, IBD, CRC, allergies, and autoimmune diseases [13].

2.2 Description of Prebiotics

Technically, prebiotic materials have been identified as non-digestible components in food, conferring benefits linked with the adjustment of the host's probiotic microbiota in the gut [12]. All those materials that provide nutrition to gut microbiota and promote growth for long-term survival in the GIT, are considered prebiotics. The accepted definition given by the International Scientific Association for Probiotics and Prebiotics (ISAPP) for a material to be classified as a prebiotic is "A substrate that is selectively utilized by microorganisms in the gut, conferring a health benefit" [14]. Prebiotics are naturally present in most foods prepared with materials sourced from agricultural products, and hence, they foster the growth of beneficial bacterial species in the gut. Fibers in prebiotic materials provide valuable assistance in the smooth functioning of the digestive system, and in this way, overall health conditions are improved.

Consequently, the standard approach for sustaining the beneficial microbiota in the gut would be the addition of diverse materials sourced from plants in the diet. For instance, fresh seasonal or preserved fruits, legumes, root vegetables, tubers, unrefined flour from whole and multi-grains, nuts and seeds, which are stocked with naturally occurring dietary fibers as sources of prebiotics.

The dietetic quality of a regular meal with a mixture of functional ingredients is as important as the daily requirement of calories. This approach is even more critical for providing nutrition for elderly and sick people undergoing repeated antibiotic therapy, who have weaker gut microbiota [15]. Balanced meals enriched in dietary fiber-prebiotics are also significant for those individuals with a reduced physically active routine and with a lower requirement of calories [16].

2.3 Difference between Dietary Fibers and Prebiotics

The relationship between fibers in food and prebiotics often leads to diverse opinions on differentiating the two terminologies. ISAPP has proposed a practical similarity of prebiotics with fibers [14]. This comparison allows us to identify the measures of both, which influence the propagation of gut microbiota, needed to contribute to the host's health. Fiber is a considerable, nonetheless inadvertently overlooked, component in the routine meals of many people. Even though not all types of fibers can be assimilated by humans, yet, these can be used by the microbial strains inhabiting the gut. As a result, microorganisms growing in the gut collectively constitute a composite community of several species. DF acting as prebiotics, provides nutrition to probiotic strains, which are normally resident in the gut, or ingested by some people through the intake of supplements formulated with probiotics [14].

Soluble dietary fibers (Table 1) are identified as a form of abundant prebiotics available in most items of fleshy fruits, vegetables, and cereals like oats. Most fibers are non-digestible carbohydrates derived from plants, although their inclusion in the diet from assorted food sources is useful in supporting the regularized digestive system. Prebiotics and fibers both stimulate gut health by regulating bowel movements. Published reports have indicated that dietary fibers, through the regulation of gut functioning, could be beneficial in reducing various gut problems such as GIT-health syndromes [7], irritable bowel disease, CRC, allergies, and autoimmune diseases [13] and Crohn's Disease [17].

2.4 Sources of Prebiotics

Most fibers in a diet containing components from different plant sources act as prebiotics and are non-digestible materials Nonetheless, these provide useful fermentable oligo and polysaccharides (Table 2).

Table 2 Sources of Prebiotics Derived from Plants*.

Source-1 Substrates Cereals/Grains	**Source-2 Substrates Vegetables**	**Source-3 Substrates Fruits**	**Source-4 Substrates Beans, Seeds**
Wheat, Barley	Floret Vegetables	Mango fruit peels	Soybean
Rye	Leafy vegetables	Apple peels	Locust bean
Pearl millet	Beetroot	Banana peels	Seeds from Melon, castor oil, pumpkin, sesame
Maize	Mustard-leaves	Banana-Pseudostem	Legumes

Finger Millet	Tubers (Yam, Sweet Potato)	Blue and Black Berries	Oil bean (*Pentaclethra macrophylla*)
Sorghum Millet	Root Vegetables	Capers buds and caper berries	Peanut press cake, Tapioca, soybean curd starter
Brown Rice	Bamboo-shoot tips	-Melons	Soybean curd
Ragi Millet	Tapioca, Cassava	Coconut flesh	Peanut press-cake
Red rice	Shoots of Spring onion	Eggplant (Aubergine)	Locust bean
Rolled Oats	Leaves of *Gynandropis pentaphylla*, (a tropical annual herb used as a vegetable in Africa and Asia)	Table Olives	Peas, Chickpeas
Glutinous Rice	Celery	Cucumbers	Black-Gram lentil

*Information compiled from published reports [9-11, 18-20]

Prebiotics may enhance the vigour and metabolic function of beneficial gut microflora. Prebiotic materials are resistant to low pH conditions and remain unchanged by digestive enzymes in the stomach. They securely move in the passage of GIT and are fermented in the large intestine by the inhabitant microbial species. Such prebiotic materials efficiently modify the balance and activity of beneficial microbiota. The reason is that the gastric enzymes required for the hydrolysis of bonds in the polymer molecules of prebiotics are not present in the digestive system. Consequently, the prebiotic materials make their safe way via the small intestine and reach the colon, where these can be fermented by commonly present probiotic strains of *Lactobacillus*, and *Bifidobacteria* [21].

Prebiotics are classified according to the number of monomer saccharides linked in the composition of dietary fibers, for example, di-saccharides (2 units), oligo-saccharides (>2), and poly-saccharides (n units) [22, 23]. Compared to unfermentable fibers, fermentable fibers have a much more compelling effect, in terms of effective prebiotics, on the metabolism of gut microbiota and the maintenance of consumers' gut health [24]. The widely used standard for the categorization of prebiotic materials is based on oligosaccharides (Table 3).

Table 3 Categorization of Prebiotics derived from plants [22-24].

Category of Prebiotic Material	**Abbreviated form for general use**
Oligo-saccharides	OS
Xylo-oligosaccharides	XOS
Fructo-oligosaccharides	FOS
Isomalto-oligosaccharides	IMO
Transgalacto-oligosaccharides	TOS
Galacto-oligosaccharides	GOS
Mannan-oligosaccharides	MOS
Soybean oligosaccharides	SBOS

2.5 Prebiotic Materials in Commercial Use

Several prebiotic products are marketed for dietary consumption, such as oligosaccharides. These are selected for their ability to surpass the activity of gastric enzymes, nevertheless, they can be selectively used by the microbial population resident in the gut. Various functional prebiotic materials are often used as mixer ingredients in commercial synbiotic formulation and are also available as individual prebiotic products. The most researched materials are FOS, GOS, and Inulin. Prebiotic materials are sold in health shops for use with or without probiotics. Frequently used prebiotic items contain inulin, FOSs, GOSs, IMOSs, XOSs, lactulose, polydextrose, and lactitol etc. [25]. Supplementary poly-saccharides pectin, cellulose, hemicellulose, or starch, are also used in a few commercial prebiotic compounds and in the formulation of synbiotic products [26].

Commercial supplement products are available in designed combinations of prebiotic materials with specific strains of probiotic microbial cultures. These synbiotic preparations, if integrated into the diet of adults in reasonable measures (about 5-20 gm per day depending on the type of constituent-prebiotic material), encourage the growth of essential gut bacteria *Bifidobacteria* and *Lactobacilli* in the GIT [27]. Oligosaccharide XOSs are composed of 2–10 xylose units linked with β-(1,4) bonds, and these are produced from xylan-containing plant material like banana-pseudostem via enzymatic hydrolysis [28]. XOSs have the ability to boost the growth of beneficial gut microflora, hence they have been recognized as one of the critical dietary fibers. Consequently, XOSs have established their use as an effective prebiotic ingredient in synbiotic products on a commercial scale [29].

3. Prebiotics Regulate the Functioning of Probiotics in the Gut

Food preparations with an active population of probiotic cultures combined with prebiotics are characterized as nutraceuticals or functional foods, gaining widespread acceptance in the health food market [3, 16, 30]. Globally, consumers have become interested in the intake of functional diets to sustain their health and improve the quality of their lives [31]. Specific strains of lactic acid bacteria have established their beneficial probiotic health effects like maintenance of intestinal microbiota by the prevention of pathogenic species in the intestine. Reports have suggested live cells of probiotic strains are suitable starter cultures for the production of fermented foods and functional beverages. Besides, their metabolites also have applications as food additives and they can be used by adding directly to foods [32].

Furthermore, various strains of lactic acid bacteria have been extensively studied for their ability to ferment prebiotic oligosaccharides like XOSs. These LAB include species of *acidophilus, casei, crispatus, delbrueckii, johnsonii, sakei, Levilactobacillus brevis* (previously known as *Lactobacillus brevis*), *Limosilactobacillus fermentum* (previously known as *Lactobacillus fermentum*), *Lactococcus lactis, Lactiplantibacillus plantarum* (previously known as *Lactobacillus plantarum*), *Lacticaseibacillus rhamnosus* (previously known as *Lactobacillus rhamnosus*), etc. [33].

Prebiotic materials individually or in mixtures combined with probiotic strains in the formulation of synbiotic products, can balance gut microbiota and sustain gastrointestinal health [34]. Therefore, prebiotics have become part of nutraceuticals because of their role in moderating the gut microbiota via their metabolic activities. However, different prebiotic materials can affect the growth and functions of different strains of probiotics. In a study performed *in-vitro*, the growth medium was prepared with a variety of prebiotic materials, inulin, fructo-oligosaccharides and galacto-oligosaccharides, incorporating them individually to test the growth of two typical probiotic strains *Lacticaseibacillus rhamnosus* and *Bifidobacterium animalis* subsp. *lactis*. The results revealed that all three sources of prebiotics accelerated the growth of both probiotic strains in the fermentation medium grown under both conditions, mono-culture, or co-culture. However, results demonstrated that each prebiotic substrate affected the growth of bacteria at a different rate. It is probably due to the mechanism of *Lactobacillus* strains in the fermentation process producing a specific enzyme galactosidase to utilize the prebiotics added as a carbohydrate substrate [35].

Another example is the use of FOS, which has proven a very effective carbohydrate source acting as a prebiotic for the growth of probiotics. FOS has been reported to increase the growth rate of two strains, Bf-1 and Bf-6, of *Bifidobacterium* [36]. The *bifidobacteria* were able to hydrolyze FOS for their use, for the reason that they produce a viable enzyme fructo-furanosidase, which is required to break down FOS. Studies have proven two enzymes galactosidase and fructo-furanosidase being involved in the hydrolysis of prebiotic materials GOS and FOS, respectively. Enzymes from microbial sources have been reported as useful biocatalysts for the processing of raw natural substrates derived from edible parts of plants and other agricultural residual materials [37-39].

Substrates used as prebiotics are fermented selectively in the gut, allowing actual modifications, both in the gut microbial community and their activity providing benefits to the host [40]. The purpose for the use of prebiotics lies in the understanding that it should increase the proliferation of essential probiotics in the gut and assist in the synthesis of their metabolites, which affect the alleviation of gut health issues and CRC [13]. Prebiotics can employ health-beneficial effects on the colon through their use by specific strains of bacteria synthesizing useful metabolite compounds [41]. For the sustainability of resident microflora, prebiotic materials serve nutrients that effectively steer the growth of probiotic bacterial species [42], which could depend on the molecular structure of prebiotic materials.

Studies have revealed that foods containing inulin (prebiotic) can improve the growth of propionate producers in Bacteroidetes inhabitants. In a study, the traditionally processed meat products were re-formulated for an inulin-rich product, towards the production of functional foods used to reduce polyps in two animal models of colorectal cancer [43]. The inulin component in diet also benefits in reducing the Firmicutes population. It should be considered that higher percentages of Bacteroidetes and Firmicutes are predominantly related to those diseases, which are associated with gut inflammation [44, 45]. Some of the essential prebiotics that can be easily taken by the GIT microbiota are referred to as non-digestible oligosaccharides. Such prebiotics have unique glycosidic bonds of the anomeric carbon from monosaccharide units, and these bonds cannot be hydrolyzed by the gastric enzymes of humans [46]. The commonly used non-digestible oligosaccharides-prebiotics are fructo-oligosaccharides, galacto-oligosaccharides, and xylo-oligosaccharides, which can influence the composition of microbiota to ease the severity of colorectal cancer [47]. The impacts exerted by galacto-oligosaccharides have been studied on the ecology of gut microbiota of adult hosts taking antibiotic medication, where prebiotic was found supporting an increased number of *Bifidobacterium* spp. and *Lactobacillus* spp resident in the intestine [48].

A team of researchers studied the genetic expression of enzymes implicated in the intake of xylo-oligosaccharides by *Lactobacillus* spp [49]. A randomised controlled study in Kenyan infants reported the prebiotic galacto-oligosaccharides relieving the antagonistic effects of fortification with iron on the gut microbiome [50]. The influence of galacto-oligosaccharide mixture has been studied on immunity parameters and metabolomics in the gut microbiota of elderly persons [51]. Prebiotic impacts caused by xylo-oligosaccharides have also been reported to improve the microbiota balance in human studies by Lin et al [52].

4. Metabolites Produced from Prebiotics' Fermentation in GIT

Prebiotics being indigestible by human gastric enzymes usually move unchanged in the gastrointestinal tract and are available to gut bacteria as suitable substrates for fermentation. As a result, the main production of short-chain fatty acids (SCFAs), like acetic, propionic, and butyric acid, occurs [53]. These SCFAs perform important functions in maintaining gut microbial ecology and influence their metabolic system. Moreover, lactic acid produced by LAB can aid in neutralizing the alkaline pH in the colon and thus establishes a more neutral environment for beneficial bacteria to grow. *Bifidobacterium* and *Lactobacillus* inhibit pathogens under favorable intestinal pH due to the synthesis of their metabolites [54]. This has been reported that SCFAs influence the drop in alkaline pH of the gut, inhibiting the growth of species of microbial pathogens [54, 55]. The SCFAs are absorbed by epithelial cells in GIT for use as a source of energy and as metabolic regulators. This activity improves the growth of villi, crypt development, tight junctions, and mucin production [55]. The action of butyrate influences the formation of the intestinal epithelium [56]. SCFAs are also important for promoting salt and water absorption in the colon by the process of nutrient control and ion transporters, which can also help prevent diarrhoea triggered by a condition of short-bowel syndrome (SBS) [57]. These factors result in effective remedial actions for conditions of irritable bowel syndrome and inflammatory bowel disease. These findings indicate that the release of SCFAs by probiotics with the use of prebiotics may be a significant mechanism for sustaining gut health.

The definite contribution of prebiotics to human health is coupled with their capacity to adjust the viability of probiotics, and subsequently with the regulation of secretion of metabolites, extracellular polysaccharides, and SCFA in the gut. With the regular intake of a diet comprising functional food elements (synbiotic preparations), prebiotic materials and probiotic cultures are supplemented in the gut. Their presence in the gut encourages the state of a microbial balance in the host's GIT-microbiota. Studies have recognized the beneficial properties of probiotics actively sustaining in the gut, supporting the deterrence of intestinal disorders, defense against cancer, stimulation of immune function, and reducing symptoms of irritable bowel syndrome and cholesterol level, and contributing to several therapeutic benefits [16]. Some of these impacts, as discussed above, are facilitated by the activities of SCFAs, which are produced by probiotics with the fermentation of prebiotic substrates in the gut.

Probiotic strains actively residing in the gut implement respective health effects by various mechanisms. Principally for their endurance in GIT, probiotics strive for nutrients available in the form of prebiotic materials, and in this approach, they obstruct the growth of harmful microorganisms by hindering their adherence to gut epithelial cells. The lactic acid bacteria produce antagonistic complexes like bacteriocins and organic acids that impose an inhibition stimulus on the pathogen's development and deter the colonization of any opportunistic organisms [58]. Other activities applied by probiotics are regulating the immune system by affecting immune-globulin production, increasing the cytotoxic property of natural killer cells, and the adjustment of cytokine secretion. The beneficial metabolite exopolysaccharide (EPS) has been studied for effectively alleviating gastritis in *Helicobacter pylori*-infected mice by a mechanism of down-regulating mRNA expression levels of pro-inflammatory cytokines IL-6, IL-8, IL-1β and TNF-α, and supporting the up-regulation of mRNA expression of inflammatory cytokine IL-10 in gut cells. EPS was also found to be effective in positively regulating the ecology of GIT microflora [59-61]. Consequently, in consideration of several benefits as discussed above, the use of probiotics along with suitable prebiotic materials in functional foods has created a wide-reaching enterprise in the food industry.

5. Dietary Intervention Studies

Studies have incorporated the interventions of prebiotics with probiotics to achieve complex advantages in diverse systemic illnesses related to inflammatory, gastrointestinal, cardiovascular, and neurological [60]. Helpful probiotics resident in the host's GIT system would selectively use certain prebiotics materials for developing and sustaining their growth in the gut [31]. Thus, the inclusion of selected prebiotics in the intervention study is supposed to enhance the number of favorable gut bacteria and exclude other infective bacteria. Furthermore, the integrity of the gut barrier and properties related to immunomodulation develop in the presence of SCFAs, which are released through the fermentation of oligosaccharides [30]. The intake of diets containing DF and grains has been correlated with lowered risks of CRC, proposing a shielding impact of these prebiotic molecules [61].

The topic of the quality of consumed carbohydrates and human health has been studied in some animal models and also *in-vitro* studies, and has been reviewed in systematic and meta-analyses [62, 63]. Prebiotics, as nutrients for probiotics, can help retain intestinal microbial homeostasis and mitigate the condition of dysbiosis, which could be beneficial in preventing gut inflammation and CRC. These nutrients can deter the onset of dysbiosis by reassuring the growth of beneficial bacteria needed for the production of short-chain fatty acids, the maintenance of the barrier of the intestinal epithelium, the development of anti-inflammatory immunity, and pro-apoptotic mechanisms [64]. The beneficial bacteria sustaining in gut microbiota with the support of prebiotics, produce metabolites effective as antimicrobials for pathogens.

Probiotics degrade polymer prebiotics into oligo and monosaccharides which connect with the lectin receptor on the surface of epithelial cells, this binding mechanism blocks the settlement of opportunistic disease-causing strains at the receptor site [55]. Furthermore, some species of gut residents stimulate the immune system by signaling the dendritic cells [54, 55]. The consumption of prebiotics-rich diets influences gut microflora composition and their metabolic activity. The chemical structure of prebiotics controls their physiological effect on gut microbiota that can use these prebiotics as an energy source in the intestine [54]. Hence, the properties of prebiotics based on their structural configuration are associated with the fluctuations in the gut-microbiota and can cause improvements in hosts' metabolism linked to several health disorders like obesity, inflammations, glucose homeostasis syndrome, and abnormal plasma lipid levels [65].

Furthermore, the use of prebiotics indirectly causes a decline in triglyceride levels in the serum and thus they might affect the absorption of minerals in the large intestine, protecting against inflammatory bowel syndrome by the production of butyrate [66]. Therefore, prebiotics can be considered as an important functional food for the colon, which can help in the improvement of general health through the microbiota residing in the colon [67]. The sustainability of well-known probiotic strains depends on selecting the most profitable combination of prebiotic substrates.

Therefore, ingesting correctly chosen probiotics and DF as natural sources of prebiotics may be useful in developing positive effects, both for individual probiotics and several strains working synergistically [68]. Although, the consumption of most prebiotic materials is without serious risk to health; however, the consumption of their excess quantities might induce unwanted effects – the commonly experienced effects are bloating and gas production causing abdominal pain with flatulence [56].

Although the prebiotic materials are available in the form of a variety of plant-DF (Table 1, Table 2 and Table 3), however, for the intervention studies, the most frequently used DF are inulin, fructo-oligosaccharides, and galacto-oligosaccharides [54, 69]. Their widely accepted use as prebiotics has also been supported by results from *in vitro* studies [70, 71]. FOS and GOS were tested *in vitro* for the requirements of the current criteria for effective prebiotics [72]. In addition, reports of studies have revealed that a minimum dose of 4 g a day of FOS or higher up to 8 g would be required to improve significantly the population of *Bifidobacteria* in the human gut [73]. The mixing of a few prebiotic materials in optimal doses may increase the probiotic population and stimulate their action [67]. Besides, the use of prebiotic sources as an unaccompanied material or mixed with probiotic strains in synbiotic preparations can improve gut health by preventing the onset of IBD, IBS, and CRC by selectively stimulating the metabolism of health-promoting bacteria (Figure 1).

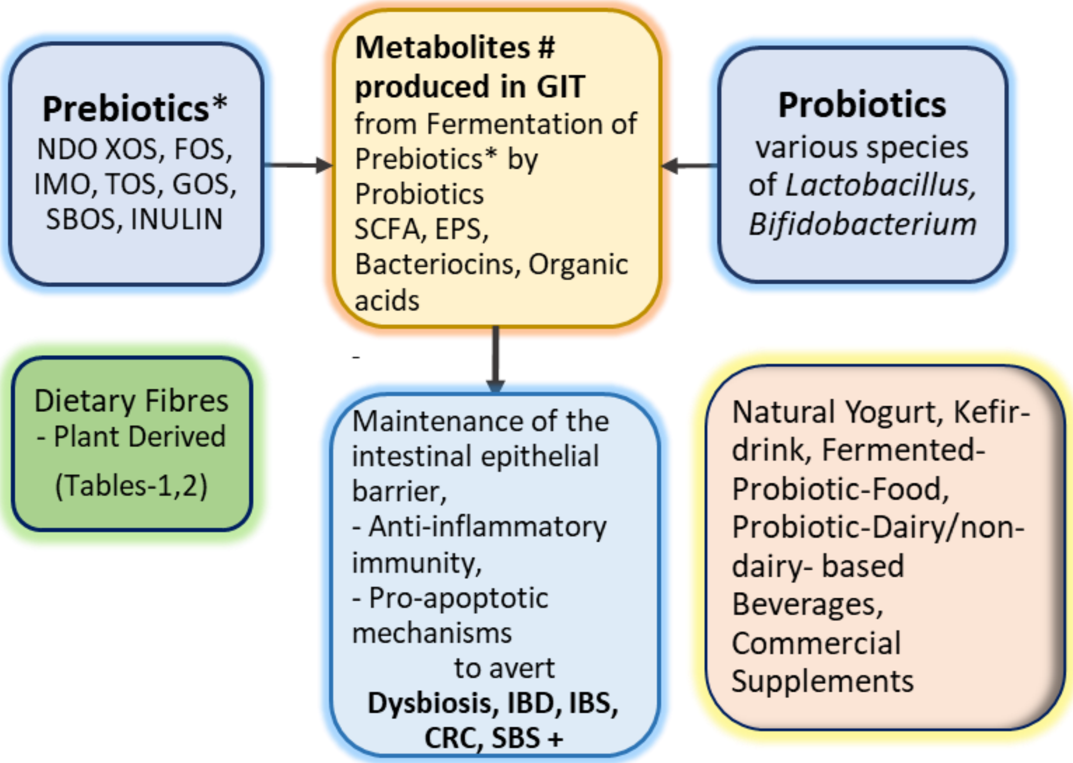

Figure 1 Dietary interventions using Prebiotics, Probiotics or a mixture of both (Synbiotics) to avert IBD, IBS, CRC and SBS [18, 52, 56, 58, 74]. ***NDO** (Nondigestible oligosaccharides), XOS (Xylo-oligosaccharides), FOS (Fructo-oligosaccharides), IMO (Isomalto-oligosaccharides), TOS (Transgalacto-oligosaccharides), GOS (Galacto-oligosaccharides), SBOS (Soybean oligosaccharides). **#** SCFA (Short-chain fatty acids), EPS (Extracellular polysaccharides). **+** IBD (Inflammatory bowel disease), IBS (Irritable bowel syndrome), CRC (Colorectal cancer), SBS (Short-bowel syndrome).

6. Prebiotics Studied for Their Use in Functional Food

The awareness of functional food for well-being, which is essentially correlated to the diet consumed, has been rising [74]. Thus, consumers are more interested in buying food products containing required nutritional components with health promotion properties [75]. This has regulated an approximately 10% increase in the functional food business, opening the market for new nutraceutical products, such as food with prebiotic-DF and probiotic components [76]. This has been again stressed in studies that prebiotics are dietary ingredients needed to improve the establishment of gut microbiota, which in turn adjusts the state of health by hindering the development of diet-related disorders [77].

Furthermore, prebiotics sourced from different plant materials (Tables 1-3) may amend and enhance the physicochemical and sensorial quality of food. Hence, these natural substrates, placed in four different groups in Table 2 are potential ingredients for developing new food products [78]. In addition, to supply cost-effective and consumer-friendly options, the food industry can incorporate prebiotics sourced from various seasonal and regional agricultural materials in the formulation of economically attractive products [79, 80]. The standard strategy has been the direct combination of the prebiotics into food products by simple fortification [75]. FOS are oligomers of fructose and are synthesized enzymatically through the transfructosylation of sucrose by the activity of the enzyme fructosyltransferase [81]. The capability of common probiotics *Lactobacilli* and *Bifidobacteria* to ferment particular prebiotic substrates containing oligosaccharides and polysaccharides can also be significant and explored for developing synbiotic functional foods [82].

Therefore, it is worth evaluating the prebiotic potential of different foods and the ingredients to prepare foods. The prebiotic index (PI) value is used as an evaluation to decide on the selection of prebiotic-rich foods. The value of PI is considered by comparing the increase in the probiotic strains' growth (an increase in the cell populations of bacteria is a constructive effect), with the growth in the presence of a less desirable ingredient (an increase in bacterial population is a negative effect) [67, 83, 84]. Ghoddusi et al. [70] testified that inulin, FOS, polydextrose, and IMO, individually or in a blend, influenced on the value of PI. Since the materials used as prebiotics have different functionalities due to their chemical structures affecting the rate of their fermentation by GIT bacteria, this factor determines an influence on PI. Figueroa-Gonzalez et al. [67] studied the proficiency of several strains of probiotics (including *L. casei* Shirota, *L. casei* 1, *L. casei* 2, *L. rhamnosus* GG, and *L. rhamnosus*) to ferment different prebiotics like inulin, GOS, and lactulose. According to the study outcomes, all assessed probiotics could grow in a medium added with the selected prebiotic. Nevertheless, their growth occurred differently at each incubation time. Remarkably, all probiotics, except *L. casei* Shirota, had higher growth in inulin and GOS than the control (lactulose).

Buddington et al. [85] reported that inulin and FOS provided adequate protection from pathogens *Salmonella typhimurium* and *Listeria monocytogenes* in mice with unusual crypt foci in their colon compared with *in vitro* samples of the cell line. Additionally, probiotic *Bifidobacterium*, and prebiotic TGO, could be applied in a murine model for the anti-infective activity against *Salmonella* [86]. In a study conducted observing the efficacy of prebiotics in the mixture, GOS proved to have an advanced performance over other prebiotic materials [82]. In a different study, the measure of SCFA synthesis was taken as a reference point for the effectiveness of prebiotics, where the level of SCFAs was calculated as a sum of all acids including acetic, butyric, and propionic.

The response surface analysis indicated that the synthesis of SCFAs in the fermentation of FOS was directly related to the use of the prebiotic substrate [87].

7. Conclusion

As discussed in previous sections, different prebiotic-DF materials can accelerate the development of strains of gut probiotics, hence they should be selected based on their composition which could favour their enhanced functionality (Figure 1). Among the four most effective prebiotics (FOS, inulin, GOS, and mannan oligosaccharide) inulin has been routinely used as a prebiotic component in the food industry. Nevertheless, to get a pure preparation of this long-chain polysaccharide, the process of its extraction from plant sources like chicory root, artichoke, and asparagus is costly. Alternatively, FOS and GOS are short-chain OS that can be obtained from plant sources like sugar cane. Yet, different sources may have marginally different properties for prebiotic specifications. Subsequently, the screening of a mixed prebiotic ratio might result in a potentially useful ingredient for the production of cost-effective functional food. Suitable ratios of mixed prebiotics should be used in synbiotic food supplements to improve probiotic stimulation and establish a balance in the gut microbiota, considering the results of intervention studies conducted with human volunteers.

8. Future Prospectives

For the research and development of prebiotic sources for their formulation in functional foods, the selection of materials should be based on their fermentability by gut bacteria. For example, prebiotics FOS, GOS, and XOS are rapidly fermented by beneficial strains of probiotics, succeeding in a higher score of the prebiotic index. Moreover, the number of sugar units in OS-prebiotic molecules i.e. the degree of polymerization (DP) is an important factor in their fermentation and PI score. Preferred prebiotics are FOS, GOS and XOS with a lower DP of 2-10, for the reason these are easily fermented and have a higher prebiotic index score, compared to inulin with a higher DP [88-90]. It should also be considered that starch and cellulose are types of agriculturally sourced substrates that need longer fermentation time, hence not preferred as efficient prebiotics, however, with the innovative process-technology they could have a different utility to synthesize other value-added products [90-96]. Although the research on a variety of bioactive materials derived from plant-bioresources, and probiotic strains is ongoing for their quality, function, and use in the biosynthesis of therapeutic compounds [97-100], and in the fortification of bioactive molecules in food [101, 102]; nevertheless, the prebiotic effect of OS also needs to be examined on the activity of those probiotic strains, which have been isolated from regional fermented food products. The emerging trend is that novel functional food to cater to consumers with different diet preferences can be prepared with combinations of prebiotic-DF substrates in the food-fermentation process, employing characterized strains of probiotics. Such products can be specifically used as nutraceuticals for supplementing gut microbiota in hosts who suffer from gut dysbiosis, food discomforts, and are allergic to certain foods or their additive ingredients.

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References

1. Million M, Diallo A, Raoult D. Gut microbiota and malnutrition. Microb Pathog. 2017; 106: 127-138.
2. Boulangé CL, Neves AL, Chilloux J, Nicholson JK, Dumas ME. Impact of the gut microbiota on inflammation, obesity, and metabolic disease. Genome Med. 2016; 8: 42.
3. Dahiya D, Nigam PS. Nutraceuticals prepared with specific strains of probiotics for supplementing gut microbiota in hosts allergic to certain foods or their additives. Nutrients. 2023; 15: 2979.
4. Schneiderhan J, Master-Hunter T, Locke A. Targeting gut flora to treat and prevent disease. J Fam Pract. 2016; 65: 33-39.
5. Webb CR, Koboziev I, Furr KL, Grisham MB. Protective and pro-inflammatory roles of intestinal bacteria. Pathophysiology. 2016; 23: 67-80.
6. Quigley EM. Gut bacteria in health and disease. Gastroenterol Hepatol. 2013; 9: 560-569.
7. Dahiya D, Nigam PS. The gut microbiota influenced by the intake of probiotics and functional foods with prebiotics can sustain wellness and alleviate certain ailments like gut-inflammation and colon-cancer. Microorganisms. 2022; 10: 665.
8. Dahiya D, Nigam PS. Clinical potential of microbial strains, used in fermentation for probiotic food, beverages and in synbiotic supplements, as psychobiotics for cognitive treatment through gut–brain signaling. Microorganisms. 2022; 10: 1687.
9. Slavin J. Fiber and prebiotics: Mechanisms and health benefits. Nutrients. 2013; 5: 1417-1435.
10. Zahid HF, Ranadheera CS, Fang Z, Ajlouni S. Utilization of mango, apple and banana fruit peels as prebiotics and functional ingredients. Agriculture. 2021; 11: 584.
11. Pathania S, Kaur N. Utilization of fruits and vegetable by-products for isolation of dietary fibres and its potential application as functional ingredients. Bioact Carbohydr Diet Fibre. 2022; 27: 100295.
12. Pineiro M, Asp NG, Reid G, Macfarlane S, Morelli L, Brunser O, et al. FAO technical meeting on prebiotics. J Clin Gastroenterol. 2008; 42: S156-S159.
13. Dahiya D, Nigam PS. Antibiotic-therapy-induced gut dysbiosis affecting gut microbiota—brain axis and cognition: Restoration by intake of probiotics and synbiotics. Int J Mol Sci. 2023; 24: 3074.
14. Gibson GR, Hutkins R, Sanders ME, Prescott SL, Reimer RA, Salminen SJ, et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nat Rev Gastroenterol Hepatol. 2017; 14: 491-502.
15. Wargo JA. Modulating gut microbes. Science. 2020; 369: 1302-1303.

16. Dahiya D, Nigam PS. Therapeutic and dietary support for gastrointestinal tract using kefir as a nutraceutical beverage: Dairy-milk-based or plant-sourced kefir probiotic products for vegan and lactose-intolerant populations. Fermentation. 2023; 9: 388.
17. Lichtenstein L, Avni-Biron I, Ben-Bassat O. Probiotics and prebiotics in Crohn's disease therapies. Best Pract Res Clin Gastroenterol. 2016; 30: 81-88.
18. Dahiya D, Nigam PS. Use of characterized microorganisms in fermentation of non-dairy-based substrates to produce probiotic food for gut-health and nutrition. Fermentation. 2022; 9: 1.
19. Brummer Y, Kaviani M, Tosh SM. Structural and functional characteristics of dietary fibre in beans, lentils, peas and chickpeas. Food Res Int. 2015; 67: 117-125.
20. Zaman SA, Sarbini SR. The potential of resistant starch as a prebiotic. Crit Rev Biotechnol. 2016; 36: 578-584.
21. Roberfroid M. Prebiotics: The concept revisited. J Nutr. 2007; 137: 830S-837S.
22. Annison G, Illman RJ, Topping DL. Acetylated, propionylated or butyrylated starches raise large bowel short-chain fatty acids preferentially when fed to rats. J Nutr. 2003; 133: 3523-3528.
23. Patterson JA, Burkholder KM. Application of prebiotics and probiotics in poultry production. Poult Sci. 2003; 82: 627-631.
24. Holscher HD. Dietary fiber and prebiotics and the gastrointestinal microbiota. Gut Microbes. 2017; 8: 172-184.
25. Guarino MP, Altomare A, Emerenziani S, Di Rosa C, Ribolsi M, Balestrieri P, et al. Mechanisms of action of prebiotics and their effects on gastro-intestinal disorders in adults. Nutrients. 2020; 12: 1037.
26. Baurhoo B, Letellier A, Zhao X, Ruiz-Feria CA. Cecal populations of lactobacilli and bifidobacteria and Escherichia coli populations after in vivo Escherichia coli challenge in birds fed diets with purified lignin or mannanoligosaccharides. Poult Sci. 2007; 86: 2509-2516.
27. Gibson GR, Probert HM, Van Loo J, Rastall RA, Roberfroid MB. Dietary modulation of the human colonic microbiota: Updating the concept of prebiotics. Nutr Res Rev. 2004; 17: 259-275.
28. de Freitas C, Terrone CC, Masarin F, Carmona EC, Brienzo M. In vitro study of the effect of xylooligosaccharides obtained from banana pseudostem xylan by enzymatic hydrolysis on probiotic bacteria. Biocatal Agric Biotechnol. 2021; 33: 101973.
29. Rashid R, Sohail M. Xylanolytic bacillus species for xylooligosaccharides production: A critical review. Bioresour Bioprocess. 2021; 8: 16.
30. Dahiya D, Nigam PS. Nutraceutical combinational therapy for diarrhoea control with probiotic beverages from fermented fruits, vegetables and cereals to regain lost hydration, nutrition and gut microbiota. Microorganisms. 2023; 11: 2190.
31. Martín R, Langella P. Emerging health concepts in the probiotics field: Streamlining the definitions. Front Microbiol. 2019; 10: 1047.
32. Elezi O, Kourkoutas Y, Koutinas AA, Kanellaki M, Bezirtzoglou E, Barnett YA, et al. Food additive lactic acid production by immobilized cells of Lactobacillus brevis on delignified cellulosic material. J Agric Food Chem. 2003; 51: 5285-5289.
33. Kanpiengjai A, Nuntikaew P, Wongsanittayarak J, Leangnim N, Khanongnuch C. Isolation of efficient xylooligosaccharides-fermenting probiotic lactic acid bacteria from ethnic pickled bamboo shoot products. Biology. 2022; 11: 638.
34. Tewari S, Dubey KK, Singhal RS. Evaluation and application of prebiotic and probiotic ingredients for development of ready to drink tea beverage. J Food Sci Technol. 2018; 55: 1525-1534.

35. Scott KP, Grimaldi R, Cunningham M, Sarbini SR, Wijeyesekera A, Tang ML, et al. Developments in understanding and applying prebiotics in research and practice—An ISAPP conference paper. J Appl Microbiol. 2020; 128: 934-949.
36. Shin HS, Lee JH, Pestka JJ, Ustunol Z. Growth and viability of commercial Bifidobacterium spp. in skim milk containing oligosaccharides and inulin. J Food Sci. 2000; 65: 884-887.
37. Sunnotel O, Nigam P. Pectinolytic activity of bacteria isolated from soil and two fungal strains during submerged fermentation. World J Microbiol Biotechnol. 2002; 18: 835-839.
38. Nigam PS. Microbial enzymes with special characteristics for biotechnological applications. Biomolecules. 2013;3: 597-611.
39. Dahiya D, Nigam P. Sustainable biosynthesis of esterase enzymes of desired characteristics of catalysis for pharmaceutical and food industry employing specific strains of microorganisms. Sustainability. 2022; 14: 8673.
40. Ambalam P, Raman M, Purama RK, Doble M. Probiotics, prebiotics and colorectal cancer prevention. Best Pract Res Clin Gastroenterol. 2016; 30: 119-131.
41. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, et al. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol. 2014; 11: 506-514.
42. Bach Knudsen KE. Microbial degradation of whole-grain complex carbohydrates and impact on short-chain fatty acids and health. Adv Nutr. 2015; 6: 206-213.
43. Fernández J, Ledesma E, Monte J, Millán E, Costa P, de la Fuente VG, et al. Traditional processed meat products re-designed towards inulin-rich functional foods reduce polyps in two colorectal cancer animal models. Sci Rep. 2019; 9: 14783.
44. Ley RE, Bäckhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. Proc Natl Acad Sci USA. 2005; 102: 11070-11075.
45. Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Human gut microbes associated with obesity. Nature. 2006; 444: 1022-1023.
46. Mano MC, Neri-Numa IA, da Silva JB, Paulino BN, Pessoa MG, Pastore GM. Oligosaccharide biotechnology: An approach of prebiotic revolution on the industry. Appl Microbiol Biotechnol. 2018; 102: 17-37.
47. Bruno-Barcena JM, Azcarate-Peril MA. Galacto-oligosaccharides and colorectal cancer: Feeding our intestinal probiome. J Funct Foods. 2015; 12: 92-108.
48. Ladirat SE, Schoterman MH, Rahaoui H, Mars M, Schuren FH, Gruppen H, et al. Exploring the effects of galacto-oligosaccharides on the gut microbiota of healthy adults receiving amoxicillin treatment. Br J Nutr. 2014; 112: 536-546.
49. Maria A, Margarita T, Illia I, Iskra I. Gene expression of enzymes involved in utilization of xylooligosaccharides by Lactobacillus strains. Biotechnol Biotechnol Equip. 2014; 28: 941-948.
50. Paganini D, Uyoga MA, Kortman GA, Cercamondi CI, Moretti D, Barth-Jaeggi T, et al. Prebiotic galacto-oligosaccharides mitigate the adverse effects of iron fortification on the gut microbiome: A randomised controlled study in Kenyan infants. Gut. 2017; 66: 1956-1967.
51. Vulevic J, Juric A, Walton GE, Claus SP, Tzortzis G, Toward RE, et al. Influence of galacto-oligosaccharide mixture (B-GOS) on gut microbiota, immune parameters and metabonomics in elderly persons. Br J Nutr. 2015; 114: 586-595.

52. Lin SH, Chou LM, Chien YW, Chang JS, Lin CI. Prebiotic effects of xylooligosaccharides on the improvement of microbiota balance in human subjects. Gastroenterol Res Pract. 2016; 2016: 5789232.
53. EFSA Panel on Dietetic Products, Nutrition, and Allergies (NDA). Scientific opinion on dietary reference values for carbohydrates and dietary fibre. EFSA J. 2010; 8: 1462.
54. Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. Nat Rev Microbiol. 2021; 19: 55-71.
55. Pourabedin M, Zhao X. Prebiotics and gut microbiota in chickens. FEMS Microbiol Lett. 2015; 362: fnv122.
56. Davani-Davari D, Negahdaripour M, Karimzadeh I, Seifan M, Mohkam M, Masoumi SJ, et al. Prebiotics: Definition, types, sources, mechanisms, and clinical applications. Foods. 2019; 8: 92.
57. van der Hee B, Wells JM. Microbial regulation of host physiology by short-chain fatty acids. Trends Microbiol. 2021; 29: 700-712.
58. Dahiya D, Nigam PS. Biotherapy using probiotics as therapeutic agents to restore the gut microbiota to relieve gastrointestinal tract inflammation, IBD, IBS and prevent induction of cancer. Int J Mol Sci. 2023; 24: 5748.
59. Kotani A, Miyaguchi Y, Kohama M, Ohtsuka T, Shiratori T, Kusu F. Determination of short-chain fatty acids in rat and human feces by high-performance liquid chromatography with electrochemical detection. Anal Sci. 2009; 25: 1007-1011.
60. Oniszczuk A, Oniszczuk T, Gancarz M, Szymańska J. Role of gut microbiota, probiotics and prebiotics in the cardiovascular diseases. Molecules. 2021; 26: 1172.
61. Aune D, Chan DS, Lau R, Vieira R, Greenwood DC, Kampman E, et al. Dietary fibre, whole grains, and risk of colorectal cancer: Systematic review and dose-response meta-analysis of prospective studies. BMJ. 2011; 343: d6617.
62. Reynolds A, Mann J, Cummings J, Winter N, Mete E, Te Morenga L. Carbohydrate quality and human health: A series of systematic reviews and meta-analyses. Lancet. 2019; 393: 434-445.
63. Oliero M, Calvé A, Fragoso G, Cuisiniere T, Hajjar R, Dobrindt U, et al. Oligosaccharides increase the genotoxic effect of colibactin produced by pks+ Escherichia coli strains. BMC Cancer. 2021; 21: 172.
64. Mahdavi M, Laforest-Lapointe I, Massé E. Preventing colorectal cancer through prebiotics. Microorganisms. 2021; 9: 1325.
65. Scavuzzi BM, Henrique FC, Miglioranza LH, Simão AN, Dichi I. Impact of prebiotics, probiotics and synbiotics on components of the metabolic syndrome. Ann Nutr Disord Ther. 2014; 1: 1009.
66. Mandalari G, Nueno Palop C, Tuohy K, Gibson GR, Bennett RN, Waldron KW, et al. In vitro evaluation of the prebiotic activity of a pectic oligosaccharide-rich extract enzymatically derived from bergamot peel. Appl Microbiol Biotechnol. 2007; 73: 1173-1179.
67. Figueroa-Gonzalez I, Rodriguez-Serrano G, Gomez-Ruiz L, Garcia-Garibay M, Cruz-Guerrero A. Prebiotic effect of commercial saccharides on probiotic bacteria isolated from commercial products. Food Sci Technol. 2019; 39: 747-753.
68. Martinez RC, Bedani R, Saad SM. Scientific evidence for health effects attributed to the consumption of probiotics and prebiotics: An update for current perspectives and future challenges. Br J Nutr. 2015; 114: 1993-2015.

69. Awad WA, Ghareeb K, Abdel-Raheem S, Böhm J. Effects of dietary inclusion of probiotic and synbiotic on growth performance, organ weights, and intestinal histomorphology of broiler chickens. Poult Sci. 2009; 88: 49-56.
70. Ghoddusi HB, Grandison MA, Grandison AS, Tuohy KM. In vitro study on gas generation and prebiotic effects of some carbohydrates and their mixtures. Anaerobe. 2007; 13: 193-199.
71. Manderson K, Pinart M, Tuohy KM, Grace WE, Hotchkiss AT, Widmer W, et al. In vitro determination of prebiotic properties of oligosaccharides derived from an orange juice manufacturing by-product stream. Appl Environ Microbiol. 2005; 71: 8383-8389.
72. Wichienchot S, Prasertsan P, Hongpattarakere T, Gibson GR, Rastall RA. In vitro fermentation of mixed linkage gluco-oligosaccharides produced by Gluconobacter oxydans NCIMB 4943 by the human colonic microflora. Curr Issues Intest Microbiol. 2006; 7: 7-12.
73. Manning TS, Gibson GR. Microbial-gut interactions in health and disease. Prebiotics. Best Pract Res Clin Gastroenterol. 2004; 18: 287-298.
74. Dahiya D, Nigam PS. Probiotics, prebiotics, synbiotics, and fermented foods as potential biotics in nutrition improving health via microbiome-gut-brain axis. Fermentation. 2022; 8: 303.
75. Gonçalves DA, Teixeira JA, Nobre C. In situ enzymatic synthesis of prebiotics to improve food functionality. In: Value-addition in food products and processing through enzyme technology. London: Academic Press; 2022. pp. 253-267.
76. Birch CS, Bonwick GA. Ensuring the future of functional foods. Int J Food Scie Technol. 2019; 54: 1467-1485.
77. Florowska A, Krygier K, Florowski T, Dłużewska E. Prebiotics as functional food ingredients preventing diet-related diseases. Food Funct. 2016; 7: 2147-2155.
78. Nobre C, Cerqueira MÂ, Rodrigues LR, Vicente AA, Teixeira JA. Production and extraction of polysaccharides and oligosaccharides and their use as new food additives. In: Industrial biorefineries & white biotechnology. Amsterdam: Elsevier; 2015. pp. 653-679.
79. de Paulo Farias D, de Araújo FF, Neri-Numa IA, Pastore GM. Prebiotics: Trends in food, health and technological applications. Trends Food Sci Technol. 2019; 93: 23-35.
80. Varzakas T, Kandylis P, Dimitrellou D, Salamoura C, Zakynthinos G, Proestos C. Innovative and fortified food: Probiotics, prebiotics, GMOs, and superfood. In: Preparation and processing of religious and cultural foods. Cambridge, MA: Woodhead Publishing; 2018. pp. 67-129.
81. Nobre C, Simões LS, Gonçalves DA, Berni P, Teixeira JA. Fructooligosaccharides production and the health benefits of prebiotics. In: Current developments in biotechnology and bioengineering. Amsterdam: Elsevier; 2022. pp. 109-138.
82. Dahiya D, Nigam PS. Nutrition and health through the use of probiotic strains in fermentation to produce non-dairy functional beverage products supporting gut microbiota. Foods. 2022; 11: 2760-2773.
83. Mandalari G, Nueno-Palop C, Bisignano G, Wickham MS, Narbad A. Potential prebiotic properties of almond (Amygdalus communis L.) seeds. Appl Environ Microbiol. 2008; 74: 4264-4270.
84. Palframan R, Gibson GR, Rastall RA. Development of a quantitative tool for the comparison of the prebiotic effect of dietary oligosaccharides. Lett Appl Microbiol. 2003; 37: 281-284.
85. Buddington KK, Donahoo JB, Buddington RK. Dietary oligofructose and inulin protect mice from enteric and systemic pathogens and tumor inducers. J Nutr. 2002; 132: 472-477.

86. Asahara T, Nomoto K, Shimizu K, Watanuki M, Tanaka R. Increased resistance of mice to Salmonella enterica serovar Typhimurium infection by synbiotic administration of Bifidobacteria and transgalactosylated oligosaccharides. J Appl Microbiol. 2001; 91: 985-996.
87. Liong MT, Shah NP. Optimization of cholesterol removal by probiotics in the presence of prebiotics by using a response surface method. Appl Environ Microbiol. 2005; 71: 1745-1753.
88. You S, Ma Y, Yan B, Pei W, Wu Q, Ding C, et al. The promotion mechanism of prebiotics for probiotics: A review. Front Nutr. 2022; 9: 1000517.
89. Batsalova T, Georgiev Y, Moten D, Teneva I, Dzhambazov B. Natural xylooligosaccharides exert antitumor activity via modulation of cellular antioxidant state and TLR4. Int J Mol Sci. 2022; 23: 10430.
90. Harris S, Monteagudo-Mera A, Kosik O, Charalampopoulos D, Shewry P, Lovegrove A. Comparative prebiotic activity of mixtures of cereal grain polysaccharides. AMB Express. 2019; 9: 203.
91. Drosos A, Boura K, Dima A, Soupioni M, Nigam PS, Kanellaki M, et al. A cell-factory model of Saccharomyces cerevisiae based on bacterial cellulose without GMO for consolidated bioprocessing of starch. Food Bioprod Process. 2021; 128: 202-214.
92. Panitsa A, Petsi T, Kordouli E, Nigam PS, Kanellaki M, Koutinas AA. Carbohydrate nanotubes production and its techno-economic validation. Bioresour Technol Rep. 2023; 22: 101460.
93. Plioni I, Kalogeropoulou A, Dimitrellou D, Kandylis P, Nigam PS, Kanellaki M, et al. Ethanol from cellulose and cellobiose of woody-substrates in a single stage of 3-combined-bioprocesses employing a non-GM yeast cell-factory. Biocatal Agric Biotechnol. 2023; 50: 102733.
94. Plioni I, Kalogeropoulou A, Dimitrellou D, Kandylis P, Kanellaki M, Nigam PS, et al. Effect of cellulose crystallinity modification by starch gel treatment for improvement in ethanol fermentation rate by non-GM yeast cell factories. Bioprocess Biosyst Eng. 2022; 45: 783-790.
95. Kalogeropoulou A, Plioni I, Dimitrellou D, Nigam PS, Kanellaki M, Koutinas A. One-step hydrolysis ethanol fermentation of cellobiose and pinewood-cellulose by cell factories of non-GMO saccharomyces cerevisiae using kissiris and γ-alumina as support. BAOJ Microbiol. 2022; 6: 1-8.
96. Drosos A, Boura K, Dima A, Karabagias IK, Nigam PS, Kanellaki M, et al. Consolidated bioprocessing of starch based on a bilayer cell factory without genetic modification of yeast. Environ Technol Innov. 2021; 24: 101844.
97. Dahiya D, Manuel JV, Nigam PS. An overview of bioprocesses employing specifically selected microbial catalysts for γ-aminobutyric acid production. Microorganisms. 2021; 9: 2457.
98. Mackin C, Dahiya D, Nigam PS. Honey as a natural nutraceutical: Its combinational therapeutic strategies applicable to blood infections—Septicemia, HIV, SARS-CoV-2, Malaria. Pharmaceuticals. 2023; 16: 1154.
99. Sharma H, Rai AK, Chettri R, Nigam PS. Bioactivities of Penicillium citrinum isolated from a medicinal plant Swertia chirayita (vol, pg,). Arch Microbiol. 2021; 203: 5843.
100. Panitsa A, Petsi T, Kandylis P, Nigam PS, Kanellaki M, Koutinas AA. Chemical preservative delivery in meat using edible vegetable tubular cellulose. LWT. 2021; 141: 111049.
101. Bontzolis C, Plioni I, Dimitrellou D, Boura K, Kanellaki M, Nigam PS, et al. Isolation of antimicrobial compounds from aniseed and techno-economic feasibility report for industrial-scale application. Int J Food Sci Technol. 2022; 57: 5155-5163.

102. Dahiya D, Terpou A, Dasenaki M, Nigam PS. Current status and future prospects of bioactive molecules delivered through sustainable encapsulation techniques for food fortification. Sustain Food Technol. 2023; 1: 500-510.