Emerging paradigms in prebiotics research: implications for human health and nutrition

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Abstract

Introduction: Understanding the complex link between our gut health and general well-being has drawn more attention in recent years. Prebiotics can promote mineral absorption, influence metabolism, improve immune system regulation, and fight infections.

Aim: This article focuses into the evolving paradigms in prebiotics research, highlighting their regulation, diverse applications, impact on diseases, and their growth on the global market.

Discussion: Prebiotics are Generally Recognized as Safe (GRAS), novel foods and food additives by the Food and Drug Administration (FDA), EU and Japan, respectively. The multifaceted applications of prebiotics go across various sectors, ranging from functional foods and dietary supplements to cosmetics. A comprehensive review of prebiotics' effects on human health and illness prevention is a significant strength of the paper. Prebiotics support a healthy microbiome by feeding helpful gut flora, which may reduce the risk of a variety of illnesses and improve general health. In parallel, it covers an overview of the prebiotics industry in the world, considering aspects including consumer knowledge of gut health and growing prebiotic demand.

Conclusion: Prebiotics are anticipated to have a significant role in determining the direction of nutrition and preventive healthcare as research advances and consumer demand for natural health solutions rises.

Keywords: prebiotics, diseases, applications, regulation, United States of America, European Union, Japan

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Introduction

The field of prebiotics research has witnessed a significant evolution in recent years, driven by advancements in understanding the intricate relationship between gut microbiota and human health. The idea of prebiotics has drawn a lot of interest and is the category of compounds that the gut flora breaks down.[1] The gut microbiota refers to the diverse group of microorganisms that live inside the human gastrointestinal system.[2] According to the report, the human colon contains 10^{10} to 10^{12} live microorganisms per gram.[3] The stomach, small intestine, and large intestines are resident for multiple microbial colonies known as gut microbiota, which are essential for maintaining human health, where mostly anaerobes reside in the large intestine.[4] *Lactobacilli* and *Bifidobacteria* should be the kind of bacteria that are activated.[5]

A prebiotic is defined as "a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon and thus improves host health", according to Gibson and Roberfroid.[6] They presented the idea of prebiotics as an alternate strategy for modifying the gut flora. Over the past 15 years, prebiotics have been the topic of much investigation in an effort to comprehend their mechanisms of action and clarify the positive health benefits they have on the human host.[5]

There are a few criteria to follow for an ingredient in food to qualify as a prebiotic, such as,

- Not being absorbed, resisting gastric acidity or hydrolysed in the upper digestive tract;
- It is fermented by intestinal microflora
- function as a selective substrate for one or a small number of helpful bacteria that are naturally present in the colon and are encouraged to develop and/or become metabolically active.
- Instigate systemic and luminal impacts that are advantageous to the host's health.[7]

Consequently, they have the power to change the colony's flora in favour of a healthier composition. Various polysaccharides, oligosaccharides, microalgae, and uncultivated plants from a variety of sources are typically referred to as prebiotics.[8] The main sources of newly discovered prebiotics include algae, fruit juice, seeds and peels, traditional Chinese medicine, and other microorganisms that contain polymers, polyphenols, and polypeptide polymers.[9,10] Prebiotics must be able to endure digestive processes before they reach the colon in order to have these effects, and they should ideally remain throughout the large intestine so that the advantages can be seen, such as the ability to improve immune system control, resist infections, affect metabolism, boost mineral absorption, and improve health.[11]

The creation of completely novel candidate prebiotic substances has been made possible by the objective of promoting a larger variety of microbial species.[4] Candidate prebiotics include certain peptides, proteins, and lipids (both ethers and esters) that cannot be digested, such as certain oligo and polysaccharides.[12] These substances cannot be digested by human digestive enzymes or absorbed in the upper gastrointestinal system due to their

Table I: Important prebiotic and their potential benefits[15]

Prebiotic types	Chemical Ccontent	Methods of production	Potential benefits
Fructooligosaccharides (FOS)	Two-to-one glycosidic connections connect the units of glucose and fructose.	Monomers of fructose are polymerised.	Boost immunity, lower triglycerides, enhance mineral absorption, suppress pathogenic germs, prevent cancer, and manage diabetes
Galactooligosaccharides (GOS)	Glucose and galactose are linked together via β (1→3) and β (1→4) connections.	Lactose transgalactosylation with -galactosidase	Boost bifidogenic activity
Xylooligosaccharides (XOS)	Xylose units linked through β (1→4) bonds	Plant xylans are hydrolysed by enzymes.	Non-oncogenic nature, demonstrate a favourable impact on the flora in the intestinal tract, and are not digestible
Soybean oligosaccharides (SOS)	Terminal galactose (Stachyose) connected to (Raffinose)galactose -(1–6)	Not Specified	Boost IgG levels, control the weight of the body, and strengthen immune response
Isomaltooligosaccharides (IMO)	Up to eight glucose monomers formed by α (1→6) glycosidic linkage	Liquified starch transglucosylation, extraction from honey, fermentable foods	Boost the gut flora
Fructans	Fructose with β (2→1) linkage	Hydrolysis by enzymatic means utilising fructozyme L	Alter gut physiology to offer protection from infections and raise glucose levels
Guar gum	D-mannopyranosyl (1–4) and D-galactopyranosyl (1–6) residues joined together	Utilising cellulase for enzymatic hydrolysis	Increase blood sugar and cholesterol
Pectin oligosaccharides (POS)	(1–4)-α-D-GalA (galacturonic acid) -(1,2)-α-L-Rha	Pectinase's enzymatic degradation of water	Anti-inflammatory effect
ß-glucans	Glucose molecules linked together by beta-glycosidic bonds	Pleurotus sp. (pleuran) mushrooms, extraction from natural sources followed by purification processes and from yeast	Gut health promotion, immune support, antioxidant activity, cholesterol management, and blood sugar regulation
Inulin-type fructans	Fructose molecules linked together by β(2→1) bonds, with a terminal glucose molecule	Roots of traditional Chinese medicine *Morinda officinalis* or Indian mulberry	Composition and activities of the gut microflora, stool production, absorption of Ca and other minerals, production of gastrointestinal endocrine peptides, immunity and resistance to infections, Lipid homeostasis

chemical structure.[13] These substances, which are often called "colonic foods," are foods that transit through the gastrointestinal system and serve as substrates for endogenous colonic bacteria, giving the host energy, metabolic substrates, and essential micronutrients.[14]

There are many types of prebiotics where largely consist of oligosaccharide carbohydrates (OSCs), which are a subset of carbohydrate families (further explained in Table I).

Prebiotics can improve the healthy gut microbiota, which has a positive impact on host health, significantly affecting the gut flora and leading to favourable impacts on metabolic function.[16] They are transformed in the intestinal tract by bacteria from the gut because host enzymes are unable to break them down.[17] According to Alomaim, altering lipid metabolism can improve calcium absorption, which benefits bowel and immune system functions.[17,18] The effects of prebiotics have been studied in a

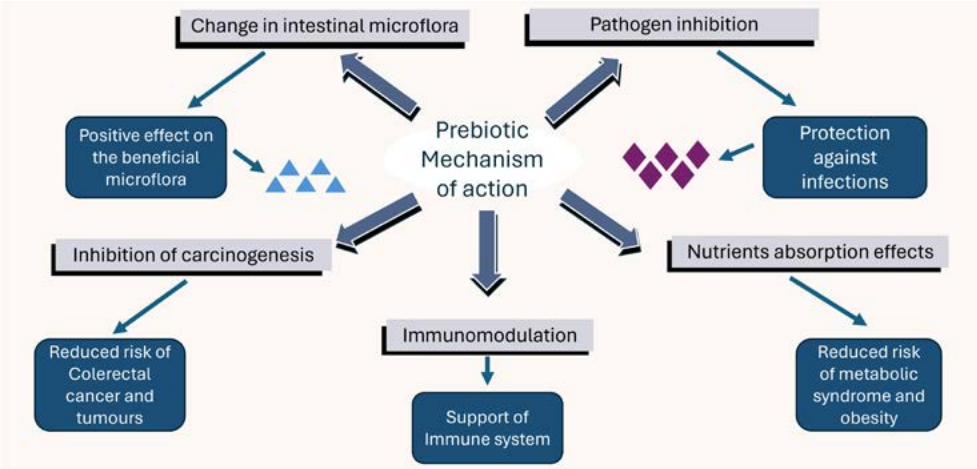

Figure 1: Combined overview of the metabolic efficiency and immunomodulation effects of prebiotics

number of fish-based trials. When selected prebiotics (β-glucan, galactooligosaccharides, and maltooligosaccharides) were administered to *Channa* striata fingerlings, improvements in growth performance, nutrient digestibility, immune regulatory gene expression were observed when compared to probiotics.[19] Based on their structure and composition, certain bacteria can utilise them as a source of carbon and energy.[4] There have been a number of models put up that can demonstrate the prebiotic effect in various bodily regions.[20] The metabolic efficiency and immunomodulation effects of prebiotics represented in Figure 1.[21] The article covers the impact of prebiotics on various diseases, its regulatory requirements, applications on different areas and the global market scenario.

Regulations

Regulation is considered for prebiotics, as well as for many other types of food and dietary supplements, to ensure their safety, efficacy, and proper labelling.[22] The regulation of prebiotics is essential to safeguard public health, enhance consumer confidence, and ensure that prebiotics deliver their intended health benefits without causing harm.[23] Consumers should look for prebiotic products that comply with relevant regulations and are backed by scientific evidence to make informed choices about their health and well-being. Regulation helps determine the positive effects and health benefits of prebiotics by assessing scientific evidence and clinical studies to support claims related to their impact on gut health, immune function, and overall well-being. It also ensures that prebiotics are safe for consumption and do not pose any risks to human health (such as assessing potential allergenicity, toxicity, and any adverse effects associated with their use). The Consumer Protection Act ensures that consumers are not misled by false or exaggerated claims about the benefits of prebiotics.[24] These health claims made on product labels or in advertising must be authorised and supported by scientific evidence. To fulfil the requirement mentioned above, regulations must be followed as per the regulatory bodies.[25]

Prebiotics are not specifically governed by a single worldwide regulatory organisation, but depending on the region, they might be covered by a number of different regulatory bodies.[26]

United States of America (USA)

Prebiotics are categorised as dietary ingredients, which are items that are meant to be ingested as part of a diet. Vitamins, minerals, herbs, botanicals, and other substances are all included in the category of dietary ingredients, which are regulated by the Food and Drug Administration (FDA) agency as per the regulatory framework. The definition of dietary ingredients includes some prebiotic compounds such as fibre, oligosaccharides, and indigestible carbs.[27] The FDA controls them in accordance with its regulatory framework. Prebiotics are regarded as dietary supplements when they are advertised and sold as stand-alone goods in the form of pills, capsules, tablets, or powders.[28] The Dietary Supplement Health and Education Act (DSHEA) of 1994 mandates that the FDA regulate dietary supplements.[29] Dietary supplement producers are required to guarantee product safety, accurate labelling, and adherence to good manufacturing practices (GMPs). The FDA manages the voluntary Generally Recognised as Safe (GRAS) notification system, which enables producers to confirm the security of fresh or existing substances, including prebiotics.[30] When a substance is deemed GRAS, it signifies that qualified professionals generally concur that it is secure when used as intended. Manufacturers are able to submit a GRAS notification to the FDA, supplying data and scientific proof to back up the safety conclusion. Although the GRAS designation is not required for prebiotic compounds, it gives businesses a way to verify safety.[31] The FDA controls prebiotic product labels to ensure accuracy and ward off false advertising. Prebiotic product health claims must adhere according to the Federal Food, Drug, and Cosmetic Act's regulations. Prebiotics may make qualified health claims that are backed by scientific evidence but do not fulfil the criteria for an authorised health claim that requires a large amount of scientific agreement. Qualified health claims are those that describe the structure or function of the prebiotic and how it helps preserve normal body processes. The FDA is in charge of ensuring that prebiotic labelling and health claims adhere to these rules.[32] In the United States of America (USA), a variety of federal and state laws, rules, and organisations are in charge of regulating consumer protection. The main federal body tasked with upholding consumer protection rules is the Federal Trade Commission (FTC) Act in 1914.

European Union (EU)

The European Food Safety Authority (EFSA) analyses health rights regarding food items inside the European Union (EU). According to EU regulation 2015/2283, prebiotic compounds may be approved as novel foods.[26] They need approval before they can be sold in the EU. The European Commission must receive a dossier from the manufacturers outlining the prebiotic's benefits and safety. The dossier should provide thorough details about the prebiotic's composition, manufacturing process, suggested applications, and intended intake levels.[33] The safety assessment should also include scientific data, such as possible allergenicity, toxicological, and dietary factors.[34]

Some of the prebiotic health claims, such as those for chicory inulin, have been authorised. Before 1997, inulin, GOS, and FOS were utilised in the EU and are regarded as safe food components. Prebiotic medications created after 1997, however, are seen to be distinct and require safety approval; certain Human milk oligosaccharides (HMOs) for example, are given this designation.[35] To present, the EU has only issued one prebiotic, chicory inulin, a health claim saying that it "improves bowel performance". This approval based on data demonstrating that there is a causal connection between ingesting a non-fractionated mixture of monosaccharides (10% of total carbohydrate), disaccharides that contain inulin-type fructans, and inulin obtained from chicory with a mean degree of polymerisation (DP) of 9, and the maintenance of normal defecation as demonstrated by an

increase in stool frequency.[36] This approval is based on data demonstrating that there is a causal connection between ingesting a non-fractionated mixture of monosaccharides (10% of total carbohydrate), disaccharides that contain inulin-type fructans, and inulin obtained from chicory with a mean DP of 9. This connection is associated with the maintenance of normal defecation, as demonstrated by an increase in stool frequency.[36] For the evaluation, the European Commission sends the file to the EFSA for review. Based on the provided information, the EFSA evaluates the prebiotic substance's safety and any claimed positive effects. The European Commission considers the assessment after the EFSA evaluation and decides whether to approve the prebiotic ingredient as a new food. The prebiotic may be sold and used in the EU market if approved. Considering the labelling specifications, a prebiotic substance must adhere to the EU's labelling criteria once it has been approved as a new food. The prebiotic's features and the circumstances under which it should be used should be accurately represented on the label. It should not deceive customers and should give them the information they require about the product.[37]

Japan

Prebiotics are categorised in Japan as Specified Functional Ingredients (SFI). They are compounds with functional qualities and health advantages that have been scientifically proven.[38] This group includes prebiotics, which encourages the development and activity of beneficial microorganisms in the stomach.[39]

The approval process in Japan requires manufacturers to submit safety and efficacy data to the Ministry of Health, Labor and Welfare (MHLW) for permission before using prebiotics in food and health products. The information should back up the claimed functional qualities or health advantages as well as show that the prebiotic is safe. This may consist of research investigations, clinical tests, or other pertinent scientific data.[40] The MHLW examines the manufacturer's effectiveness and safety data. To ascertain if the prebiotic satisfies the requirements for approval, they evaluate the scientific data. Prebiotics must pass this review procedure to be used in foods and healthcare items.[22] In Japan, any claims about the health benefits of food and health products containing prebiotics must be backed up by data from credible sources. In order to confirm the veracity of the alleged health advantages, the MHLW assesses the documentation offered by the producers to ensure that customers are given accurate and trustworthy information about the goods they use. For pharmaceutical products, prebiotics may also be utilised as components in medicinal goods and food items. The Pharmaceuticals and Medical Devices Agency (PMDA) issued laws and guidelines for the approval and use of pharmaceutical substances must be followed in certain situations by manufacturers.[41]

South Africa

The South African Health Products Regulatory Authority (SAHPRA) of South Africa (SA) would generally regulate prebiotics. The term "novel fibres" in South Africa refers to "edible carbohydrates," which have been found to have a physiological impact that is beneficial to health and have been approved and registered by the SAHPRA.[42] This has been confirmed by widely recognised scientific evidence. Novel fibres are defined as any oligomers (FOS), polymers (inulin), or mixtures thereof whose DP varies from 2 to 60 monomeric units for which a prebiotic claim could be made. They can also be defined as having $10 monomeric units, not hydrolysed by the endogenous enzymes in the human small intestine, produced synthetically, or derived from natural sources that are not typically consumed as fruits, vegetables, or cereals in the diet. The following criteria should be used to demonstrate prebiotic activity: the ability to withstand gastric acidity, the breakdown of food by mammalian enzymes and GI absorption; fermentation by intestinal microbiota; the induction of bifidobacteria growth throughout the entire indigenous population; and the specific induction of growth and/or activity of other indigenous GI microbiota that contribute to health and well-being.[43]

How does the regulations in USA, EU and Japan impact on SA regulations?

When establishing its own prebiotic regulatory framework, SA looked to the laws of the USA, EU, and Japan as significant models. The FDA, EFSA, and MHLW have created standards, safety procedures, and documentation criteria that SA can use to guarantee the efficacy, safety, and calibre of prebiotic products sold in its market. By matching SA's standards with internationally accepted norms, harmonising legislation with these top countries helps improve international commerce and foster consumer trust. SA can create strong evaluation procedures, precise labelling regulations, and efficient consumer protection measures by utilising the knowledge and best practices of these nations. This will improve public health outcomes and create an atmosphere that is favourable for the expansion of the prebiotic industry.[44]

Impact of prebiotics on diseases

The gut microbiota, an intricate ecology made up of trillions of bacteria, is found in the human gut.[45] The vital function that these gut microorganisms play in preserving general health and avoiding numerous illnesses has been highlighted by recent studies mentioned in the sub-sections below.[46]

Irritable bowel syndrome (IBS) and Crohn's disease

Irritable Bowel Syndrome (IBS) is a digestive illness categorised by persistent stomach discomfort and irregular bowel movements without any apparent biological reason. In one case study, 44 IBS patients participated in a randomised, double-blind, cross-over experiment.[46] The treatments include placebo followed by low-dose GOS (3.5 g/d) over a four-week period, placebo followed by high-dose GOS (7.0 g/d), and placebo followed by placebo. Lower ratings for gas, bloating, and overall alleviation were achieved in the low dosage prebiotic group compared to placebo due to more *Bifidobacteria* in these groups than in the placebo group.[46]

Crohn's disease, which affects the whole digestive system, including the mouth and the anus, is a chronic, recurrent ailment.[47,48] There is compelling evidence that the GI microbiota is closely related to the genesis of the disorder, making prebiotics an interesting therapy option for Crohn's disease. Studies have revealed that people with Crohn's disease had lower relative levels of *Bifidobacteria*.[49] The pathophysiology of Crohn's disease may be linked to this decline in *Bifidobacteria* population, which may contribute to dysbiosis and inflammation in the gut.[50]

In a group study from 2011, people with Crohn's disease benefited from taking 15 g/day of FOS for four weeks because it boosted the *Bifidobacteria* population in their stools.[51] However, the other double-blind, randomised, and placebo-controlled studies failed to show any therapeutic advantages for giving patients who are suffering with active Crohn's disease 15 g/day of FOS.[52]

Acute gastroenteritis

Everyone will likely experience acute gastroenteritis at some point. Typically, it entails consuming food or water that has been tainted with pathogenic bacteria or their poisons. Examples of typical causative agents include *Shigella*, *Yersinia enterocolitica*, *Salmonellae*, *Campylobacter jejuni*, strains of *E. coli*, cholera-causing bacteria *Vibrio cholera*, and *Clostridium perfringens*. Pathogens can either emit toxins that contaminate food before it is consumed, or they can colonise and proliferate in the gastrointestinal system before invading host tissue.[53] Such toxins impair the intestinal mucosa's ability to function, resulting in nausea, vomiting, and diarrhoea. One or more potential mechanisms at work include competitive effects from occupation of common immigration sites, lead antagonism by way of natural antimicrobial excretion, and competition for vitamins. The gut pH of a microniche may be lowered by the metabolic byproducts of these bacteria, such as acids secreted, to levels below which pathogens may successfully compete.[53] One of the studies published in the journal, includes 200 children aged 1-5 years, divided into four groups with 50 children where each received prebiotics in different manner with particular dose.[54] All patients' hospital stays, the number of diarrhoeal and vomiting episodes they experienced before and after treatment, the amount of intravenous fluid therapy they received before and after treatment, and any additional complications that occurred over the course of the trial were compared. An effective study outcome revealed that the group receiving prebiotic and bovine colostrum outperformed other groups across various metrics, including the length of hospital stays, the frequency of vomiting and diarrhoea bouts, the severity of electrolyte disturbance, the technique of rehydration, and any associated consequences. There was no apparent distinction in the groups' pretreatment clinical state.[55]

Colorectal cancer

The third most prevalent type of cancer globally is colorectal cancer, which progresses in phases beginning with a genetic mutation, adenomatous polyps, and ultimately aggressive and metastatic malignancy.[56] By inducing apoptosis, prebiotic fermentation products like butyrate have been demonstrated to both lower the incidence of colorectal cancer and decrease its progression. Additionally, a clinical study showed that symbiotic therapy (*Bifidobacterium lactis* and *Lactobacillus rhamnosus* combined with inulin) could decrease the impacts of colorectal cancer by decreasing colorectal cell growth and causing necrosis in colonic cells, which enhances the strength and efficiency of the epithelial barrier.[57]

Necrotising enterocolitis

A disorder known as necrotising enterocolitis (NEC) causes parts of the colon to swell and become necrotic and most common in preterm newborns.[58] High rates of morbidity and mortality may result from it. Prebiotics like FOS and GOS are thought to prevent NEC because they increase the proliferation of gut microbiota (like *Bifidobacteria*) and decrease the number of harmful bacteria in preterm newborns. Additionally, SCFAs can increase eating tolerance by promoting intestinal and stomach motility. The concentration of faecal *Bifidobacteria* might be increased by FOS, GOS, or their combination, according to a meta-analysis of four randomised controlled trials, however, the risk of developing NEC and its development were not significantly impacted.[59] Therefore, further clinical studies must be conducted to clarify the precise of prebiotics on NEC.[60]

Psoriasis

Chronic inflammation leads to unchecked keratinocyte proliferation and improper differentiation, which is the root cause of psoriasis, an autoimmune pathogenic chronic inflammatory skin disease.[61] Prebiotics have the potential to alter the gut flora and enhance gut health include inulin and oligosaccharides.[61] They can reestablish the equilibrium of the gut's microbes and encourage the development of advantageous bacteria. Prebiotics have been shown in certain instances to treat psoriasis through altering the gut microbiome. Faeces from 30 people with psoriasis and 30 healthy controls were included in the study. Bioinformatic methods like Phylogenetic Investigation of Communities by Reconstruction of Unobserved Taxa and Quantitative Insights into Microbial Ecology (QIIME) were used to assess the makeup of the gut microbes. The findings indicated that patients with psoriasis had higher virtual abundances of specific bacterial taxonomy, such as faecal bacterium and *Megamonas*, compared to healthy people.[62] Numerous cytokines are implicated in the pathogenesis of psoriasis as primary impact molecules. Interleukin-2 receptor in particular exhibited a favourable link with *Phascolarctobacterium* and a negative interaction with the *Dialister* in terms of inflammation-related parameters. *Phascolarctobacterium* and *Dialister* relative abundances is used to predict the severity of psoriasis. According to the association study using markers of inflammation and microbiota, microbiota dysbiosis may cause an aberrant immune response in psoriasis.[63]

Cardiovascular disease

Cardiovascular disease (CVD) incidence has risen to the point that it is now the chief cause of death globally in recent decades.[64] A

connection between diet and cardiovascular events has been demonstrated through the elements of metabolic syndrome and obesity, including dyslipidaemia and the presence of visceral fat. It is well-recognised that oxidative stress contributes to the development of CVD. This condition is associated with increased intracellular oxygen radical levels that harm DNA, proteins, and lipids. Inulin and oligofructose, two prebiotic dietary supplements, aid in reducing oxidative stress.[65] Inulin has the ability to scavenge reactive oxygen species (ROS) thanks to short-chain fatty acids. Inulin can also prevent the gut from becoming inflamed and regulate how the body responds to pathogenic bacterial assaults (LPS). This is probably because it activates the body's defences against ROS by upregulating colonic mucosal detoxifying enzymes (GSTs), which in turn aids in restoring the levels of several crucial proteins involved in the contraction of intestinal smooth muscle.[66]

High cholesterol and blood pressure

In a hypercholesterolemic rat model, prebiotic treatment reduces total serum cholesterol, according to Parnell and Reiner.[46] Prebiotics also lower cholesterol levels. In this study, rats were fed one of three diets that included 0, 10, or 20% prebiotic fibre for ten weeks. In both doses, prebiotic fibre reduced blood cholesterol levels by over 25%. This change was accompanied by an increase in caeca digesta and the increased expression of bile and cholesterol-producing genes. Additionally, the liver triacylglycerol buildup in the obese rats receiving a 10% prebiotic supplement was reduced by almost 40% (Table I). Obesity and the development of CVDs are frequently linked, but several clinical studies have revealed that probiotic and prebiotic supplementation have anti-obesogenic properties.[67]

Diabetes mellitus (DM)

There is proof that the solubility of fibre lowers postprandial insulin and serum glucose levels by raising the consistency of nutrients in the small intestine, delaying the release of glucose, preventing glucose from binding to the fibre and lowering the amount of available fibre for use, and inhibiting the action of amylase on amido.[68] Due to their ability to form gels, inulin and FOS have an impact on how well nutrients, particularly carbohydrates, are absorbed by delaying gastric emptying and/or shortening intestinal transit time. Yacon ingestion can regulate blood sugar, however, the exact mechanism by which this happens is yet unclear. Prebiotic supplement treatment was found to be associated with an increase in plasma gut peptide concentrations (peptide YY and glucagon-like peptide 1), which may explain changes in hunger and satiety.[69] Recent *in vitro* research has shown that a specific concentration of long-chain water-extractable arabinoxylans (LC-AX) stimulates specific intestinal microorganisms, like *Bifidobacterium longum*, and starts specific fermentation patterns that may be advantageous to the host (like the production of propionate). Human investigations have shown that long-term administration of LC-AX can aid type II diabetics in regaining their ability to respond to glucose and insulin.[70]

Osteoporosis

Increasing calcium and magnesium absorption can help prevent diseases like osteoporosis and is essential for bone formation. Rats' ability to absorb calcium and magnesium can be improved by adding GOS to their diets.[71] Although the authors noted that there are likely both microbial and non-microbial mediated processes, the precise mechanism in this instance is unknown, therefore, a colonic flora is necessary for GOS to have this impact.[72] In experiments on humans, 15 g of oligofructose or 40 g of inulin per day appeared to improve the apparent absorption of calcium (FOS can also alter mineral absorption). It has also been demonstrated that consuming FOS causes an increase in magnesium absorption.[73]

Lipid regulation

The control of lipids may be affected by prebiotics as well. A study on diabetic rats found that when XOS (Xylooligosaccharides) was used as a substitute for simple carbohydrates in the meals, liver triglyceride increased to a level comparable to that of healthy rats, lowering the blood cholesterol and triglyceride elevations connected to diabetes.[74] Studies have shown that prebiotics may have cholesterol-lowering effects in both animals and humans.[75]

Prebiotics, such as fructans, have been found to exhibit interesting serum or hepatic lipid-lowering properties. Additional research on FOS has shown that it also reduces blood lipids.[76] Prebiotics can help treat hyperlipidaemia caused by diabetes and other illnesses, but they haven't been shown to lower lipid levels in healthy people.[75,77]

Alzheimer's disease

Amyloid and malfunctioning tau protein buildup in the brain, together with the eventual onset of dementia, are hallmarks of Alzheimer's disease.[78] Key factors in the progress of Alzheimer's disease and the deposition of amyloid are acute and chronic neuroinflammation. Pro/prebiotics, such as lactic acid bacteria and *Bifidobacterium*, have drawn interest in this context as methods for reducing neuroinflammation.[79] The probiotic "*Bifidobacterium breve* strain A1" taken orally prevented the cognitive deterioration seen in rats with Alzheimer's disease. *Bifidobacterium breve* A1 ingestion reduced amyloid-induced immune-reactive genes and inflammation in the hippocampus, according to gene profiling study.[80]

Female reproduction

Since birth until adolescence, *Lactobacilli* species have predominated in the vaginal microenvironment.[81] After puberty, cleanliness, hormonal changes, menstruation, illnesses, and sexual activity all affect the variety of microorganisms. Because of this variability in the vaginal environment, *Lactobacilli* species are not commonly found in most women, and subsequently, there's a higher vulnerability to urogenital illnesses, including bacterial vaginosis and urinary tract infections. Bacterial vaginosis (BV) has been linked to a higher risk of preterm birth and a lower likelihood

of getting pregnant. Prebiotics may help with fertility, according to certain animal studies.[82] Prebiotics, for instance, have been linked to better embryo implantation and higher ovulation rates in animal models.[16]

Human health benefit

Any intervention, including the use of prebiotics, should have, as its major goal enhancing health and, as a result, lowering the risk or severity of sickness. Health end points targeted in human trials of orally administered prebiotics are discussed in Table II. The best strategies focus on prevention and acknowledge that early interventions that support a resilient, diverse, and healthy microbiome have the greatest potential to improve health overall.[83]

Table II: Health end points targeted in human trials of orally administered prebiotics[22]

Health end point	Prebiotic used
Diabetes type 2, the metabolic disorder, high cholesterol levels, and arthritis are all associated with being overweight or obese.	Inulin, GOS, FOS
Stimulation of gut bacteria that produce neurochemicals	GOS
Improved calcium and other mineral absorption, bone health	FOS, Insulin
Enhanced water retention, reduced erythema, and improved skin health	GOS
Allergy	GOS, FOS
Inflammatory bowel disease	Lactulose, inulin,
Urogenital health	GOS
Infants' intestine habits and overall gut health	FOS, GOS,
Vaccine response and infections	FOS, GOS, polydextrose
In preterm newborns, necrotising enterocolitis	GOS, FOS
Irritable Bowel Syndrome	GOS
Traveller's diarrhoea	GOS

Applications of prebiotics

In food

Prebiotics must not have a detrimental effect on the product's organoleptic properties in order to be used in food products. Additionally, it must maintain its stability while being used to prepare food, which entails high temperatures, low pH, or a combination of the two, as well as conditions that encourage Maillard reactions.[84] Prebiotics can be manufactured as a powder, syrup, or capsules and sold as supplements at health food shops or included in food items. Prebiotic powder can be placed on foods or mixed into drinks, or capsules can be taken with meals.[85] Applications and properties of prebiotics is mentioned in the Table III.

Prebiotics are used as functional ingredients in the food industry for beverages, wellness drinks, spreads, dairy products (powdered milk, cheese, fermented milk, ice cream, fruit juices, tea, coffee, chocolate, soft drinks in general, isotonic drinks, liquid sugar, and alcoholic beverages are among these drinks), infant food, and weaning foods. Along with meat products, dry quick meals, canned food, and sweets (jellies, puddings), candies, chocolates, chewing gum, cakes, biscuits, morning cereals, breads, and pastas, other uses include soups, sauces, and dressings.[86]

Table III: Application and functional properties of prebiotics[87]

Application	Functional Properties
Dairy products	Fibre and prebiotics, fat or sugar substitution, texture and tongue feel
Frozen desserts	Substitution of fat or sugar, texture, and melting behaviour
Fruit Preparations	Synergy of sugar substitute sweeteners, body and mouth sensation, and fibre
Beverages and drinks	Tongue sensation, foam stability, replacement of fat or sugar, and prebiotics.
Baked goods and breads	Sugar substitution, retention of moisture, fibre, and prebiotics
Breakfast cereals and extruded snacks	Sugar substitution, sharpness and expansion, fibre and prebiotics
Filling	Replacement of fat or sugar, texture, and tongue sensation
Dietetic products	Fibre and prebiotics, as well as fat or sugar substitution
Sugar confectionary	Sugar substitute, resistance to heat, and fibre
Chocolate	Fibre, a sugar substitute, and heat resistance
Soups and sauces	Prebiotics and sugar substitution
Meat Products	Fibre, fat substitution, and textural constancy

Infant formulas that include prebiotics

Infant formula is an alternative to human milk if the mother is unable to breastfeed. In order to provide nutrition equal to that of mother's milk, infant formulas must have ingredients that mimic HMO (Human milk oligosaccharides). Using a combination of short-chain GOS and long-chain FOS in place of HMO allows for gut microbial stimulation on par with that found in the mother's milk.[88] By transgalactosylating lactose, B-galactosidases operate as a catalyst and exhibit prebiotic action in the synthesis of GOS.[89] Depending on their structural composition, GOS and other oligosaccharides generated from lactose have important biological activities. For instance, by adhering to glycan-binding proteins of pathogens or to glycan-binding domains of bacterial adhesins and toxins, they might modify immune responses.[90] Sucrose is employed as a substrate for the generation of FOS utilising a mixed enzyme system that includes glucose oxidase and b-fructofuranosidase. Commercial baby formulae were examined for prebiotic oligosaccharides utilising chromatographic techniques including HPLC-RID and GC-FID. The results were in line with the GOS, FOS and GOS/FOS ranges that were specified on the labels of these packaged formulations These ranges were 1.6-5.0, 1.7-3.2, and 0.08-0.25/2.3-3.8 g/100 g product, respectively.[91]

In cosmetic industry

Skin care solutions that are made with prebiotic components like xylitol, rhamnose, glucomannan, oligosaccharides, inulin and others assist to maintain the skin's surface healthy, prevent symptoms of aging, enhance general skin health, etc.[92]

Other components high in prebiotics that are used in skin care products include oats, which help to soothe irritated skin; ginseng, which lessens skin inflammation; and pine, which shields the skin from UV rays, as discussed in Figure 2.[93]

1. Prevents breakouts of acne

Prebiotics are an effective treatment for some forms of acne outbreaks, including cystic acne as it combats any skin irritation that can cause an outbreak.[94] Research found that the prebiotic element glucomannan, when paired with probiotic compounds, successfully treats acne.[94] Prebiotics and probiotics work together to increase the effectiveness of probiotics' ability to keep acne-causing bacteria away from the skin.

2. Calms skin

Prebiotics made from sugar have calming qualities that aid to soothe inflamed skin.[4,95] Prebiotic serums are often mild and beneficial for sensitive skin which has reputation for lowering skin sensitivity. Prebiotics will help in case the user experiences rashes, inflammation, or redness.

3. Other advantages

- Preserves the pH balance of the skin; decreases blemishes[96]
- Encourages youthful skin[93]
- Control aging symptoms[97]

Global market scenario of prebiotics

Over the coming years, market growth is anticipated to be aided by rising demand for supplements and rising consumer knowledge of fibre's health benefits. The industry is also anticipated to grow as prebiotic natural herbs are grown and harvested more often throughout Europe.[99] The prominent players that are operating in the global prebiotics market in which some of them are Bright Food (Group) Corp. Ltd., Abbott Laboratories, BENEO GmbH, Cargill Inc., Kraft Foods Group, Inc., Cosucra Groupe Warcoing SA, The Kraft Heinz Company, Friesland Campina, Jarrow Formulas, Inc., Parmalat S.p.A, Royal Coson, Roquette Frères, Yakult Honsha Co., Ltd.[100]

The corporations are ramping up their new product development, mergers & acquisitions, and strategic expansion efforts. For instance, "BENEO" stated in March 2020 that it will invest more than EUR 50 million in a significant expansion of its chicory root manufacturing facility in Chile by the year 2022.[101]

There is no indication of an upgrade for BENEO's chicory root processing facility in Chile in 2024. Nonetheless, it is claimed that BENEO, with an investment of more than EUR 50 million, announced a major expansion for its chicory root production facility in Chile by 2022. After completion, the extension at Pemuco, Chile, allowed for the processing of its liquid chicory root fibres. The expansion was a component of BENEO's broader investment plan, which also included the completion of a second refining line in Pemuco, Chile, and capacity augmentation measures at practically every location.[102]

Prebiotics can be used for a variety of other purposes, including enhancing food texture and naturally sweetening it. Fructo-oligosaccharide (FOS) and inulin, two crucial prebiotic components, are in great mandate in the products which requires a calorie-free sweetening flavour.[86] Through the foreseeable term, this is boosting the overall growth of the prebiotics business. Prebiotics are even utilised more often in animal feed since they improve the general well-being such as enhancing the health, absorption, and productivity and metabolism of the animals, which have anticipated to contribute to the spectacular global market boom. Other factors influencing the market's growth include the increasing reliance on animals as a source of protein and the expanding usage of prebiotics in chicken feed to boost productivity.[103]

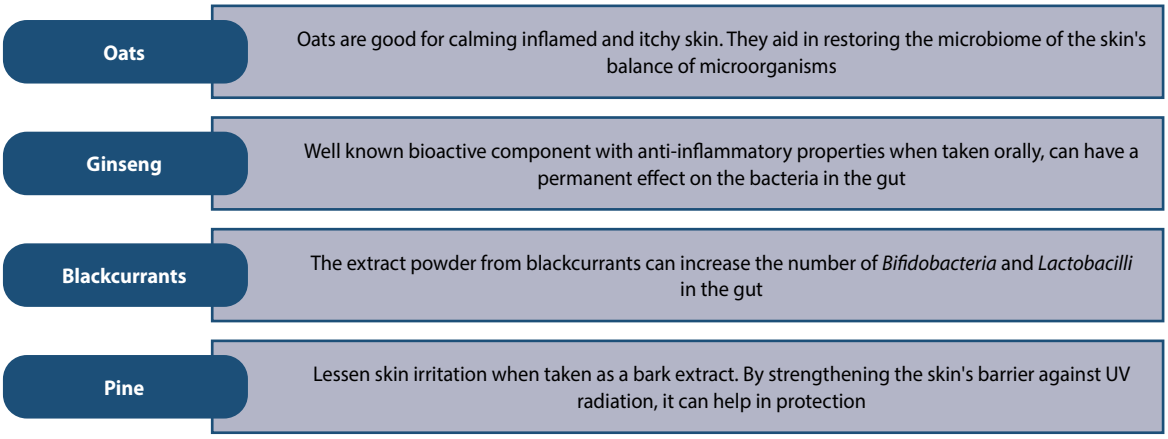

Figure 2: Application of prebiotics in cosmetics[91,93]

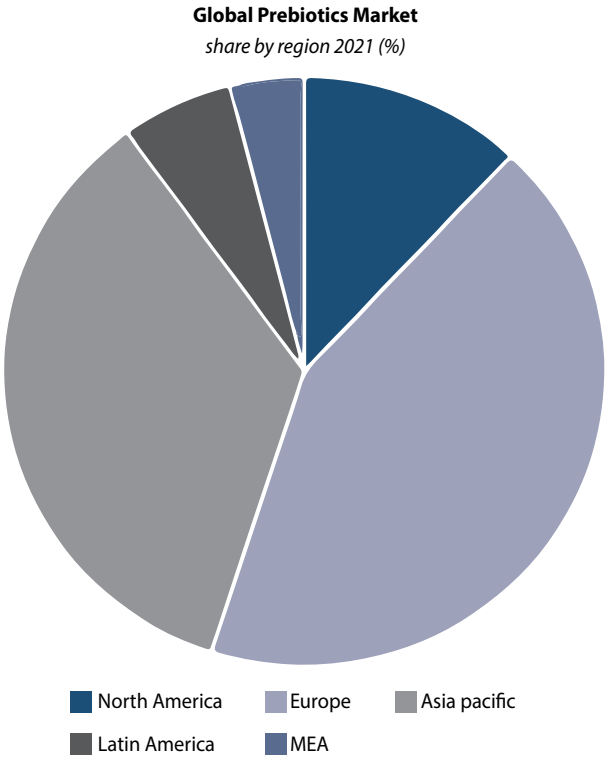

Figure 4: Projected market growth rates (2022-2030) with Asia Pacific leading at 15.4% CAGR, driven by product diversity. Europe dominated in 2021, while North America's growth remains constant.[106]

Prebiotics market in the world by region

The regions of the Asia-Pacific region, USA the EU, South America and the Middle East and Africa (MEA), make up the worldwide prebiotics market.[104] The prebiotics market is dominated by the Asia-Pacific region. The Asia Pacific market is expanding due to demand from countries with large populations and high dairy product consumption, such as India, Japan and China. Throughout the forecasted period, higher grade components for animal feed are now required due to the growing significance of animal feed components, which will be tracked by the high prevalence of illnesses like Porcine Epidemic Diarrhoea Virus (PEDv) and Bovine Spongiform Encephalopathy (BSE) (Figure 4).[105]

Prebiotics market worldwide by application

Prebiotic foods, drinks, and nutritional supplements such as dairy products, baked goods, cereals, dry food prebiotics and fermented meat products used in animal feed make up the three application-based segments of the worldwide prebiotics market.[107] Prebiotic dietary supplements are further divided into infant formula, specialist nutrients, food supplements, and nutritional supplements. The prebiotics business has been dominated by the prebiotic food and beverage market and are projected to be used more often in the food and beverage sector because of the presence of colon bacteria that promote good health as depicted in Figure 5.

Demand for these products is expected to rise as consumers become more aware of how protein may promote appropriate nutritional levels and preserve muscle strength. Additionally, it is believed that leading a healthy and active lifestyle and being more aware of the advantages of protein can significantly contribute to promoting the use of dietary supplement products.[108]

Inulin, Mannan-oligosaccharides (MOS), Galacto-oligosaccharides (GOS), and others (Oligosaccharides, chicory fructans, which is HMO, and XOS) have also been classified as subgroups of the worldwide market. In 2021, the inulin ingredients market sector held a commanding market share of more than 37% of the total revenue.[109] The rising demand for inulin in baked goods and drinks is likely to have a substantial impact on the segment's growth throughout the forecasted period. The demand for GOS products worldwide is anticipated to increase significantly between 2022 and 2030, based on the market trends and analysis.[110]

Conclusion

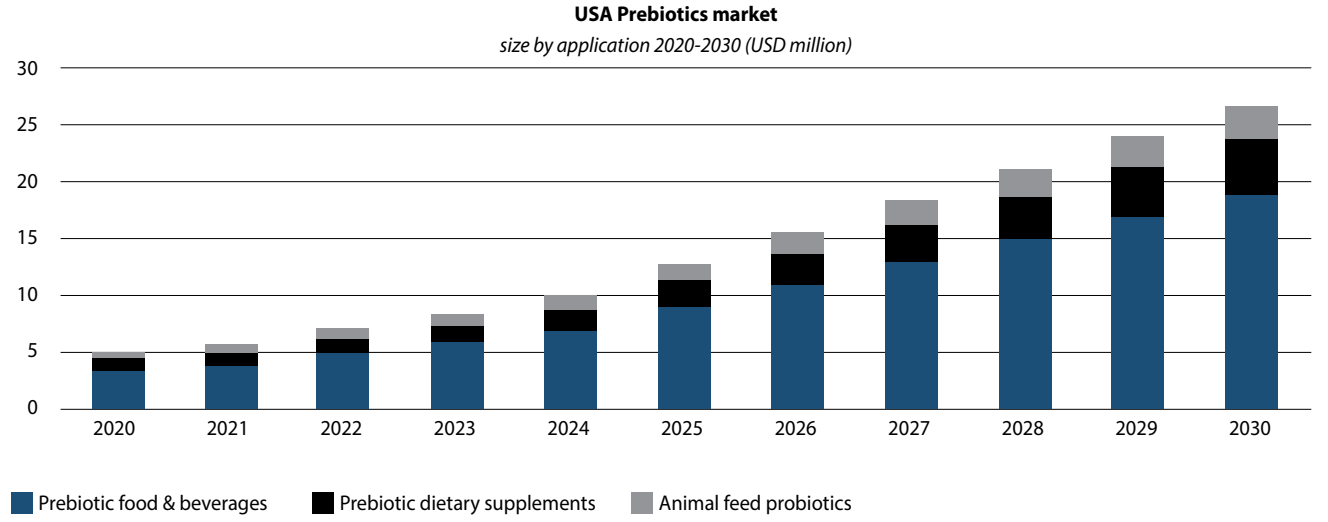

Figure 5: USA Prebiotics Market by Application (2020-2030, USD million). In 2021, the application category for food and beverages held a dominant market share of over 82.00% of the worldwide volume. Due to the expanding significance of animal proteins and the fortification of animal feed with bacteria that enhance animal gut health, the demand for prebiotics in animal feed was high globally in 2021 and is expected to rise even higher.[109]

Prebiotics are widely used as dietary food ingredients since they support healthy gut flora and may be obtained naturally from a variety of meals. Their inclusion in the food can increase health of the human and shield against a variety of diseases. Prebiotics must be regulated in order to guarantee their efficacy, safety, and appropriate labelling. The applications of prebiotics span a wide range of industries, from functional foods and dietary supplements to pharmaceuticals and animal feed. Prebiotics have been shown to be beneficial in the prevention or treatment of necrotising enterocolitis, acute infectious diarrhoea, acute respiratory tract infections, diarrhoea linked to antibiotic use, and colic in infants. Leveraging scientific advancements, adhering to regulatory standards, and staying responsive to consumer preferences is crucial for unlocking the full potential of prebiotics in shaping a healthier world. By capitalising on these insights, businesses, policymakers, researchers, and investors can contribute to the growth of the prebiotics market and foster innovative solutions for improved gut health and overall wellness. Looking to the future, personalised nutrition, novel prebiotic sources, synbiotic formulations, and exploring the gut-brain axis are poised to shape the prebiotics industry.

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