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Modulatory Potential of Dietary Plant Prebiotics on Adaptive Immunity and Gut Microbiota

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Abstract

Dietary plant-based prebiotics—including oligosaccharides e.g. GOS, FOS, XOS, resistant starches, and polyphenols—feed and enrich beneficial gut microbes, promoting short-chain fatty acid (SCFA) production and metabolic, immunological, and epithelial homeostasis. These indigestible substrates enhance colonisation by Bifidobacteria, Lactobacilli, Akkermansia, and other SCFA-producing taxa while inhibiting pathogens, thereby restoring microbial balance and countering dysbiosis. Prebiotics produce acetate, propionate, and butyrate , which serve as energy substrates and immunomodulators by inhibiting pro-inflammatory cytokines (such as IL 1β and TNF α), stimulating regulatory T and B cell differentiation through HDAC inhibition and GPCR (e.g., GPR43/109a) activation, improving gut barrier integrity and IgA synthesis. Polyphenols exert "duplibiotic" effects by both feeding beneficial bacteria and suppressing harmful species, offering additional therapeutic potential. Synergistically, synbiotics (combined probiotics and prebiotics) and postbiotics (microbial metabolites) further support intestinal microbiota and immune function, improving outcomes in metabolic, inflammatory, and gastrointestinal conditions. Experimental evidence highlights that early-life prebiotic exposure shapes adaptive immunity, for instance via B cell ontogeny and tolerogenic profiles. Collectively, this review highlights the multifaceted immunomodulatory capacity of plant-derived prebiotics on adaptive immunity and gut microbiota, suggesting applications for preventive and therapeutic strategies in metabolic and immune-mediated diseases.

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Introduction

The human gastrointestinal tract hosts a vast and diverse microbial ecosystem commonly referred to as the gut microbiota that plays a pivotal role in digestive, metabolic, and immunological health. Particularly important is the microbiota's influence on the host's adaptive immune system, where microbial constituents and their metabolites orchestrate the education, differentiation, and regulation of T and B lymphocytes, ultimately shaping immune tolerance and responsiveness. Dietary plant-derived prebiotics non-digestible carbohydrates such as inulin, fructooligosaccharides (FOS), galactooligosaccharides (GOS), resistant starches, and polyphenolsserve as substrates for fermentation by commensal bacteria in the colon. These substrates selectively support the growth of beneficial bacterial taxa, including Bifidobacteria, Lactobacilli, Akkermansia, Faecalibacterium, Roseburia, and others recognised for producing immunomodulatory metabolites like short-chain fatty acids (SCFAs). The resulting SCFAs primarily acetate, propionate, and butyrate act as central mediators of host-microbiota cross-talk by regulating gut barrier function, mucosal immunity, inflammation, and systemic metabolic responses. Beyond oligosaccharides and starches, plant polyphenols also demonstrate prebiotic-like effects by both supporting beneficial microbial growth and suppressing pathogens a concept often termed "duplibiotics". Such compounds enrich microbial diversity and enhance ecosystem resilience, which is essential to preserve microbial homeostasis under environmental or dietary perturbations. In addition to demonstrating stand-alone effects, prebiotics are frequently studied in combination with probiotics (as synbiotics) and through the actions of microbial metabolites (postbiotics), which further augment their immunomodulatory impact. Emerging evidence highlights particularly profound effects when prebiotic exposure occurs early in life, with long-lasting consequences for immune maturation, B cell ontogeny, IgA production, and oral tolerance. This review summarises current knowledge on how plant-derived prebiotics modulate gut microbiota composition and SCFA-mediated signalling to orchestrate adaptive immune responses addressing mechanistic underpinnings, immunological outcomes, and therapeutic potential in metabolic, inflammatory, and immune-mediated disorders.

Prebiotics

The immunological response, psychological well-being, and digestive health are all significantly impacted by the trillions of microorganisms that make up the human gut microbiome. Because it is linked to metabolic disorders, preserving the equilibrium of gut flora is critical. Probiotics, synbiotics, postbiotics, and prebiotics are examples of functional food ingredients that may enhance gut performance [1]. Among them are prebiotics, which are both naturally occurring and synthetic carbohydrates that cannot be broken down by the enzymes in the small intestine. These indigestible food components and carbohydrates promote the growth of beneficial bacteria in the colon, which has a positive impact on the health of both humans and animals. The primary types include lactulose, inulin, resistant starch(RS), raffinose, fructooligosaccharides(FOS), fructans, galactooligosaccharides(GOS), Xylooligosaccharides (XOS), isomaltooligosaccharides (IMO), pectin oligosaccharides (POS), mannooligosaccharides (MOS), chitooligosaccharides (CHOS) and Polyphenols [2]. Prebiotics are food elements that enhance health by stimulating the growth or activity of specific bacteria within the gastrointestinal tract. For a food component to qualify as a prebiotic, it must be hydrolysed and absorbed in the upper part of the intestinal tract, utilised by beneficial gut bacteria, modify the intestinal flora so as to promote health, and have a positive and lasting impact on the health of humans and animals. Research has shown that incorporating prebiotics into the diet increases the levels of faecal bifidobacteria while significantly reducing the levels of pathogenic bacteria. Studies have demonstrated that the introduction of prebiotics notably elevated the presence of lactobacillus and bifidobacteria in the colon and considerably diminished the population of sulfite-reducing clostridia [2]. Prebiotics serve as food sources for fermentation by beneficial bacteria, leading to the generation of metabolites such as short-chain fatty acids (SCFAs) [3]. These metabolites play a vital role in maintaining gut balance and have effects that reach beyond the digestive system. Understanding the precise mechanisms through which prebiotics promote gut health and lower the risk of various gastrointestinal issues and associated comorbidities is essential for maximising the advantages of prebiotics [4]. SCFAs are crucial for maintaining equilibrium in the microbiome's redox-equivalent production in the gut's anaerobic environment. Short-chain fatty acids

(SCFAs) are organic fatty acids with between one and six carbons. Acetate (C2), propionate (C3), and butyrate (C4) are the three primary SCFAs [2]. SCFAs can function as an energy source that is absorbed through the mucosa of the colon. SCFAs have been demonstrated to have numerous vital physiological roles in addition to serving as an energy source. These include preserving luminal pH, preventing the growth of pathogens, affecting intestinal motility, and inducing cancer cell apoptosis, which lowers the incidence of colorectal cancer [2].

GOS

Prebiotics are selectively employed by microorganisms as substrates that promote the well-being of their host organisms. The most frequently utilised formulation of this prebiotic mixture comprises 90% short-chain galacto-oligosaccharides and 10% long-chain fructo-oligosaccharides. Non-digestible carbohydrates known as GOS are made up of three to ten or more galactose molecules along with a final glucose molecule. GOS is created by the catalysis of glycoside hydrolases, usually using lactose as a substrate. The outcome is a blend of GOS with different degrees of polymerisation [5] [2]. Due to their physiological resemblance to breast milk oligosaccharides, GOS are also frequently added to milk-based products and infant formulas, effectively simulating their effects. Consuming GOS has several advantages, such as improving immune responses, reducing the production of harmful substances, improving mineral absorption, selectively stimulating beneficial microorganisms, and lessening the severity of diabetes and obesity [5].

FOS

The health benefits of nondigestible carbohydrates (NDCs) make them valuable food ingredients. Foods like complete grains and vegetables (including artichokes and garlic) contain fructans like inulin and oligofructose naturally. And fruits (e.g. bananas). Inulin, which is primarily extracted from chicory roots, is partially hydrolysed by enzymes to produce FOS (DP 2–10) [6]. Alternatively, fructose or sucrose can be used to make FOS (DP2–5). FOS is made up of a linear sequence of β-(2,1) linked fructose units, with a DP up to 10, that are joined to either a terminal α-d-glucose by an α-(2,1) bond (GFn series) or a terminal fructose by a β-(2,1) bond (Fn series) at the nonreducing end [6]. Numerous health benefits, such as preventing colon cancer, regulating serum lipid and cholesterol concentrations, managing obesity and diabetes, improving mineral adsorption, and modifying the immune system, have been associated with FOS consumption. Improved mineral absorption, decreased blood lipids, and better gastrointestinal health are some advantages of FOS and other prebiotics, like inulin [2].

Resistant Starch

Another type of prebiotic, called the resistant starch (RS), passes through the small intestine and enters the colon, where gut bacteria use it as a substrate for fermentation. Amylose and amylopectin molecules are the two main constituents of starch. However, because of its structure, RS cannot be broken down in the small intestine by human enzymes. High-amylose granular starch may be found in green bananas, high-amylose corn, and raw potatoes [4]. During this fermentation process, short-chain fatty acids (SCFAs) such as butyrate, propionate, and acetate are formed, which have numerous health benefits. A study revealed that resistant starch might help control blood sugar. Consuming RS has also been demonstrated to control intestinal bacteria, lower obesity, and prevent colorectal cancer [2].

Dietary Potential of Phenols as Prebiotics

According to the most recent definition of prebiotics, which the ISAPP published in 2017, a substance is considered a prebiotic if it improves the host's health by positively influencing the composition and operation of the microbiota. This wider definition has resulted in more intensive and thorough investigation of the synthesis and evaluation of possible prebiotics [7]. Among many plant-based dietary molecules, polyphenols have been shown to exhibit "prebiotic-like" effects [2]. Polyphenols are among plant secondary metabolites, which act as the plant's defence mechanism in situations of environmental stress such as drought, salinity and heavy metal stress [8]. Their makeup ranges from simple phenolic to sophisticated aliphatic molecules to complicated polymers with an aromatic ring in their chemical composition that has one or more hydroxyl groups [9]. By promoting the development of probiotics (such as Bifidobacteriaceae and Lactobacillaceae) or inhibiting pathogenic bacteria (such as Escherichia coli, Clostridium perfringens,

and *Helicobacter pylori*), polyphenols are believed to have prebiotic effects [2] [7]. These polyphenols have been proven to lower the chance of gastroenteritis, colon cancer, metabolic syndrome, and inflammatory bowel disease (IBD) and lowers inflammatory immune responses. One of the polyphenols that has been thoroughly studied as a prebiotic is quercetin [2] [10]. Many in vitro and animal investigations have shown that quercetin positively affects the composition of the gut microbiota. Moreover, flavan-3-ols are quite varied flavan derivatives; several studies look at the prebiotic capacity of different monomeric, oligomeric, and polymeric flavan-3-ols as isolated molecules and in the form of extracts abundant in specific chemicals. [9] Anthocyanins have also been rather well studied as they not only encourage the growth of helpful gut flora but also act as a "mediator" by processing anthocyanins, hence boosting anthocyanins' bioavailability and therapeutic potential against a range of chronic illnesses, including obesity, type II diabetes, cardiovascular disease, fatty liver disease, chronic renal failure, and osteoarthritis. Anthocyanins can change gut microbial composition by improving diversity and increasing the proportion of helpful species, therefore affecting short-chain fatty acid and bile acid production [11].

Natural Sources of Prebiotics

Prebiotics have the potential to improve gut health and overall well-being. By increasing the number of beneficial bacteria in the gut, resistant starch acts as a prebiotic. The number of probiotic bacteria in the gut may also rise as a result. To preserve the health of the gut and the entire microbiome, these particularly beneficial bacteria perform essential functions. Green bananas are abundant in it. Packed full of inulin and fructooligosaccharides (FOS), particularly red onions with added antioxidants, it combats pathogens and encourages the growth of Bifidobacteria. Delicious inulin (~5% by raw weight) that helps with digestion, blood sugar regulation, and gut health. Pectin, a soluble fibre, is abundant in apples. This prebiotic promotes heart health, reduces inflammation, and improves digestion while increasing good bacteria. The sources of beta-glucans and resistant starches are barley and oats. Associated with promoting healthy bacteria and reducing LDL cholesterol. Approximately 4-5% fructan fibre is provided by wheat bran and whole-wheat flour. As prebiotics, food sources such as chicory root, Jerusalem artichokes, dandelion greens, and legumes (beans, lentils, and chickpeas) contain resistant starch, oligosaccharides, polyphenols, and GOS. Excellent for promoting gut diversity, fibre, and proteins. Prebiotics are also found in jicama, and traditional diets use yacon and burdock roots, which provide inulin and FOS. Nuts, seeds (chia, flaxseed), avocado, and cocoa all contain prebiotic fibres like gums and resistant starch. Seaweed: Polysaccharides are a new prebiotic source [12].

Figure 1: Natural sources of prebiotics

Postbiotics

Derived from the fermentation of probiotic bacteria, postbiotics are linked to several health benefits, such as better immune regulation, better gut health, and possible disease prevention. The fermentation of probiotic bacteria produces bioactive compounds known as postbiotics. They are thought to have health benefits because they can improve immune function, regulate gut health, and have antioxidant effects [1]. Postbiotics can affect the composition of the gut microbiota, lower intestinal inflammation, and boost the activity of antioxidant enzymes. They have also been shown to have antimicrobial qualities, which lowers the quantity of harmful bacteria. Furthermore, postbiotics have demonstrated antioxidant properties that help reduce oxidative stress and enhance general health, especially in diseases like diabetes and metabolic disorders. Additionally, studies have shown that postbiotics can contribute to better food quality by boosting the texture, moisture content, and cheese yield. By affecting gut microbiota and liver metabolism, postbiotics may also help prevent non-alcoholic fatty liver disease, according to some research [1].

Synbiotics

A combination of probiotics and prebiotics, synbiotics are designed to enhance the benefits of each component. Probiotics grow and colonise the intestinal tract with the help of prebiotics, which serve as their "food". In the gastrointestinal system, this cooperative relationship produces a more favourable microecological environment [3]. Synbiotics may be useful in the treatment of diabetes and obesity, according to clinical research [3]. Probiotic efficacy is believed to be increased by preventing inactivation when probiotics and prebiotics are administered together in synbiotics, particularly in unfavourable environments. The goal of this integrated approach is to improve therapeutic outcomes for metabolic disorders by optimising the host's beneficial microorganisms' performance [3]. Additionally, they have antioxidant activity, which is good for overall health and especially for treating metabolic disorders [1]. It also helps fight oxidative stress. Additionally, by enhancing general antioxidant capacity and favorably influencing glycemic control and inflammatory biomarkers, synbiotics have demonstrated advantages in diabetic hemodialysis patients. In pregnant women with gestational diabetes mellitus, synbiotic supplementation has been linked to improvements in oxidative stress and inflammatory markers as well as a lower atherogenic index of plasma, suggesting a protective impact against cardiovascular disease risk factors [1]. Additional investigation into the effects of synbiotics on obese patients revealed improved inflammatory markers in the faeces. These results imply that by altering the gut microbiota and lowering inflammation, synbiotics have potential for treating medical conditions [1].

Dysbiosis

Through the modulation of gene expression, which results in the downregulation of proinflammatory markers, SCFAs have an impact on immune system regulation and the equilibrium between proinflammatory and anti-inflammatory responses [3]. Anti-inflammatory properties and signalling modulation via G protein-coupled receptors (GPCRs) are the main ways that SCFAs affect metabolic health. [3]. GPCR activation can affect peripheral tissues' metabolism of substrates and energy, affect the release of inflammatory cytokines, and boost the production of important gut peptides. Numerous substances produced by gut bacteria that are derived from food help to induce metabolic changes [13]. Butyric acid, a substance produced by prebiotics, can alter the pH of the intestine from 6.5 to 5.5, thereby changing the environment of the gut microbiome. An imbalance in the structure and function of the gut microbiota and their metabolites, known as dysbiosis, can be brought on by changes in dietary composition, a lack of physical activity, disrupted circadian rhythms, psychological stress, and ageing [7], and other factors. The intestinal barrier may be compromised, metabolic diseases may arise, and immunological system dysregulation may result from dysbiosis. The ensuing impaired intestinal barrier function is a contributing factor to glucolipid metabolic disorders and systemic metabolic inflammation [14].

Effects of Prebiotics and Probiotics on Gut Flora

With thousands of genes devoted to the digestion of complex carbohydrates, the gut microbiota is especially skilled at breaking down plant components. The gut microbiota ferments and produces proteins, hosts bile acids, provides the body with essential vitamins, and metabolises xenobiotics in addition to glycans. The vast lymphoid tissue that makes up the majority of the body's immune cells is linked to the colonic epithelium and is always aware of the commensal gut microbiota. To trigger an immune response, the immune receptors on intestinal epithelial or dendritic cells examine the microbial structures known as "pathogen recognition patterns". The gut microbiota is kept in a healthy homeostatic state under typical physiological circumstances (i.e. maintains a healthy local gut immunological interaction with the host (eubiosis). Furthermore, several studies have demonstrated how certain bacterial phylotypes can lessen the severity of inflammatory diseases and stimulate advantageous immune responses. In this instance, Bifidobacteria and Lactobacilli species reduce intestinal inflammation and metabolic abnormalities in obesity and ulcerative colitis. Some probiotic strains, such as L. plantarum WCFS1, reduce plasma proinflammatory cytokine levels, thereby improving inflammation. Other pertinent microorganisms, which are regarded as next-generation probiotics, such as Muciniphila, B. thetaiotaomicron, as well as F. Prausnitzii, have been linked to positive effects on the host and are also intricately interacting with the immune system [7].

Effect of Polyphenols on Gut Microbiota

In several in vitro investigations, it has been demonstrated that polyphenols (a kind of prebiotic) directly affect beneficial bacteria in pure culture. Specifically, numerous strains of Lactobacillus, Lactiplantibacillus, and Lacticaseibacillus grow faster when cultured with purified polyphenols, especially many strains of the genus *Lacticaseibacillus, Lactiplantibacillus* and *Lactobacillus*. Polyphenols also promote Bifidobacteria strains in vitro. Both Lactobacilli and Bifidobacteria have been shown to have beneficial effects on health, and several species are known as probiotics with known modes of action [7]. There are some mechanisms of action by which polyphenols promote bacterial growth that have been described [7] [10]. Polyphenols can act as electronic acceptors (as with hydroxycinnamic acids), provide carbon sources (following microbial deglycosylation), or produce proton motive forces during their metabolism (as with gallic acid). Thus, determining the gut microbiota's composition and functional contribution is of particular interest to evaluate how they enhance the host's health. The development of microbiota-based treatments, including non-pharmaceutical interventions like microbial metabolites, live microbes (probiotics and fermented foods), or dietary functional ingredients (prebiotics), depends critically on this knowledge [7].

Gut Microbiome and SCFAs

The gut is home to an extensive microbial community, and these microorganisms can influence organs such as the liver and adipose tissue. In addition, these microbes safeguard the enterocytes by competing for nutrients and receptor-binding sites, preventing pathogens from adhering to the mucus layer. In addition, the production of organic acids, hydrogen peroxide, and bacteriocins serves as antimicrobial agents against pathogenic bacteria. The microbial fermentation of dietary fibre, or complex carbohydrates, produces the SCFAs (acetate, propionate, and butyrate) in the gut lumen, where they perform a variety of physiological roles. These fatty acids can reach different tissues by entering the bloodstream or being absorbed by enterocytes. In addition to providing energy, they are essential for regulating immune and anti-inflammatory pathways. In particular, it has been reported that SCFAs suppress the proinflammatory cytokines IL-1β and TNF-α. Additionally, they support the production of mucus and preserve the integrity of the intestinal barrier, both of which are essential for gut health. Lachnospira, Lactobacillus, Akkermansia, Bifidobacterium, Roseburia, Ruminococcus, Faecalibacterium, Clostridium, and Dorea are important genera associated with the production of SCFA.

Prebiotics and probiotics are powerful modulators of the gut flora, with the potential to mitigate metabolic disorders. [13].

Interaction between SCFAs and Gut Microbiota

One of the major components of the intestinal ecosystem, the gut microbiota is a major contributor to human health. It is involved in human health by preventing pathogens, shaping and maturing immunity, controlling metabolic intake, and absorbing nutrients and drugs [15].

The main end products of bacterial fermentation are short-chain fatty acids (SCFAs). These compounds are synthesised by anaerobic microorganisms predominantly through the metabolism of protein, peptide, oligosaccharide, glycoprotein precursors, polysaccharides, and carbohydrates [16]. SCFAs exert their influence on health via three principal mechanisms: the inhibition of histone deacetylase (HDAC) activity, the activation of specific fatty acid-sensing G protein-coupled receptors (GPCRs), and the subsequent anti-inflammatory effects in both local tissues and peripheral systems that arise from the first two mechanisms. Incipient evidence indicates that SCFAs play a significant physiological role across multiple organs, including the pancreas, liver, and adipose tissue [16].

The restoration of the levels of short-chain fatty acids (SCFAs), microbial metabolites that are essential for human health, is one of the most relevant therapeutic pathways of microbiome modulation. Bacteria that produce SCFAs primarily from the breakdown of non-digestible polysaccharides, such as resistant starches and dietary fibres, are found in the intestinal microbiota. It's worth mentioning that the concentration of short-chain fatty acids (SCFAs) fluctuates over our lifetime, and these variations appear to be related to the composition of our gut microbiome, which also changes as we age. Studies conducted in vitro indicate that *Bifidobacterium* that produces acetate may offer

protection against bacterial infections, similar to what has been seen with pathogenic E. coli. Interestingly, the acetate that is produced promotes the growth of bacteria that produce propionate and butyrate, while butyrate promotes the growth of Bifidobacterium. This results in a cross-feeding between bacteria that produce SCFA. Acetate, propionate, butyrate, and the SCFAs found in the gut are all impacted by these age-related alterations in the human gut microbiota. Moreover, the bacteria that produce butyrate are the most relevant because it has the biggest physiological impact of the three main SCFAs. Acetoacetyl-CoA is produced when two molecules of acetyl-CoA condense to form butyrate, which is subsequently progressively reduced to butyryl-CoA. The enzymes that next transform butyryl-CoA into butyrate are butyryl-CoA: acetate CoA-transferase or phosphotransbutyrylase and butyrate kinase. To keep the gut environment healthy, butyrate-producing microbial communities are necessary. These communities are essential for preventing other bacteria, especially dangerous pathogens, from entering and establishing themselves. For colonocytes to produce energy and increase oxygen consumption by the epithelium, these bacteria must produce butyrate. This helps maintain an anaerobic gut environment that is harsh to opportunistic aerobic pathogens like *Salmonella* and *E. coli.* There are three ways that sugars can ferment to produce a propionate. Using a pathway that turns succinyl-CoA into propionate with the aid of vitamin B12, the succinate pathway breaks down hexoses and pentoses. Meanwhile, the acrylate pathway breaks down lactate into propionate and, via the propanediol pathway, deoxy sugars are processed, such as rhamnose and fucose. The majority of bacteria using the succinate route are members of the Bacteroidetes (Prevotella spp. as well as the Negativicutes classes, which include Veillonella spp and Phascolarctobacterium succinatutens. The bacteria that have been studied the most in the acrylate route are *Coprococcus* spp. Belonging to the family Lachnospiraceae. It is amazing to note that, depending on the original substrate, some of the members of this genus can also produce butyrate. Lastly, Roseburia inilivorans and Blautia species, both of which are members of the Lachnospiraceae family, have been found to exhibit propanediol-dependent metabolic pathways [15].

Probiotics

Originally used by Elie Metchnikoff in 1900, the term probiotic derives from the Greek terms "pro" and "bios", meaning "for life", and refers to the intake of fermented milk, which comprised helpful bacteria, that resulted in Bulgarian farmers' longevity. Probiotics were first described by Lilly in 1965 as compounds produced by one bacterium that promote the growth of another. Today, the most widely accepted definition is that issued by the Food and Agriculture Organisation of the United Nations (FAO) and the World Health Organisation (WHO) in 2001, which defined probiotics as live microorganisms that, when administered in enough quantities, provide health benefits to the host. These probiotics promote the host's resistance against infections while also supplying vital nutrients by breaking down indigestible dietary carbohydrates. Lactobacillus, Bifidobacterium, Enterococcus, Streptococcus, and Saccharomyces cerevisiae are some of the bacteria and yeast groups that are used as probiotics. Probiotics' health effects vary depending on the strains in each genus [17] [18].

Prebiotics, first described by Glenn Gibson and Marcel Roberfroid in 1995, are nondigestible food elements which enhance the growth or activity of beneficial bacteria in the colon. In 2021, the International Scientific Society for Probiotics and Prebiotics (ISAPP) defined dietary prebiotics as fermentation elements which improve the host's health by modulating the gut microbiota. Prebiotics selectively promote the growth and activity of beneficial gut bacteria such as Bifidobacteria and Lactobacilli, while inhibiting the pathogenic bacteria and maintaining a healthy gut microbiota. They also supply energy, regulate the body’s immune system, optimise gut barrier function, and affect brain function [18].

Effect of Prebiotics on Local Immunity and T-Cells of the Gut

Maintenance of immunological homeostasis and defence against infections depends on a dynamic and reciprocal relationship between the immune system and the gut microbiota. The immune system is constantly interacting with the gut microbiota, which has an impact on its growth and function. By helping to educate immune cells and encourage the development of immune tolerance, gut bacteria help prevent beneficial immunological reactions to harmless substances (like

food antigens). This stage is essential for preventing allergies or autoimmune disorders. The gut microbiota uses a variety of signalling pathways to interact with immune cells, such as T cells, B cells, and dendritic cells. Numerous mechanisms are employed by the gut microbiota to regulate the immune system. One important process is the synthesis of metabolites by certain bacteria, such as short-chain fatty acids (SCFAs), which are the fermentation products of prebiotics. Furthermore, immune cells, especially T cells, are trained and educated to react to antigens adequately by the gut microbiota. Maintaining immunological homeostasis and avoiding excessive inflammation depends on this process [19].

Role of Gut-Associated Lymphoid Tissue (GALT) in Immune Education

Gut-associated lymphoid tissue (GALT) comprises organised lymphoid structures including the vermiform appendix, Peyer's patches located in the terminal ileum, isolated lymphoid follicles within the colon, and follicles in the rectum, all of which exhibit comparable structural characteristics. These tissues are integrally connected both structurally and functionally to the follicle-associated epithelium, which plays an active role in sampling luminal contents of the gastrointestinal tract and transporting them to the underlying lymphoid region known as the sub-epithelial dome [20]. The stimulation of lymphocytes within the gut-associated lymphoid tissue (GALT) culminates in the production of precursors for effector cells, encompassing cytokine-secreting T lymphocytes and immunoglobulin A (IgA) plasma cells, which subsequently migrate from the tissue through lymphatic vessels, ultimately entering the circulatory system. The IgA plasma cells produced through this mechanism will exhibit binding specificity towards intestinal microbiota [20].

Microfold (M) cells located above Peyer's patches facilitate the sampling of luminal antigens through transcytosis, subsequently delivering these antigens to resident antigen-presenting cells (APCs), including dendritic cells and macrophages. These APCs process microbial and dietary antigens and either migrate to mesenteric lymph nodes (mLNs) or engage with naïve T and B lymphocytes within Peyer's patches (PPs) and isolated lymphoid follicles (ILFs). Depending on the antigenic milieu, cytokine environment, and signals received from the microbiota upon encountering antigen within the gut-associated lymphoid tissue (GALT), naive CD4+ T cells develop into several subsets, including regulatory T cells (Tregs), T helper 1 (Th1), Th2, Th17, and T follicular helper (Tfh) cells, Tregs induced within GALT, primarily through dendritic cell–derived transforming growth factor-beta (TGF-β) and retinoic acid, play a pivotal role in establishing oral tolerance to dietary antigens and commensal microorganisms. Both T cell–dependent and T cell–independent immunoglobulin A (IgA) responses are initiated within Peyer's patches and ILFs. Commensal bacteria, notably segmented filamentous bacteria (SFB), promote germinal centre formation and immunoglobulin class switching toward high-affinity IgA, thereby contributing to mucosal immune homeostasis [21]. GALT functions as a specialised microenvironment for the activation and differentiation of regulatory lymphocyte populations, including T follicular regulatory cells and regulatory B cells (Bregs), which produce interleukin-10 (IL-10). This cytokine is critical for maintaining immunological equilibrium. Additionally, short-chain fatty acids (SCFAs), such as butyrate produced by gut microbiota, further facilitate the induction of Tregs and Bregs [21]. Collectively, GALT serves as a central immunological education site, orchestrating antigen sampling, directing adaptive T and B cell differentiation, imprinting tissue-specific homing characteristics, and modulating immune tolerance or protective responses following microbial and dietary stimuli.

Function of GALT in Immune Homeostasis

The human gastrointestinal tract harbours a complex and diverse microbiota, consisting of approximately 40 trillion microorganisms, which confer critical benefits to human health. These benefits include the inhibition of pathogenic colonisation, detoxification of bile acids, metabolism of non-digestible carbohydrates, and the production of essential metabolites vital for host well-being. The intestinal immune system is required to maintain a delicate equilibrium by tolerating these commensal microbes while simultaneously mounting effective immune responses against invading pathogens. Disruption of this homeostatic balance can result in intestinal disorders, notably inflammatory bowel diseases (IBD), such as Crohn's disease (CD) and ulcerative colitis (UC) [21]. The intestinal immune regions are generally classified as

inductive sites, such as the gut-associated lymphoid tissues (GALT), where adaptive immune cells initiate priming and differentiation, and the mesenteric lymph nodes (MLN), which drain the intestine. The intestinal lamina propria (LP) and epithelium, where primed adaptive immune cells are located and maintained in order to improve barrier integrity and protective immunity, are the effector sites.

Human Peyer's patches (PP) comprise tens to hundreds of individual follicles and are located on the anti-mesenteric border along the entire length of the small intestine. As they approach the terminal ileum, their density steadily rises until they all come together at the ileocecal junction to create a lymphoid ring. PPs serve as specialised sites for adaptive immune priming and encompass distinct microanatomical niches that facilitate the efficient initiation and amplification of immune responses [21]. The luminal surface of PP is covered by a specialised follicle-associated epithelium (FAE), characterised by a sparse mucus layer and a high concentration of specialised epithelial cells termed microfold (M) cells. In murine models, M cells have been demonstrated to play a critical role in transcytosing luminal particulate antigens—including bacterial, viral, and secretory IgA (SIgA)-bound antigens—into the PP parenchyma. Furthermore, PP is implicated in human B cell maturation processes, notably by supporting the clonal expansion and somatic diversification of systemic marginal zone B cell subsets. It has also been proposed that cellular trafficking through PP contributes to the maturation of immature transitional B cells and may be involved in the deletion of autoreactive B cell clones [21].

Murine isolated lymphoid follicles (ILF) are considered a significant source of T-cell-independent IgA responses. A comparable function has been suggested for human ILF, based on their composition, which includes dendritic cells and macrophages expressing A proliferation-inducing ligand (APRIL), as well as B cells expressing the Transmembrane activator and CAML interactor (TACI) [21]. Nevertheless, human intestinal IgA+ clones exhibit extensive somatic hypermutation, implying that T-cell-independent IgA differentiation in humans is likely limited. Furthermore, the presence of T follicular helper (Tfh) cells, follicular dendritic cells62, CD40 ligand (CD40L) expression, and elevated levels of activation-induced deaminase (AID)—the enzyme essential for somatic hypermutation in germinal centre B cells—indicate that human ILF primarily function as critical sites for the initiation of T-cell-dependent B cell responses. Recent research on germinal centre B cell populations indicates that IgA1, IgA2, IgG, and IgM B cell responses may be supported by isolated lymphoid follicles (ILF) [21].

Immunomodulatory Effects of Prebiotics on T-Cells

Prebiotics, probiotics, and synbiotics are recognised for their significant positive impacts on human health, primarily through their capacity to alter the composition and functionality of the gut mucosa, gut microbiota, and immune system. Owing to these beneficial properties, prebiotics, probiotics, and synbiotics have been explored as potential preventive and therapeutic interventions for a range of diseases, including cancer, diabetes, allergies, and autoimmune disorders [22].

Prebiotics and probiotics can modulate both the gut and systemic immune systems, particularly influencing the host's innate and adaptive immune responses. This modulation encompasses the stimulation of regulatory T and B cells (Treg and Breg), as well as Th1, Th2, Th17, and humoral immune responses. While probiotics exert direct effects on these immune components, prebiotics influences them indirectly through alterations in the microbiota and also directly by interacting with various elements of the innate and adaptive immune systems independently of the microbiota [23].

Notably, antenatal supplementation with prebiotics has been shown to modulate B cell function prenatally. Experimental studies in murine models demonstrated that gestational administration of galacto-oligosaccharides (GOS) and inulin to pregnant dams increased the frequency of regulatory B cells (Breg) expressing CD9 in both the uterus and placenta, as well as Breg expressing CD25 in the placenta, relative to control diet groups. This prebiotic-induced tolerogenic milieu within feto-maternal tissues was also observed in the fetus, evidenced by elevated frequencies of CD9+ Breg in fetal bone marrow and CD25+ Breg in the fetal intestine. Importantly, CD9+ Breg cells were found to secrete interleukin-10 (IL-10), underscoring

their immunoregulatory function. Additionally, giving prebiotics during pregnancy can alter the expression of genes involved in B cell development, which may improve B cell ontogeny in the gut. This process facilitates the maternal transmission of specific B cell-mediated immune factors to the offspring, promoting the establishment of a tolerogenic B cell immune imprinting in both the fetus and neonate.

Prebiotic supplementation during adulthood appears to exert minimal impact on the frequency of peripheral B cells in humans; however, it has been shown to increase the frequency of immunoglobulin-secreting B cells within secondary lymphoid organs in animal models. Evidence suggests that early-life prebiotic supplementation modulates B cell populations both within gut-associated lymphoid tissue (GALT) and peripheral compartments, whereas supplementation during adulthood predominantly affects B cells locally within the intestinal environment. Several studies conducted on rat models have examined the impact of prebiotic supplementation over a period of several weeks on immunoglobulin secretion by plasma B cells. One such study demonstrated that administering lactulose to rats for three weeks resulted in increased secretion of IgA and a higher number of IgA-positive B cells within gut-associated lymphoid tissue (GALT). Additional research indicated that rats receiving prebiotics such as pectin, glucomannan, konjac mannan, or chitosan exhibited significantly elevated serum concentrations of IgA, IgM, and IgG, alongside an increased frequency of IgA-, IgM-, and IgG-producing plasma B cells in mesenteric lymph nodes (MLN) and the spleen, compared to control diet groups. Furthermore, faecal IgA levels were found to be higher in rats supplemented with fructooligosaccharides (FOS) relative to those supplemented with inulin, oligofructose, or no prebiotics. It was also demonstrated that FOS supplementation enhanced the proportion of B cells in Peyer's patches (PP) and their IgA secretion in a dose-dependent manner [22].

SCFAs and Immune Regulation

Short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, are critical mediators of the gut microbiome's influence on both local and systemic immune responses. Numerous human and animal studies have demonstrated that butyrate within the intestinal environment suppresses the production of proinflammatory cytokines such as IFN-γ, TNF-α, IL-6, and IL-8, while simultaneously promoting the expression of anti-inflammatory cytokines, including IL-10 and TGF-β [24] Butyrate's anti-inflammatory properties have been well-established, primarily through its inhibition of the NF-κB signalling pathway, as evidenced by various in vitro and in vivo investigations [25]. The mechanism underlying butyrate's suppression of NF-κB-mediated inflammatory signalling is thought to involve the reduction of reactive oxygen species via enhancement of the antioxidant system. Furthermore, butyrate has been shown to stimulate the production of antimicrobial peptides (AMPs) by intestinal epithelial cells through its interaction with the G protein-coupled receptor GPR43, activation of the MEK/ERK and JNK signalling pathways, and modulation of cellular proliferation processes. Additionally, butyrate enhances AMP secretion by macrophages [25]. Through its function as a histone deacetylase 3 (HDAC3) inhibitor, butyrate facilitates the differentiation of monocytes into macrophages and induces the expression of AMP-related genes such as S100A8 and S100A9, as well as calprotectin, without eliciting an increase in proinflammatory cytokine production. This impact enhances bactericidal activity both in vitro and in vivo. Moreover, both butyrate and propionate have been found to induce apoptosis in activated and non-activated neutrophils via caspase activation, a process that appears to be independent of SCFA receptor pathways involving Gαi/o and Gαq proteins.

Butyrate

Through two key mechanisms, butyrate is essential to the adaptive immune response: by influencing monocyte-derived dendritic cells (DCs) and by having direct effects on T lymphocytes. Within the intestinal environment, DCs are pivotal in initiating adaptive immune responses in naïve T cells, thereby serving as a crucial link between innate and adaptive immunity. Immature DCs contribute to the maintenance of immune tolerance, whereas mature DCs are capable of activating immune responses [26] Butyrate therapy seems to dramatically affect human monocyte-derived DC differentiation, maturation, and ability to activate T lymphocytes [26] Many studies have also examined the modulating effects of butyrate on cytokine production by DCs; these studies have demonstrated that butyrate inhibits the generation of the pro-inflammatory

cytokine interleukin-12 (IL-12) following DC stimulation. Furthermore, butyrate-conditioned DCs markedly enhance the production of interleukin-10 (IL-10) by promoting the priming of Type-1 regulatory T cells (Tr1). Through the activation of the G protein-coupled receptor 109a (GPR109a) in macrophages and DCs, butyrate plays a vital role in regulating the balance between pro-inflammatory and anti-inflammatory T lymphocytes. Specifically, butyrate facilitates the conversion of naïve T cells into FoxP3-positive regulatory T cells while concurrently suppressing interferon-gamma (IFN-γ)-producing T cells [25].

Butyrate, through its histone deacetylase (HDAC) inhibitory activity, leads to increased acetylation of the Foxp3 protein, thereby elevating Foxp3 protein levels in regulatory T (Treg) cell cultures. Beyond its direct impact on CD4+ T lymphocytes, butyrate also modulated gene expression in CD8+ cytotoxic T lymphocytes, influencing the expression of effector molecules such as interferon-gamma (IFN-γ) in a dose-dependent manner [25]. Moreover, by reprogramming mitochondrial metabolic flux inside CD8+ memory T cells (Tmem), butyrate improved their memory potential and recall capacity. Additionally, butyrate has been shown to induce intrinsic epigenetic modifications in B cells via its HDAC inhibitory effect, promoting class-switch DNA recombination and consequently suppressing autoimmune responses through modulation of the antibody response [25].

Acetate and Propionate

Microbiota-derived short-chain fatty acids, specifically acetate and propionate, play pivotal immunomodulatory roles that influence adaptive immunity through signalling via G-protein-coupled receptors (GPCRs) and epigenetic mechanisms. Propionate also has potent inhibitory effects on the production of pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α), in monocytes, dendritic cells (DCs), and T lymphocytes [27]. In contrast, acetate demonstrates comparatively limited efficacy in these cell types, with the notable exception of its ability to attenuate interferon-alpha (IFN-α) production, potentially mediated by upregulated expression of GPR43 on plasmacytoid DCs. Propionate, in particular, facilitates the differentiation of regulatory T cells (Tregs) through modulation of DC function. Similar to butyrate, propionate enhances the expression of indoleamine 2,3-dioxygenase 1 (IDO1) and aldehyde dehydrogenase 1A2 in DCs, thereby promoting the conversion of $FoxP3^+$ Tregs and suppressing the induction of inflammatory interferon-gamma (IFN-γ) producing T cells [27]. y Acetate uniquely influences T cell survival by augmenting α-tubulin acetylation and upregulating CD30 expression, which stabilises microtubule structures and enhances anti-apoptotic BCL-2 signalling pathways, ultimately improving T cell persistence. Acetate and propionate, taken together, aid in the control of adaptive immunity by inhibiting the release of pro-inflammatory cytokines, fostering immunoregulatory T cell populations, and improving T cell survival and function through mechanisms involving GPCR activation—particularly GPR43 and GPR41—and HDAC inhibition [27].

Challenges and Future Perspectives

Despite mounting evidence of prebiotics' potential in modulating gut microbiota and adaptive immunity, current literature exhibits important limitations. Most human studies are short-term, small, and heterogeneous in design, varying in dose, duration, study population and prebiotic type, impeding comparability and meta-analysis. Many trials measure microbiota shifts via faecal samples, which are proxies rather than direct measures of in situ fermentation or metabolite flux along the gastrointestinal tract. Additionally, inter-individual variability due to baseline microbiota, diet, age, geography, genetics or metabolic phenotype contributes to responder vs. non-responder effects that remain poorly understood [28] Moreover, validated biomarkers linking microbiota modulation with physiological outcomes (e.g., immune markers, inflammation, cognitive function) are rarely included, and mechanistic pathways are often inferred rather than demonstrated [29]

To move the field forward, long-term randomised controlled trials are needed. These should enrol larger and more diverse cohorts, use standardised protocols for prebiotic dosing and analytical methods, and include multi-omic analyses coupled with clinical endpoints. Trials must establish clear cause effect relationships between selective microbial shifts, SCFA production and host immune or metabolic outcomes. The regulatory

landscape for prebiotics remains fragmented. In the European Union, the term "prebiotic" is not authorised as a health claim under Regulation (EC) No 1924/2006 unless accompanied by an EFSA-approved specific claim. Only substances with strong mechanistic and clinical evidence—like chicory-derived inulin for bowel function—have attained approved claims, while most prebiotic terms remain prohibited or implied general claims. Meanwhile, the EU's ILSI/ISAPP Roadmap recommends a rigorous dossier that demonstrates chemical definition, selective microbiota modulation, physiological benefit, and cause-and-effect documentation across multiple trials.

In contrast, in the U.S., Canada, Japan, and other countries, dietary supplements containing prebiotics may carry structure-function claims under DSHEA or equivalent regulations, provided they do not promise disease treatment and are supported by credible scientific evidence. Despite this broader flexibility, regulators in these regions have still issued warnings to companies making unsubstantiated health claims, underscoring the importance of scientific rigour. Looking ahead, harmonisation of scientific and regulatory frameworks, especially on standardised trial design, biomarker validation, and mechanism elucidation, will be essential to enable credible prebiotic health claims and guide clinical translation [30].

Conclusion

Prebiotics are pivotal for gut health and general well-being. Their capacity to selectively increase the growth of healthy gut bacteria, including Bifidobacteria and Lactobacilli, helps to improve digestion, boost immunological function, and lower the risk of numerous gastrointestinal illnesses. Current research indicates that prebiotics may have an impact on metabolic health, mental health, and the avoidance of chronic diseases. Despite these advantages, more long-term human research is needed to better understand individual reactions, appropriate dosages, and their effects on different populations. Next-generation prebiotics and tailored nutrition techniques may have broader implications in clinical and functional health settings. Integrating prebiotics into the daily diet, whether through whole foods or supplementation, is a promising, natural method for supporting and improving the human microbiome. Synbiotics and postbiotics make these benefits even better. Early-life prebiotic exposure plays a significant role in imprinting long-term immunological tolerance, according to evidence. Future studies should focus on clarifying mechanisms, optimising formulations, and identifying responder subgroups for customised therapeutic application, despite the potential of treating metabolic, inflammatory, and gastrointestinal illnesses.

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