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*Review*

# How Do Diet Patterns, Single Foods, Prebiotics and Probiotics Impact Gut Microbiota?

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**Abstract:** The human gastrointestinal tract hosts a complex and dynamic population of commensal bacterial species, which have coevolved with the host, generating a symbiotic relationship. Some compounds present in foods, such as polyols, prebiotic fibers, or phenolic compounds, are poorly metabolized and absorbed by the host before the transformation guided by the colonic microbiota. By influencing gut microbiota, diet plays a fundamental role in understanding the beneficial effects of the gut microbiota on the host, including its long-term metabolism. The idea that probiotics can act not only by influencing the colonizing microbiota opens the door to a wider range of probiotic possibilities, encouraging innovation in the field. Furthermore, it has been shown both that some probiotics increase phagocytosis or the activity of natural killer cells. Current prebiotics are mainly based on carbohydrates, but other substances, such as polyphenols and polyunsaturated fatty acids, could exert prebiotic effects. A prebiotic substance has been defined as 'a substrate that is selectively used by host microorganisms that confer a health benefit', and so can interact with the gut microbiota through competition for nutrients, antagonism, cross-feeding, and support for microbiota stability. Influencing its composition in terms of richness and diversity, food components have a key impact on the intestinal microbiota. Eating habits can strongly influence the composition of the intestinal microbiota. A healthy intestinal microbiota is essential for maintaining general health, and diet is one of the major modulators of this fascinating world of microorganisms. This must give us one more reason to adopt a healthy lifestyle.

**Keywords:** diet; prebiotics; probiotics; microbiota; healthy intestine; microorganisms



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## 1. Introduction

An intestine with a healthy microbiota produces beneficial effects for the entire body, and nutrition is one of the key factors for maintaining this synergistic relationship. In this review, we wanted to ask what can modify the intestinal microbiota, what is the role of diet, fiber, prebiotics, and probiotics, and are there specific dietary patterns or foods that can improve the health of the intestinal microbiota?

### *1.1. The Human Intestinal Microbiota*

The human gastrointestinal tract hosts a complex and dynamic population of commensal bacterial species, which have coevolved with the host, generating a symbiotic relationship. The number of microorganisms that inhabit the gastrointestinal tract is estimated to exceed one hundred trillion microbial cells per gram, of almost two thousand different species [1]. As a result of the vast number of bacterial cells in the body, the host and the microorganisms that inhabit it are often referred to as the "superorganism" [2]. Each individual has its own bacterial fingerprint, i.e., its own species profile, different from that of other individuals. Interindividual variability is due to childhood transitions,

the use of antibiotics, as well as lifestyle, dietary and cultural habits [3]. However, there is a "core" of at least 57 species common to all individuals. The dominant gastrointestinal microbial phyla are *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, *Fusobacteria*, and *Verrucomicrobia*, with the two phyla *Firmicutes* and *Bacteroidetes* accounting for 90% of the intestinal microbiota [4]. The richest phylum is that of *Firmicutes* (Gram-positive), which includes 46–58% of the total bacteria. It is made up of more than 200 different genera, such as *Lactobacillus*, *Bacillus*, *Clostridium*, *Enterococcus,* and *Ruminococcus*. The phylum *Bacteroidetes* (Gram-negative) comprises approximately 30–40% of the bacteria present in the intestinal microbiota and is represented in particular by the genera *Bacteroides* and *Prevotella*. The *Actinobacteria* phylum is proportionally less abundant (3–7%) and is mainly represented by the genus *Bifidobacterium*. Although less than 1%, the methanogenic *Archaea Methanobrevibacter smithii* and *Methanosphaera stadtmanae* [4] are also present. A rich and diverse microbial community leads to a well-balanced and healthy gut microbiota composition. On the contrary, an altered intestinal bacterial composition can derive from various factors, such as drugs, infections, ageing, lifestyle, surgery, and poor diet. Dysbiosis has been associated with the pathogenesis of many inflammatory diseases and infections [3].

The density and composition of microbial communities differ significantly along the gastrointestinal tract. The stomach and small intestine harbor a relatively low number of organisms due to growth inhibition derived primarily from bile salts, pancreatic exocrine secretions, and frequent peristalsis. In the colon, on the other hand, with ecological niches rich in substrates, being pH neutral, and with redox potential, microorganisms reach levels of $10^{11}$–$10^{12}$ cells per gram of intestinal content; predominantly anaerobic, such as Bacteroides, Parabacteroides, Bifidobacterium, Lactobacillus, and Clostridium [5].

The normal interaction between intestinal microbes and their human host is a symbiotic relationship, beneficial to both: the host provides a nutrient-rich habitat, and the microbiota provides useful elements for its health [4]. The intestinal microbiota is involved in essential functions for maintaining health, such as the development of the immune system, proper intestinal function in digestion, maintenance of the integrity of the intestinal barrier, metabolic homeostasis, production of vitamins, synthesis of amino acids and neurotransmitters, bile acid metabolism, protective functions [6].

There is a great deal of evidence of the structural activity of the microbiota in favor of the gastrointestinal tract, for example: *Bacteroides thetaiotaomicron* induces the expression of the small proline-rich protein 2A (sprr2A), necessary for the maintenance of the desmosomes of the epithelial villi; *Lactobacillus rhamnosus* produces two soluble proteins (p40 and p75) that can prevent apoptosis of epithelial cell apoptosis; *Akkermansia muciniphilia* can increase the levels of endocannabinoids that control barrier function by decreasing endotoxemia.

Regarding protective functions, a peculiar activity of the microbiota is that of competing with potentially dangerous and pathogenic bacteria, through the production of substances capable of inactivating them [7]; the alteration of intestinal pH [8]; the removal of nutrients [9], and finally maintenance of the integrity of the mucous barrier, formed by bacteria, mucus, and epithelial cells [10].

The metabolic functions of the intestinal microbiota are performed through the production of a large number of metabolites, most of which are products of bacterial fermentation.

Our colon receives digested material (which will then be transported to the left colon and excreted with the feces), and undigested material, such as resistant starch, dietary fibers, simple sugars, alcohols, proteins, and endogenous substrates, i.e., flaked epithelial cells, intestinal mucus, and enzymes.

These substrates are fermented by the microbiota, especially *Bacteroides*, *Roseburia*, *Bifidobacterium*, *Fecalibacterium*, and *Enterobacteria*, leading to the formation of organic acids, hydrogen, ethanol, succinate, methane, $CO_2$; as well as potentially bioactive compounds useful for the host, such as short-chain fatty acids (SCFA) [4]. Having a huge enzymatic heritage available, the intestinal microbiota can be seen as a community of cells capable of cooperating in many metabolic reactions necessary for the biotransformation of foreign

molecules that we cannot easily metabolize, such as drugs, xenobiotics, polyphenols, and antibiotics [11].

Considering the ability to influence the function of distal organs and systems, in many respects the intestinal microbiota resembles an endocrine organ [12,13]. The microbiota has the ability to produce a wide range of hormone-like compounds that play an important role in regulating the activity of distal organs, including the brain [14]. The influence of the microbiota on the regulation of metabolic activity has been recognized: growing evidence suggests its involvement in glucose and weight. The microbiota is also believed to play a role in the regulation of the hypothalamic–pituitary-adrenal axis, through the production or release of neurotransmitters such as serotonin and modulation of tryptophan availability. Unlike other endocrine organs, the microbiota has intense plasticity and can alter dramatically and rapidly in response to diet.

The microbiota satisfies more important conditions than any conceptual definition of an organ since, despite the evident physical dissimilarity, it is capable not only of influencing, but also of responding to the secretions of other organs [15].

### *1.2. Relationship between Diet and the Human Intestinal Microbiota*

Some compounds present in foods, such as polyols, prebiotic fibers, or phenolic compounds, are poorly metabolized and absorbed by the host before the transformation guided by the colonic microbiota [16]. In fact, of the thousands of species that inhabit the large intestine, beneficial microorganisms are responsible for this action [17]. For the maintenance of a good state of health, the balance in the relationship between the species of beneficial, commensal, and even opportunistic microorganisms is of fundamental importance. The alteration of this balance fuels harmful pathologies, such as metabolic syndromes [18], malabsorption problems [19], or inflammatory bowel disease (IBD) [20].

By influencing gut microbiota, diet plays a fundamental role in understanding the beneficial effects of the gut microbiota on the host, including its long-term metabolism [21,22]. It has been recognized that the type of diet and eating habits are the factors that most affect the balance of the intestinal microbiota [3]. However, in several studies the efficacy of diets in the variations of the fundamental phyla of the intestinal microbiota (*Bacteroidetes* and *Firmicutes*) has been debated; in fact, it seems that this is capable of influencing the intestinal microbiota more at lower phylogenetic levels [23]. For example, an altered carbohydrate intake regimen could impact specific bacterial groups: It has been observed that adopting low carbohydrate diets has resulted in a reduction of *Bifidobacterium* spp., *Roseburia* spp. and *Eubacterium rectale*; reduction also occurred in the short-chain fatty acid (SCFA) content, mainly due to a dramatic loss of butyric acid [24]. An important contribution to the change of the intestinal microbiota populations also comes from the nature of carbohydrates, as well as from the resistance to digestion. It has been observed that the consumption of resistant starch (RS) can increase the amount of *Ruminococcus bromii*, *Roseburia,* and *E. rectale*, while resistant starch combined in a low carbohydrate high protein (WL) diet can increase *Oscillibacter valericigenes*, but can decrease the abundance of *Roseburia* and *E. rectale* [25]. Similarly, a high-fiber diet can promote the growth of the *Bifidobacterium*, *Ruminococcus*, and *Lactobacillus-Enterococcus* groups [26].

To obtain such results in microbes, the main techniques used so far have ranged from culture-dependent microbiology to FISH (fluorescent in situ hybridization) and qPCR (quantitative PCR) to NGS (Next Generation Sequencing) technologies. Furthermore, to conduct investigations on metabolites, most of the studies have achieved robust results thanks to the aid of chromatographic techniques and more recently thanks to NMR analysis [23].

### *1.3. Probiotics*

The first official definition of a "probiotic" was drawn up in 2001 by a commission mandated by the Food and Agriculture Organization of the United Nations, after the Argentine government requested in 2000 that FAO form a group of experts to evaluate the health and nutritional properties of probiotics in foods. In this way, we wanted to

obtain an international and unique recognition of what we can define as a concept that is part of human history. The definition given was quite broad to encompass a large variety of microorganisms, hosts, benefits, target sites, and product types, thus maintaining the essence of the historical definitions offered in previous decades and establishing an important consensus base. In 2014, this concept was reaffirmed and grammatically corrected in a document drawn up by the International Scientific Association for Probiotics and Prebiotics (ISAAP) on the scope and appropriate use of the term probiotic, leading to the consensus definition of probiotics as 'live microorganisms which, administered in adequate amounts, confer a benefit on the health of the host'.

Unlike what was reported in some initial definitions, according to which probiotics work "by contributing to the intestinal microbial balance of the host" [27] or by "improving the properties of the indigenous microflora" [28], in the current shared definition of probiotics their effects not only include those mediated by the intestinal microbiota as, in fact, other types of mechanisms are known. The idea that probiotics can act not only by influencing the colonizing microbiota opens the door to a wider range of probiotic possibilities, encouraging innovation in the field [6].

Lactobacillus, Bifidobacterium, and Saccharomyces strains have a long history of safe and effective use as probiotics, while *Roseburia* spp., *Akkermansia* spp., *Propionibacterium* spp., and *Faecalibacterium* spp. show promise for the future [6]. Much of our understanding of probiotic mechanisms is based on research using human models of ex vivo, in vitro, animal or cell culture human models. Not all mechanisms have been confirmed in humans and do not exist in every probiotic strain. In fact, although multiple mechanisms are likely co-expressed in a single probiotic, the importance of any given mechanism will depend on many factors. For example, in an inflamed gut, the ability to down-regulate inflammatory mediators and increase epithelial barrier function may be more important [29,30], while the ability to increase short-chain fatty acids (SCFA) and hydration in the colon may be essential for normalizing intestinal motility [31].

The maximum expression of the beneficial effects of a probiotic can be influenced by many factors, such as the properties of the basic host microbiota [6].

It is important to emphasize that the persistence of probiotics in the intestine is related to the properties of the basic microbiota [32]. The persistence of Bifidobacterium longum subsp. longum AH1206 in the human gut was predicted by the low host abundance of *B. longum* and low levels of microbial carbohydrate utilization genes. In this study, no clinical endpoints were monitored, but long-term persistence could be a contributing property to physiological benefits [6]. However, the results of several clinical studies that did not provide for the subdivision of participants according to the basic microbiota suggest that probiotic function is not necessarily dependent on the presence of a specific basal microbiota [33,34].

Probiotic microorganisms act through a variety of means, including modulation of immune function, production of organic acids and antimicrobial compounds, interaction with resident microbiota, host interfacing, improvement of barrier integrity intestinal tract, and enzyme formation. Certainly, evidence of the cause and effect relationship of the mechanisms of action of probiotic microorganisms in human hosts has yet to be collected, but technological advances in genome sequencing and microbiota analysis, as well as surgical advances that allow in vivo sampling in real time, should help acquire new data in the coming years [6].

### *1.4. Modulation of Immune Functions*

Furthermore, it has been shown both that some probiotics increase phagocytosis or the activity of natural killer cells and interact directly with dendritic cells [35], and that the ability of some probiotics to upregulate antibody secretion, obtaining better defenses against pathogens and increasing responses to vaccines [36,37]. In addition, probiotic strains can increase levels of anti-inflammatory cytokines with implications for the reduction of colon

cancer and colitis [38]. The fimbriae, capsules, and surface structures expressed by some probiotics represent a mechanistic driver for many of these activities [6].

### *1.5. Production of Organic Acids*

Probiotic species belonging to the Lactobacillus and Bifidobacterium genera produce lactic and acetic acids as the primary end products of carbohydrate metabolism. As shown in various model systems [39], these organic acids, when produced in situ, can lower the luminal pH, discouraging the growth of pathogens. SCFAs, mainly acetic, butyric, and propionic acids, are derived from the colonic fermentation of undigested dietary fiber, undigestible carbohydrates or resistant starch. By participating in anti-inflammatory mechanisms and sending signals to numerous organs, its presence in the human body in sufficient quantities is essential for the health and well-being of the host [40]. The production of SCFA has been verified for numerous probiotics, for example: *Bifidobacterium longum SP07/3* and *Bifidobacterium bifidum MF20/5* are able to produce acetic, propionic, and lactic acid; while *Lactobacillus salivarius* spp. *salcinius JCM 1230* and *Lactobacillus agilis JCM 1048* propionic, butyric, and lactic acid [41]. The effect of oral consumption of *Lactobacillus plantarum P-8* on human intestinal microflora was also tested: after four weeks of administration, there was an increase in *Bifidobacterium* and other beneficial bacteria, while *Desulfovibrio* and other opportunistic pathogens decreased, in addition to statistically significant increases in acetate and propionate levels in all age groups tested [42]. Other scientists tested the anti-aging potential of a probiotic containing *Lactobacillus paracasei* spp. in combination with *paracasei BCRC 12188*, *Lactobacillus plantarum BCRC 12251* and *Streptococcus thermophilus BCRC 13869*. The study was carried out in mice for 12 weeks and demonstrated that long-term administration of the probiotic blend increased SCFA production, which could regulate antioxidant enzymes, inhibiting cell apoptosis and brain damage, resulting in improved memory and learning abilities in galactose-treated aged mice [43].

### *1.6. Interaction with the Intestinal Microbiota*

Probiotic strains can interact with the gut microbiota through competition for nutrients, antagonism, cross-feeding, and support of microbiota stability [44]. By producing acetate, *Bifidobacteria* can feed other members of the gut microbiota. Due to saccharolytic metabolism, which leads to the production of organic acids and the production of bacteriocins, many probiotic strains are antagonistic toward other microorganisms. Bacteriocins can be active against pathogens in many sites, including the human urinary tract and the intestines of humans and animals [45]. The strains of *B. longum AH1206* and *B. bifidum ATCC15696* are known to persist in the intestine of the newborn, although in the present case the decrease in pathogens has not been related to the production of bacteriocins [32]. The ability of some probiotic strains to enhance Helicobacter pylori may involve some inhibition of the pathogen. However, there is strong evidence that probiotics in this context reduce the adverse effects of antibiotics used in treatment [46].

### *1.7. Probiotic-Host Interactions*

Interactions of probiotic strains with host tissues are mediated by macromolecules found on the cell surface, including both protein components (such as surface layer-associated proteins, mucin-binding proteins, pili and LPxTG-binding proteins) and the non-protein components, such as lipoteichoic acid, peptidoglycan, and exopolysaccharides [6]. These structures have been shown to affect binding to intestinal and vaginal cells, mucin, and immune or dendritic cells, resulting in increased transit times and improved barrier integrity. When comparing the genome of *Lactobacillus rhamnosus GG* with that of *Lactobacillus rhamnosus GR-1*, it is possible to have an example of the different surface structures: the first microorganism uses pili to interact with the intestine, while the second has a unique group of exopolysaccharides that help vaginal activity [47].

### *1.8. Improvement of the Barrier Function*

The intestinal barrier represents a functional unit responsible for two main tasks crucial for the survival of the individual: allowing the absorption of nutrients and protecting the body from the entry of unwanted, often harmful macromolecules [3]. Various strains of *Lactobacillus* and *Bifidobacterium* probiotics are able to increase the expression of "tight junction" proteins, which bind one enterocyte to another [48]. Furthermore, in 3D models of primary small intestine cells combined with piglet immune cells, the ability to increase transepithelial membrane resistance was verified, even in coculture with pathogens or after pathogen stress.

### *1.9. Production of Molecules with Local Effects*

Small molecules produced by some probiotic strains have been described in the literature with different effects on the host and its microbiota. Among the most interesting discoveries, we certainly find the production of neurochemical substances capable of influencing brain function, such as oxytocin, gamma-aminobutyric acid, serotonin, tryptamine, noradrenaline, dopamine, and acetylcholine [49]. It has also been shown that, by adding *Lactobacillus helveticus NS8* to the diet of the stressed rat used in the model system, plasma levels of corticosterone and adrenocorticotropic hormone were lower, while normal levels of serotonin and norepinephrine in the hippocampus were restored.

### *1.10. Production of Enzymes*

Microbial enzymes, such as β-galactosidase and bile salt hydrolase, produced and released by some probiotic strains, are capable of improving lactose digestion and blood lipid profiles, respectively [50]. For example, in yogurt, the presence of Streptococcus thermophilus facilitates the digestion of lactose. Its predisposition to be permeabilized by bile when it enters the small intestine promotes the release of the microbial β-galactosidase, which breaks down lactose into its more easily digestible constituents, i.e., glucose and galactose. This results in a clinical benefit for lactose intolerant. The EFSA (European Food Safety Authority) considered that evidence of this effect was sufficient to authorize a health claim regarding Streptococcus thermophilus and Lactobacillus bulgaricus as constituents of yogurt that can alleviate the symptoms of lactose maldigestion.

## 2. Prebiotics

Prebiotics were first defined in 1995. Then, in 2017 an update to the definition was provided via an expert consensus document, as scientific advances made it necessary to clarify what did and did not constitute a prebiotic substance [51,52]. Thus, a prebiotic substance has been defined as 'a substrate that is selectively used by host microorganisms that confer a health benefit'. The desire to optimize the microbial world associated with humans to achieve improved health has led to the development of compounds targeting an ever-expanding group of microorganisms. Prebiotics are no longer seen simply as growth stimulators of bifidobacteria and lactobacilli, but are now recognized for their effects on the metabolic and physiological systems [52]. Although the intestine remains the gateway to most of these effects, it is not the only one. In fact, numerous studies are being conducted to obtain further information on the influence of prebiotics on the microbial communities of the urogenital tract, oral-nasal areas, and skin [53]. To understand how they work and, above all, how to exploit prebiotics to "direct" the microbiota and obtain a health benefit, it must be borne in mind that microorganisms live in complex functional ecosystems [6] within which bacteria have a multitude of roles, including the conversion of incoming dietary carbohydrates, proteins and some fats into metabolites that can have positive or negative effects on the health of the host [54]. Current prebiotics [52] are mainly based on carbohydrates, but other substances, such as polyphenols and polyunsaturated fatty acids, could exert prebiotic effects.

Microorganisms such as bifidobacteria are able to metabolize low molecular weight carbohydrates very efficiently, possessing a range of cellular and extracellular glycosidases

and specific transport systems [55], while other microorganisms, such as those belonging to the genus Bacteroides, are able to use high molecular weight polysaccharides. In this regard, some bacteria could be of considerable importance as they possess the ability to initiate the breakdown of particular substrates [56]. For example, *Ruminococcus* spp. can facilitate the degradation of resistant starch, leading to the release of low-molecular-weight dextrins which can then be metabolized by the microbial community. The path from a polysaccharide to a short-chain fatty acid is a complex and indirect metabolic network. Acetate and lactate, which are the main metabolic end products of bifidobacteria and lactic acid bacteria, are used by other microorganisms to produce, e.g., propionate and butyrate [57].

Another complication in these studies is represented by the response of the fact that the ecosystem to carbohydrates is strongly influenced by the microorganisms already present: the individual microbiomes dominated by *Prevotella* are able to ferment carbohydrates more rapidly than those dominated by *Bacteroides* [39]. Furthermore, a study showed that when these different fecal inoculums, dominated by *Prevotella* or *Bacteroides*, were incubated with fructooligosaccharides (FOS) or with two different arabinoxylans, the profile of the short-chain fatty acids produced was markedly different and related to the microbiome. In another study, an in vitro batch fermentation model containing the human microbiota and isomalt oligosaccharides as a carbon source showed a similar influence of the starting microbiome on carbohydrate fermentation [21]. The 16S ribosomal DNA sequencing-based microbiome studies have increased awareness of the richness of the gut microbial ecosystem. However, these do not provide an understanding of the functional interactions between members of the gut microbiota. It is now becoming clear that although individual gut microbiomes can be quite diverse, there is a high level of functional redundancy, and some specific ecological functions are performed by a range of bacteria in different individuals [58].

Since understanding the functional ecology of the gut microbiota is imperfect, uncovering the mechanisms of action of prebiotics presents a challenge. Despite this, the mechanisms through which a prebiotic can lead to health benefits have been described thanks to research conducted using in vitro or animal models. In many cases, it is difficult to establish whether they actually occur in the human gut microbiota [6].

### *2.1. Defense against Pathogens*

Defense activity against pathogens can be studied in vitro thanks to the use of model systems [59]. Through the administration of prebiotics and the propagation of beneficial bacteria, a reduction in luminal pH will be obtained, inhibiting pathogen growth. The establishment of a stable population of commensal microorganisms will reduce the availability of nutrients for the invading microorganisms, making colonization difficult. In studies carried out in elderly individuals, ten weeks of daily galactooligosaccharide (GOS) consumption induced increases in immune function, in particular by increasing phagocytic and natural killer cell activity [60,61].

In a recent study, the antimicrobial potential of olive fiber polyphenols was verified [62]. LOPP (liquid-enriched olive pomace powder) and POPP (pulp-enriched olive pomace powder) were subjected to simulated in vitro gastrointestinal digestion followed by in vitro fecal fermentation. The olive pomace powders showed antiadhesion activity ranging between 1.4 and 22% against Bacillus cereus, Listeria monocytogenes, Escherichia coli, and Yersinia enterocolitica. The most pronounced effect was found for POPP against Gram-positive bacteria: adhesions of Bacillus cereus and Listeria monocytogenes were inhibited by at least 20%. POPP is composed primarily of insoluble fiber, but also contains a significant amount of free and bound phenolic compounds (particularly oleuropein, aglycone, and hydroxytyrosol), which may act as antiadhesion agents of intestinal mucin. Luteolin, for example, has been retained in higher amounts in the undigested fraction of POPP and has been described to possess antimicrobial activity against several bacterial species [63].

### *2.2. Immune-Modulation*

Although the exact mechanisms are still unclear, there is evidence that prebiotic intervention may be able to reduce type 2 T-helper cell responses, affecting the allergic process. The most favorable data were collected from studies conducted on newborns. In a double-blind, randomized, placebo-controlled study of 259 infants, the administration of infant formula enriched with GOS and long-chain FOS was associated with a less than 50% reduction in the incidence of atopic dermatitis, wheezing, and urticaria. compared to infants not fed prebiotic milk [64]. A double-blind, placebo-controlled study showed that healthy infants at risk of atopy [65] who were fed a hypoallergenic formula enriched with prebiotics for six months had a more than fivefold reduction in the onset of allergies five years after feeding.

### *2.3. Increased Mineral Absorption*

Most mineral absorption occurs through active transport mechanisms in the small intestine. The fermentation of prebiotics, leading to the production of short-chain fatty acids, causes a reduction in the luminal pH. This drop in pH can increase the solubility of calcium, providing a greater driving force for passive absorption [66]. Studies have shown that the consumption by young adolescents of a mixture of FOS and inulin or GOS can cause a marked increase in the mineralization of the bone and absorption of calcium [67]. This early intervention could reduce the incidence of osteoporosis later in life. However, this hypothesis is supported by data from animal models, and long-term studies in humans are lacking.

### *2.4. Improved Intestinal Function*

Improvements in bowel function have often been attributed to a simple fecal buildup from consuming dietary fiber. However, animal studies have shown that short-chain fatty acids produced by prebiotic fermentation can regulate intestinal hormones which in turn are able to modulate the local motor responses of the intestine [68]. Additionally, the water-binding ability of prebiotic carbohydrates has the effect of softening the stool, making it easier to pass [69].

### *2.5. Metabolic Effects*

Numerous meta-analyses have investigated the metabolic effects of prebiotics. Although the results varied between studies, it is possible to conclude that prebiotic intervention has a positive effect on glucose homeostasis, inflammation, and blood lipid profile in humans [70].

Underlying much research on prebiotics, barrier function and inflammation is the hypothesis that fermentation products, such as short-chain fatty acids, are likely mediators of beneficial effects. However, at least in vitro, GOS can directly stimulate the expression of tight junction proteins in intestinal epithelial cell lines and decrease transepithelial flux [71]. On the other hand, with respect to the ability of inulin to improve the glycemic response, this could be due to direct inhibition of the intestinal isomaltase-saccharase enzyme complex, but so far these results come from studies in mice [72].

### *2.6. Effect on Satiety*

Short-chain fatty acids produced by fermentation in the intestinal tract can interact with specific fatty acid receptors (FFAR2 and FFAR3) and regulate lipolysis and the release of glucagon-like peptide-1 [73]. Because these receptors are found in many tissues, they may be a key link in understanding the relationship between prebiotic fermentation and systemic health benefits. SCFAs can regulate appetite through several mechanisms [74]. Interaction with colonic L cells, for example, results in the production of anorexigenic hormones such as PYY and GLP-1. Propionate that reaches the liver through the hepatic portal vein, on the other hand, stimulates gluconeogenesis that acts as a satiety signal. According to a study in mice, acetate, the main short-chain fatty acid formed by prebiotic

fermentation, can cross the blood–brain barrier and enter the hypothalamus, promoting anorexic signals [75].

## 3. Interaction between Food Components and Intestinal Microbiota

Influencing its composition in terms of richness and diversity, food components have a key impact on the intestinal microbiota. While, on the one hand, the high intake of animal proteins, saturated fats, sugars, and salt could stimulate the growth of pathogenic bacteria to the detriment of beneficial ones, on the other hand, the consumption of complex polysaccharides and vegetable proteins could be associated with an increase in the quantity of beneficial bacteria. Furthermore, omega-3, polyphenols, and micronutrients appear to be able to confer health benefits through modulation of the intestinal microbiota [3].

### *3.1. Carbohydrates and Intestinal Microbiota*

Carbohydrates can be classified into digestible and non-digestible substrates. Digestible ones (such as glucose, fructose, and galactose) are enzymatically degraded in the small intestine and rapidly released into the blood in the form of glucose. The non-digestible ones, macroscopically called "dietary fibers", reach the large intestine as they are resistant to digestion in the small intestine.

Dietary fibers can be classified according to their solubility in water and their ability to be easily fermented by colonic bacteria. Inulin, pectins, beta-glucans, FOS, and GOS are considered water-soluble and fermentable fibers, whereas cellulose, hemicellulose, lignin, and resistant starch are considered insoluble and nonfermentable.

Fermentable dietary fibers undergo saccharolytic fermentation by intestinal bacteria which essentially leads to the production of monosaccharides, short-chain fatty acids (in particular acetate, propionate, and butyrate) and gases (i.e., methane and carbon dioxide). Therefore, carbohydrates accessible to the microbiota, called MACs, become available as prebiotics to be metabolized into short-chain fatty acids3. SCFAs are involved in colon homeostasis by stimulating epithelial cell proliferation and differentiation, salt and water absorption, maintaining mucosal integrity, and reduction of inflammation [76]. The types and amounts of short-chain fatty acids produced are primarily determined by the composition of the gut microbiota and the amount of carbohydrates consumed. Consequently, bacterial populations detected in feces are influenced by the type and amount of non-digestible carbohydrates ingested in the human diet [77].

### *3.2. Proteins and Intestinal Microbiota*

Fermentation of amino acids occurs in the distal colon by the main microbial phyla including Firmicutes, Bacteroidetes, and Proteobacteria. Compared to saccharolytic fermentation, proteolytic fermentation produces fewer short-chain fatty acids. Instead, it determines the release of branched-chain fatty acids (such as isobutyrate, 2-methylbutyrate and isovalerate) and potentially toxic substrates such as ammonia, whose amines include nitrosamines and trimethylamine N-oxide [3].

Depending on the type of protein introduced by the host, the effects on the composition of the gut microbiota vary. Consumption of animal-derived proteins, particularly red meat and dairy products, can lead to an increase in the abundance of bile-tolerant anaerobic bacteria, such as *Bacteroidetes*, *Alistipes*, and *Bilophila*, inducing an increase in the production of trimethylamine N-oxide, a compound known for its pro-atherogenic potential [9]. Furthermore, a study has shown that high consumption of proteins of animal origin could increase the risk of inflammatory bowel disease (IBD) through an accumulated production of hydrogen sulfide ($H_2S$) by bacteria (for example *Desulfovibrio* spp.) that reduces sulphate from food inorganic sulphates and sulfur amino acids [78]. However, in terms of vegetable proteins, a study demonstrated how the consumption of pea proteins led to an increase in Bifidobacterium and Lactobacillus, and a reduction in pathogenic Bacteroides fragilis and Clostridium perfrigens [79].

### *3.3. Fats and Intestinal Microbiota*

As demonstrated, the amount and type of dietary fat influence the composition of the intestinal microbiota [80]. Several studies conducted in animals have shown that a high intake of dietary fats, particularly saturated fats (SFA), causing a decrease in Bacteroidetes and an increase in Firmicutes and Proteobacteria, could lead to intestinal dysbiosis. In addition, alterations of the intestinal barrier could occur due to the abundance of sulfate-reducing bacteria, which, being able to reduce the disulfide bonds in mucus, cause defects and increase intestinal inflammation [3]. Regarding monounsaturated fatty acids (MUFA), a recent review has shown that these have no effect on richness/diversity indices, on the distribution of phyla, and on the relationship between Bacteroidetes and Firmicutes [81]. At the family and genus level, however, diets rich in monounsaturated fatty acids (such as the "Mediterranean diet") could be positively correlated to the genera Parabacteroides, Prevotella, and Turicibacter and the family Enterobacteriaceae, while they could be negatively correlated to the genus Bifidobacterium.

Moving on to polyunsaturated fatty acids (PUFAs), these are divided into omega-3 and omega-6. Omega-3 PUFAs, present mainly in oily fish, can exert a positive action on the microbiota, restoring its healthy composition and increasing the production of anti-inflammatory compounds. On the other hand, the high omega-6/omega-3 PUFA ratio, prevalent in the Western diet, has been associated with increased permeability of the intestinal barrier permeability and metabolic endotoxemia through a mechanism driven by the intestinal microbiota [3]. A different family of PUFAs is the conjugated isomers of linoleic acid, the so-called 'CLA'. These, derived from the bio-hydrogenation of linoleic acid by bacteria present in the rumen, are found in foods of animal origin, such as beef, lamb, butter, and dairy products, and dietary supplementation with CLA in mice can promote significant changes in the composition of the intestinal microbiota: at the phylum level, there was a decrease in *Firmicutes* and an increase in *Bacteroidetes*, while at the species level, an enrichment of *Butyrivibrio*, *Roseburia*, and *Lactobacillus* was found, with a consequent increase in butyrate in feces and acetate in plasma [82]. These effects on the composition of the gut microbiota could partially explain the beneficial properties attributed to CLAs.

### *3.4. Salt and Intestinal Microbiota*

As evidenced by several studies in mice, a diet rich in salt can cause alterations in the composition of the intestinal microbiota, with a possible increase in the *Firmicutes/Bacteroidetes* ratio. This results in impaired short-chain fatty acids, which can be associated with changes in intestinal permeability and immune homeostasis [3].

### *3.5. Food Additives and Intestinal Microbiota*

Food additives, such as artificial sweeteners and emulsifiers, are incorporated into almost all processed foods, often to promote shelf life and improve texture and taste. Most non-caloric artificial sweeteners pass through the human gastrointestinal tract undigested by the host, and thus directly encounter the gut microbiota. Several reports have shown that the consumption of these substances could alter the intestinal microbiota and induce adverse microbiota-mediated effects in the host, such as glucose intolerance [3]. A study in which healthy volunteers, who normally did not consume artificial sweeteners, received a dose of 5 mg/kg saccharin for one week, developed lower glucose tolerance, increased *Bacteroides* spp. and *Lactobacillus* spp., and decreased *Clostridiales* spp. In another study, it was reported that by administering low-dose aspartame water (5–7 mg/day) of aspartame for eight weeks, the intestinal microbiota of the rats used in the model underwent significant changes: a greater abundance of *Enterobacteriaceae* and *Clostridium* leptum was detected, together with elevated fasting glucose levels and impaired insulin responses [83]. Furthermore, according to an in vitro study, food emulsifiers, such as lecithins and mono and diglycerides of fatty acids, could increase bacterial translocation through epithelia, promoting systemic inflammation, and altering the localization and composition [84].

### *3.6. Micronutrients and Intestinal Microbiota*

Vitamins and minerals are essential for the regulation of energy metabolism, cell growth and differentiation, and for immune function. Numerous vitamins can be synthesized by the intestinal microbiota, such as thiamine, riboflavin, niacin, biotin, pantothenic acid, folate, and vitamin K. Furthermore, several studies have shown that vitamin D could have an impact on the composition of the microbiota, modulating it and increasing the abundance of potentially beneficial bacterial strains [3]. Even antioxidant substances such as carotenoids could influence the intestinal microbiota. Recent studies have shown that, on the one hand, lutein extracted from black currants has promoted the growth of bifidobacteria and lactobacilli and the reduction of *Bacteroidetes* spp. and *Clostridium* spp. On the other hand, the anti-inflammatory effects of beta-carotene are mediated by the intestinal microbiota [3].

As for metals, they are involved in numerous bacterial physiological processes that affect the intestinal microbiota. A study, in fact, highlighted the increased activity of the Clostridium difficile in mice colonized by the pathogen and fed a diet containing an excess of zinc [85]. Furthermore, as demonstrated, the availability of iron influences the composition of the microbiota: in mice, a diet rich in heme determined the reduction of microbial diversity, increasing the abundance of *Proteobacteria* and reducing the presence of *Firmicutes* [86].

### *3.7. Polyphenols and Intestinal Microbiota*

As is now known, polyphenols are involved in the prevention of numerous diseases such as diabetes and obesity and therefore represent a topic of growing interest for the scientific community. However, their absorption and bioavailability in humans remain unclear and controversial. In general, researchers agree that the mutual interactions of the intestinal microbiota and phenolic compounds have a significant impact on the bioavailability of these compounds [3]. Several studies have shown that phenolic compounds can lead to an increase in beneficial microorganisms and, through the integration of anthocyanins, an increase in *Bifidobacterium* spp., *Lactobacillus*, and *Enterococcus* spp. has been detected. At the same time, by modulating the transformation of phenolic compounds into smaller metabolites, the microbiota plays a key role in the bioavailability and properties of proanthocyanidins [87].

## 4. Effect of Diets on Intestinal Microbiota

Eating habits can strongly influence the composition of the intestinal microbiota. Westernization of the diet can reduce the intestinal microbial diversity in terms of phyla and gender, leading to dysbiosis, alteration of barrier function, permeability, and normal functioning of immune cells, increasing the risk of the onset of chronic diseases. However, when it comes to elimination diets, such as low FODMAP or gluten-free diets, although they can improve the symptoms of some diseases such as IBS and celiac disease in selected patients, the long-term effects on the intestinal microbiota require clarification. To date, the Mediterranean diet remains the best solution to obtain a diversified and stable microbiota, which ensures the regular activity of host immune functions. Therefore, by increasing the knowledge of the interactions between food compounds and specific intestinal bacteria, a new nutritional approach could be adopted, based on the construction of a personalized diet aimed at modulating and restoring a healthy intestinal microbiota [3].

### *4.1. Effect of Vegan and Vegetarian Diets on Microbiota*

Unlike omnivores, vegetarians do not consume any type of meat or fish. Vegans represent a subgroup of vegetarians who also exclude products of animal origin such as eggs, milk and dairy products from their diet. A work showed that in vegans and vegetarians compared to omnivores, higher ratios of *Bacteroides/Prevotella*, *Bacteroides thetaiotaomicron*, *Clostridium clostridioforme*, *Klebsiella pneumoniae,* and *Faecalibacterium prausnitzii* were found; and lower ratios of *Clostridium cluster XIVa* and *Bilophila wadsworthia* [88]. Another work, on the other hand, has shown that in vegans and vegetarians the count of species of Bi-

fidobacterium and Bacteroides is lower, while no difference has been detected between vegans and omnivores by quantifying the fecal levels of short-chain fatty acids and by the production of methane through breath [89].

These studies suggest that vegan and vegetarian diets influence the microbiota, but it is not possible to draw conclusions on its composition due to the different methodologies used for its identification, and the heterogeneity of the sample in terms of size, influences of geographical origin, age, gender, and body mass. Furthermore, the effects on modulation of the intestinal microbiota of polyphenols, very present in vegan and vegetarian diets, must be considered [3].

### *4.2. Effect of Gluten-Free Diet on Microbiota*

Celiac disease is an autoimmune disease in which gluten causes severe intestinal inflammation. Since it can restore the normal intestinal mucosa in celiac patients, in the 1960s the gluten-free diet was recognized as a potential cure and, at the moment it remains the only possible therapy for those suffering from this disease. Some scientists have studied the effects of a gluten-free diet administered to healthy subjects for one month, finding a decrease in *Bifidobacterium*, *Clostridium lituseburense,* and *Faecalibacterium prausnitzii* and an increase in *Enterobacteriaceae* and *Escherichia coli* counts [90]. Others have shown that the greatest variations occur in the Veillonellaceae family, significantly decreasing its abundance in the intestines of those who adopt a gluten-free diet [91].

Although most of the work carried out to evaluate changes in the microbiota following the adoption of a gluten-free diet has important limitations, including small sample sizes and the use of low-yield techniques (such as and molecular ones not based on sequencing), a decrease in beneficial bacteria, such as Bifidobacterium and Lactobacillus, has been demonstrated. This determines a decrease in short-chain fatty acids, with a consequent reduction in their positive effects on the metabolism and immunity of the host [3]. Furthermore, the increase in harmful species, such as *Staphylococcus*, *Salmonella*, *Shigella*, and *Klebsiella*, could influence the microbial profiles and long-term homeostasis of the intestinal mucosa of healthy subjects [90].

### *4.3. Effect of Ketogenic Diet on Microbiota*

The ketogenic diet is a high-fat, very low-carbohydrate, normal calorie diet used in individuals with drug-resistant epilepsy and GLUT1 deficiency syndrome. Although it appears to be an effective diet therapy for weight reduction in obese patients, maintaining the achieved body weight is usually problematic [3].

A study focused on the comparison of the microbiota composition of patients treated with the ketogenic diet before and after three months of diet, demonstrating an enrichment in *Desulfovibrio* spp., involved in the exacerbation of intestinal inflammation [92]. Some scientists, studying the microbiota of children affected by epilepsy before and after three months of the ketogenic diet, have found a decrease in bifidobacteria, *Eubacterium rectale* and *Dialister* and an increase in *E. coli* during the intervention [93]. Because this diet involves a reduction in carbohydrate intake, the decrease in beneficial gut microbiota bacteria, such as bifidobacteria, is associated with a limited host intake of polysaccharides. Therefore, although the ketogenic diet has a positive impact on a wide range of diseases, the long-term effects of this diet on the composition of the intestinal microbiota, and consequently on the homeostasis of the mucus layer and on immune functions, remain to be clarified, more specifically in healthy subjects adopting the ketogenic diet for weight loss [3].

### *4.4. Effect of Glucose or Fructose Rich Diets on Microbiota*

Excess sugar in modern dietary habits has been linked to obesity, various metabolic diseases such as type II diabetes mellitus and cardiovascular disease. In a recent work, by feeding different diet regimens (normal diet, high glucose diet and high fructose diet) to mice for 12 weeks, the impact of the high sugar diet on the gut microbiota was studied [94]: mice fed the high-glucose diet and the high-fructose diet showed less microbial diversity

than mice fed the normal diet; in particular, a decrease in *Bacteroidetes* and an increase in *Proteobacteria* were found, as well as a significant increase in intestinal permeability. Therefore, diets high in glucose or fructose can shape the intestinal microbiota, increasing the *Firmicutes/Bacteroidetes* ratio and the proportion of *Proteobacteria*, also causing alteration of intestinal permeability and increased expression of inflammatory cytokines in the colon.

### *4.5. Effect of Low-FODMAP Diet on Microbiota*

FODMAPs (an acronym for "Fermentable, Oligo-, Di-, Monosaccharides And Polyols", created in 2004 by Monash University) are a group of highly fermentable but poorly absorbed carbohydrates and polyols. In recent years, several doctors have used the low FODMAP diet, especially for the treatment of diseases, such as IBS and IBD [3]. One study showed that IBS patients treated with a low-FODMAP diet had similar concentrations of short-chain fatty acids and a 47% reduction in bacterial abundance compared to the usual diet [95]. A low FODMAP diet, in fact, could reduce the introduction of prebiotics, leading to a low presence of beneficial bacteria within the intestinal microbiota. To counteract these imbalances and, in particular, restore Bifidobacterium levels, integration with probiotics would seem to be a good solution. However, larger studies are needed to understand both the long-term effects of low FODMAP diets on microbiota composition and the potential benefits of probiotic supplementation [3].

### *4.6. Effect of Western Diet on Intestinal Microbiota*

The western diet is a widely adopted dietary habit in economically developed countries and increasingly also in developing countries, characterized by a high intake of total fats, animal proteins and refined sugars. As demonstrated, high consumption of animal protein increases the abundance of bile-tolerant microorganisms, such as *Alistipes*, *Bilophila,* and *Bacteroides* and decreases the levels of *Firmicutes* that metabolize dietary plant polysaccharides such as *Roseburia*, *Eubacterium rectale* and *Ruminococcus bromii* [22]. Several studies have shown that this type of diet has harmful effects on the intestinal microbiota, inducing poor microbial diversity and dysbiosis, negative effects on the intestinal mucosa, and inflammation.

### *4.7. Effect of Mediterranean Diet on Microbiota*

The concept of "Mediterranean diet" was developed to describe the typical eating habits of the inhabitants of the Mediterranean basin, mainly in large parts of Greece and southern Italy.

This diet, which is focused on the consumption of fruits, vegetables, olive oil, nuts, legumes, and whole grains, provides high amounts of MUFA, PUFA, polyphenols and other antioxidants, prebiotic fibers, low glycemic index carbohydrates, and proteins of vegetable origin. This diet has been linked to numerous health benefits, such as reducing mortality risk and the prevention of many diseases such as diabetes, metabolic syndrome, cognitive impairment, and depression [3]. Regarding its effects on the intestinal microbiota, the correlation between a lower adherence to the Mediterranean diet and a higher *Firmicutes-Bacteroidetes* ratio has been demonstrated. Furthermore, higher counts of bifidobacteria and total short-chain fatty acids were related to increased consumption of plant-derived nutrients, such as plant proteins and polysaccharides [96–99]. There is no doubt that adherence to the Mediterranean diet has a beneficial effect on the intestinal microbiota and associated metabolomic profile, resulting in an increase in total bacteria, *Bifidobacteria*/*E. coli*, the relative proportion of *Bacteroides* and total SCFAs, as well as a decrease in *E. coli* levels [100,101].

## 5. Conclusions

The interaction between diet and the gut microbiota is reciprocal. On the one hand, the microbiota digests the nutrients introduced through food. On the other hand, what we eat can have a strong impact on the composition of the intestinal microbiota. Studies,

both in animal models and in humans, have shown that any change in diet can induce a change in the composition of the intestinal microbiota. In healthy individuals, a balanced diet can ensure the formation of a good microbiota, in which all species of microorganisms live in a balanced system. It has been demonstrated that a diet rich in saturated fats, with a high consumption of red meat and refined carbohydrates, low in fish and foods of vegetable origin, can profoundly modify the structure and functions of the intestinal microbiota, causing dysbiosis. This phenomenon triggers pro-inflammatory mechanisms, which can have a direct effect on the immune system. Dysbiosis appears to be a common feature of several pathological conditions, including obesity, cardiovascular disease, and cancer. On the contrary, the Mediterranean diet, characterized by a fair amount of fiber and bioactive compounds, is among the dietary models that most favors the health of the intestinal microbiota. Subjects adopting a Mediterranean diet pattern appear to have greater production of short-chain fatty acids and a greater degree of diversity among microbial populations than those adopting a more western-style diet. For this reason, the composition of the microbiota of those who follow a Mediterranean diet seems to be more favorable to the prevention of cardio-metabolic pathologies and some types of cancer. When the first zero-sugar drinks with artificial sweeteners appeared on the market, it was thought they could be a useful tool in the fight against obesity induced, among other things, by the exaggerated consumption of sugary drinks. so much so that zero sugar drinks are still very popular among consumers. Although the substances used to sweeten these beverages are generally considered safe by regulatory agencies, several animal model studies have shown that the consumption of synthetic sweeteners produces an imbalance between the microbial populations of the intestinal microbiota, resulting in an increase in the production of pro-inflammatory factors. Given the role of intestinal microorganisms in human health, can the consumption of fermented foods have positive effects on health? The effect on the intestinal microbiota and on the body has been studied for some years. Fermented foods are foods or beverages produced through controlled microbial growth which, through an enzymatic action, modifies the starting food matrix, to obtain a different food in terms of shape, texture, and flavor. The most famous fermented food is undoubtedly yogurt in which the bacteria used *Streptococcus thermophilus* and *Lactobacillus delbrueckii* spp. *Bulgaricus*, thanks to their synergistic work, transform lactose, milk sugar, into lactic acid. It is important to underline that fermented foods are not always synonymous with probiotic food; to earn this title, the microorganisms inside them must remain alive up to the intestine and be in such quantities as to be able to confer a benefit on human health. The common yogurt obtained through the action of *Streptococcus thermophilus* and *Lactobacillus delbrueckii* spp. *Bulgaricus*, is a fermented food, but these two microorganisms do not survive the acidic environment of the stomach. Only yogurts to which bacteria capable of reaching the intestine intact and exerting their beneficial effects are added can be defined as probiotic foods. Fermented foods have gained great popularity in recent years due to their proposed health benefits. Some examples of fermented foods are: kefir, kombucha tea, sauerkraut, tempeh, natto, miso, kimchi, sourdough bread. In some clinical studies, it has emerged that a diet rich in fermented foods, consumed regularly, can increase the diversity of the intestinal microbiota and reduce inflammation. These effects would seem to be mediated by the formation of bioactive compounds derived from fermentation by the intestinal microbiota which would therefore act as a mediator. Furthermore, the results of some studies suggest that the consumption of fermented foods enriches the intestine with lactic acid bacteria. However, the clinical evidence of these effects is still rather limited and although the studies are promising, more insights are still needed. Therefore, if you like fermented foods, they can be part of a healthy diet, checking, at the time of purchase, e.g., in the case of yogurt and kefir, that there are no unwanted ingredients, such as added sugars.

Therefore, how can a healthy microbiota be achieved through nutrition? Very simple: following a Mediterranean diet model, i.e., keeping the fiber intake high through the consumption of legumes, vegetables, whole grains, fresh fruit, and dried fruit, and adopting a healthy and active lifestyle. Fermented foods can also be part of the diet, but their consump-

tion should be constant to experience benefits. Finally, the diet must never be monotonous but always varied. It has been observed that monotonous diets lead to a reduction in the biodiversity of the intestinal microbiota. A healthy intestinal microbiota is essential for maintaining general health, and diet is one of the major modulators of this fascinating world of microorganisms. This must give us one more reason to adopt a healthy lifestyle.

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