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Review

Diet, Probiotics and Physical Activity: The Right Allies for a Healthy Microbiota

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Abstract. *The intestinal microbiota, which has gained a foothold in the field of research, represents a significant factor for human health because of its ability to form relationships with the organism through the modulation of pathophysiological processes. Dysbiosis, which is caused by non-specific intestinal inflammation and leads to a condition of persistent low-grade inflammation, may be caused by poor eating habits and an unhealthy lifestyle, as well as psycho-physical stress and a sedentary lifestyle. Diet, prebiotics and probiotics, and moderate and aerobic exercise can, in order to increase well-being and reduce the chance of recurrence, all be deemed effective methods of improving gut-microbiota pretreatment or mitigating diseases or dysbiosis. This study shows the ways in which good living habits, correct nutrients, and constant aerobic activity in chronic and immune conditions, can modify gut microbiota and microbiome characteristics, as well as the relationship between intestinal function and human health.*

It is now known that the causes of most chronic diseases are hidden in our daily life. Several scientific studies underline how appropriate nutritional and exercise choices, associated with breathing and meditation techniques, are essential to slow down the aging processes, promote a healthier and longer life expectancy, prevent typical chronic diseases of our society or facilitate healing or simply promote a better quality of life (1-4). There is growing scientific evidence that the essential triad for health conservation and restoration is the combination of body feeding practices, the right amount of food, fitness or regular exercise, and the use of techniques that promote a healthy mind, spirit, and inner happiness (5, 6). It has been known since ancient times, that nutrition is one of the most powerful means of prevention and promotion of chronic diseases. Hippocrates, the famous Greek physicist and the father of western medicine (460-370 BC), said that if we could give everybody the correct amount of nutrition and exercise, either in defeats or overweight, we would find the way into health (7). Even modern medicine has finally returned to the fore the importance of the amount and quality of nutrients we introduce into our bodies every day (8). Indeed, extensive scientific evidence shows that a healthy long life is useful if fat build-up is avoided in the abdomen, if empty calory foods (such as sugars and refined meals) are removed from the essential nutrients and animal protein and fats, and when the amount of vegetables, such as vegetables, legumes, whole grains, and nuts, which have been minimally processed, is reduced (9-11). These high-fiber foods, for example, are processed by gut bacteria, known as microbiota, to produce metabolites that protect against autoimmune and allergic diseases (12, 13). Antioxidant and anti-inflammatory properties are provided by the vitamins and other phyto-compounds found in them. The word "microbiota" refers to the intestinal flora, which can be altered by still-unknown

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environmental causes and can lead to a variety of changes during one's existence, ranging from the onset of infectious diseases to recurrent intestinal diseases such as Crohn's disease and Ulcerative colitis, as well as tumor diseases (14, 15). Many microorganisms make up the microbiota, which can be found on all surfaces of the host's mucous membranes, however the majority live in the gastrointestinal tract (16, 17). The metagenome, also known as the second genome, is made up of the genes of these microorganisms. It's not shocking, then, that this vast array of gene products plays an important role in maintaining the organism's homeostasis (18, 19). The relationship between the intestinal microbiota and its host is essential for immune system control, food digestion, drug metabolism, detoxification processes, vitamin production, and pathogenic bacteria adhesion prevention (20-22). Environmental factors such as diet, medication therapies, and physical activity have an effect on the microbiota's composition (Figure 1). Furthermore, it varies depending on the individual's gender, age, and geographic origin (23, 24). Dysbiosis is a condition caused by an overgrowth of pathogenic microorganisms (25). Antibiotic treatment, alcohol misuse, and an unhealthy diet combined with a sedentary lifestyle may all contribute to dysbiosis and the development of chronic inflammatory diseases including diabetes, cancer, and inflammatory bowel disease (26, 27). Exercise is beneficial not only to our appearance and sense of well-being, but also to the bacteria that colonize our intestines (28). While it is well known how commensal bacteria interact with the host to determine their wellbeing, it was only recently discovered that there is a complex relationship between physical activity and the composition of the intestinal microbiota (29). These findings were discovered after comparing the bacterial profiles of professional athletes and those of sedentary or inactive people (30). Physical activity appears to favor the abundance of species associated with the development of metabolites required to maintain the integrity of the intestinal barrier, preventing pathogens from entering the circulation and causing chronic systemic inflammation (31). Most patients with intestinal bowel disease (IBD) have a dysbiotic microbiota, which is no coincidence. The good news is that an unbalanced microbiota is a real trigger, not just a side effect of the pathological situation. Several studies have proven this thesis: for example, fecal transplantation or the use of probiotics and antibiotics have been shown to aid in symptom remission (32). This suggests that when the microbiota is in good shape, the disease follows suit, and *vice versa*. Patients with IBD typically have a far less diverse intestinal microbiota than healthy people, as well as an increase in pro-inflammatory bacteria like Enterobacteriaceae, especially *E. coli* and *Fusobacterium* (33, 34). At the same time, bacteria that generate butyrate, an essential molecule for intestinal and immune health, are declining (35).

Gut Microbiota

Because of its ability to create relationships with the organism and modulate patho-physiological processes, the intestinal microbiota, represents a significant element for human health (36). It consists of a group of non-pathogenic bacteria that perform specific physicochemical functions. The human microbiota is believed to be made up of around 100 trillion microbes, with a total weight of 1.5-2 kg. Firmicutes, Bacteroides, Actinobacteria, Proteobacteria, and Fusobacteria are five microbial phyla that colonize the intestine and differ from person to person due to a variety of factors (Figure 2) (37). The Firmicutes, which are mostly expressed by Gram positive Clostridia, and the Bacteroidetes, which are mostly Gram negative, are the two major phyla found in the adult organism and make up about 90% of the human intestinal microbiota (38). It was possible to show that bacterial colonization is affected by diet over the course of a person's life thanks to metagenomic studies (39). In reality, Clostridium bacteria are more prevalent in the microbiota of omnivores and less prevalent in the microbiota of vegetarians (40). The existence of three microbial variants known as enterotypes may be highlighted (41). Each enterotype represents a colonizing bacteria ecosystem with distinct phylogenetic and functional characteristics. The enterotype is a microorganism classification scheme focused on the bacteriological ecosystem of the intestine. The bacteria in the human intestine are classified into three broad classes (or enterotypes), each with a distinct bacterial species (Figure 3) (42). Belonging to one of these three classes has little to do with race, age, or gender, but it does have something to do with diet and lifestyle. This means that our enterotype will shift over our lives as a result of our diet, lifestyle, and use of antibiotics or other medications. The ability to generate vitamins and acquire energy from various substrates found in the intestine is affected by belonging to one of many enterotypes (43). Basically, depending on what we consume and the enterotype we belong to, we can extract energy from food during digestion to a greater or lesser extent. The predominance of a bacterial genus characterizes each enterotype.

ENTEROTYPE 1 is characterized by a Bacteroides predominance and the ability to recover maximum energy from carbohydrate and protein fermentation. Additionally, people who have this enterotype produce more biotin, riboflavin (vitamin B2), pantothenic acid (vitamin B5), and ascorbic acid (vitamin C) (44). Enterotype 1 is often linked to a Western diet that is high in animal proteins and fats but low in fiber and vegetables (45). This enterotype has been linked to a higher level of intestinal inflammation and, as a result, a higher level of overall inflammation (46). For this enterotype, the consumption of fruits, whole grains, and fiber has to be increased.

Prevotella bacteria are preponderant in ENTEROTYPE 2, which degrade certain proteins found in the mucosal layer of

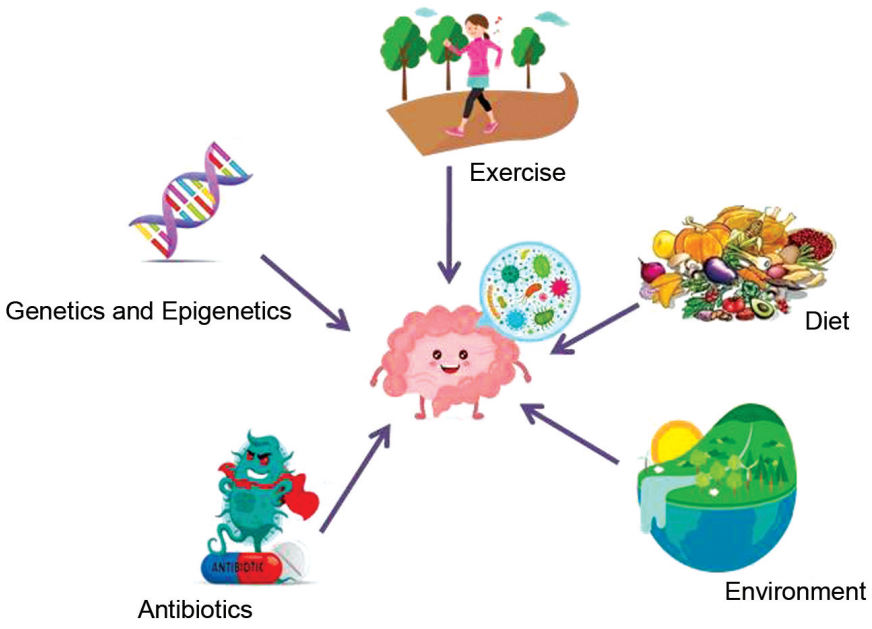

Figure 1. *Numerous factors such as diet, genetics, antibiotics, exercise, and the environment influence the gut microbiome.*

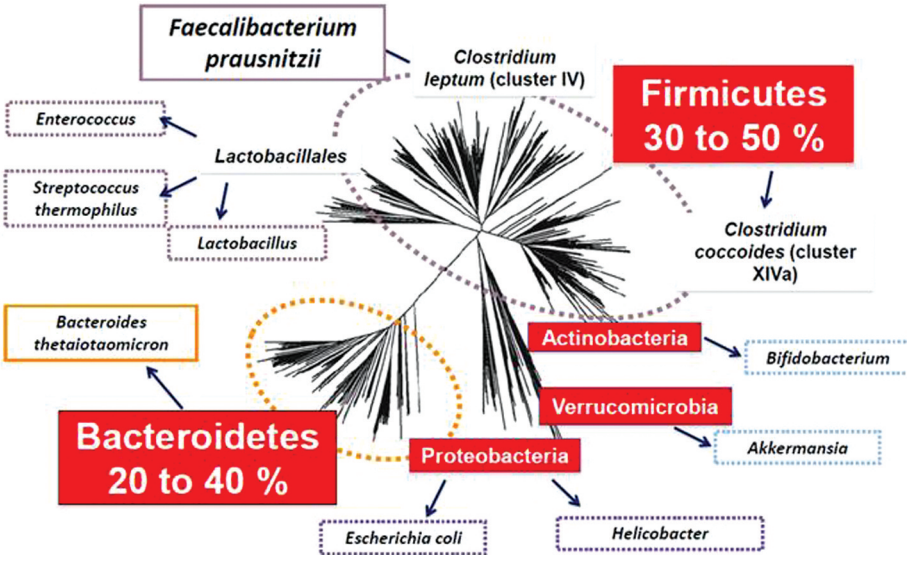

Figure 2. *Phylogenetic diversity of the human gut bacteriome.*

the intestine and produce high levels of thiamine (vitamin B1) and folic acid (vitamin B9). Enterotype 2 is linked to a high-fiber, high-carbohydrate diet (47). To avoid an overgrowth of *Candida Albicans*, those with this enterotype should pay attention to the cereals they eat, preferring whole grains (48).

A preponderance of bacteria from the genus Ruminococcus characterizes ENTEROTYPE 3 (49). The enterotype 3 bacteria have the ability to colonize the superficial mucosa. Furthermore, the bacteria that make up this enterotype can absorb simple sugars, suggesting that

Table I. *Intestinal microbiota and Eubiosis functions.*

Fermentative decomposition of sugars produces organic acids and CO_2
Putrefactive decomposition of protein residues produces phenol, Indole, Cresol, NH3, and H2S
Fat oxidation and cholesterol and triglyceride control in the blood
Vitamin K, B1, B6, B12, PP or B3, Folic acid, Pantothenic acid synthesis
Biliary acids, Bilirubin, and steroid hormones decomposition
Drug biotransformation and absorption
Trophic feature, short chain fatty acid development (acetate, propionate, butyrate), enterocyte defence and reconditioning
Immunological function: The GALT system comprises 40% of all immune cells in the body.
Antimicrobial activity, acidification, antibiotic synthesis, spatial exclusion, H_2O_2 processing, Fe removal, and bile salt deconjugation
Mucous barrier effect, a physical barrier between the mucous layer and the outside world
Modulation of gene expression in intestinal epithelial cells: development of flora-friendly environments

they can play a role in immune system modulation (50, 51). Since it is easier to digest simple carbohydrates and sugars, ENTEROTYPE 3 can be linked to a propensity to gain weight (52). To prevent *Candida Albicans* overgrowth and insulin resistance issues, those with this enterotype should pay attention to the amount of fiber and cereals they consume, preferring whole grains (53).

Microbiota: Eubiosis *vs*. Dysbiosis

In eubiosis, the intestinal microbiota plays a defensive function by acting as a shield against microorganisms that reach the digestive tract, preventing intestinal infections. In this way, the microbiota and immune system work together to protect the body from infection (54). When pathogenic microorganisms outnumber those of the microbiota, it's called dysbiosis (55). The microbiota has the unusual ability to always keep the gut-associated lymphoid tissue (GALT) active, operating on an immunomodulatory system that enables it to identify what is harmful or not to the host organism (56, 57). Furthermore, the GALT gathers information about the resident microbial community, the inflammatory condition, the climatic situation (temperature, humidity, *etc.*), and the homeostasis inside the tube itself via the filaments of dendritic cells located within the digestive tract (58, 59). As a result, GALT and microbiota work together in a synergistic manner. The digestive role of the microbiota is unquestionably important; in reality, it digests vegetal polysaccharides and promotes B vitamin absorption (60, 61). It plays a critical role in the synthesis of many important vitamins, including vitamin K, which is necessary for blood coagulation (62). Furthermore, in the presence of eubiosis, it can reduce toxins in food, favoring their removal (63). As the intestine is colonized by pathogenic agents for humans, it releases contaminants, gases such as methane and hydrogen, and neurotoxins, resulting in abdominal distension and the emergence of irritating symptoms such as abdominal bloating, flatulence, diarrhea, and constipation (64). Table I shows the functions of the microbiota in eubiosis. In contrast to eubiosis, which controls inflammation, dysbiosis causes a shift in intestinal bacterial composition in favour of pathogenic microorganisms, resulting in the activation of proinflammatory cytokines and PAMPs (65). As a result, dysbiosis may be linked to both inflammation and a lack of immune system effectiveness (66, 67). The gut microbiota is characterized by a balanced composition of several bacterial groups, *i.e.*, increased bacterial biodiversity, when it is in a balanced state. The gut microbiota is healthier when the bacterial diversity is high (68).

When we talk about dysbiosis, we must keep in mind that there are many forms, each of which is defined by an abundance of pathobionts: certain potentially pathogenic bacteria that usually colonize our bodies will proliferate in some cases, causing disorders or pathologies. *Enterobacteriaceae* is an example of a bacterial family (69, 70).

Loss of commensals: on the other hand, a substantial loss of normally present bacteria may result in dysbiosis at various levels. A reduction in *L. reuteri* has been linked to autism spectrum disorders, for example (71). Furthermore, decreased bacterial diversity: poor diets, AIDS, diabetes, and other diseases are only a few of the factors that lead to a decrease in alpha-diversity and, as a result, dysbiosis (72, 73).

Bad eating habits (junk food or an abundance of simple sugars) and an unhealthy lifestyle combined with psycho-physical tension and sedentary lifestyle can all contribute to dysbiosis (74). The modern man is more prone to dysbiosis, which causes non-specific intestinal inflammation, leading to a state of chronic low-grade inflammation, due to poor dietary habits and an unhealthy lifestyle (precooked and added foods, fast meals, and an unhealthy lifestyle) (75). In summary, pathogens are opportunistic species that induce acute inflammation and disturb the gut microbiota's complex equilibrium, causing it to shift from eubiosis to dysbiosis. Functional alterations in T lymphocytes and the mucosa-localized immune system tend to be another cause of chronic intestinal inflammation. These changes are caused by a

variety of factors, including genetic, environmental, and immune characteristics, as well as diet and lifestyle (76, 77). The intestinal microbiota influences the immune system's growth and activities by influencing epithelial tissue responses as well as systemic immune responses (78, 79). In addition, in response to the involvement of the microbiota, the mucosal epithelium changes the expression of mucus and nutrient receptors and differentiates (80, 81). According to recent scientific studies, dysbiosis can play a role in the onset of autoimmune diseases including rheumatoid arthritis, by activating pro-inflammatory cells (Th1, Th17), as well as B cells, which promote the inflammatory cascade (82, 83). Furthermore, the host epithelium and immune system have been shown to alter the structure and function of the microbiota, which may affect antitumor responses to immune therapies (84, 85). An irregular immune response to intestinal bacterial flora is thought to play a role in the pathogenesis of chronic inflammatory bowel disease, especially in genetically predisposed people (86). The reduction of microbial diversity in IBD patients, as well as the connection between the existence of specific strains like *Mycobacterium paratubercolosis* and *Escherichia coli* and Crohn's disease, are some of the key findings that support this hypothesis (87, 88). There was a rise in *Escherichia coli* and *Streptococci* in patients with irritable bowel syndrome, indicating that the symptoms are followed by a decrease in Lactobacilli and Bifidobacteria, resulting in a mild inflammatory condition of the colon mucosa in these patients (89). Because of the contact with commensal bacteria, the inflammatory response in the intestine is modulated by active immunological processes that take place in the lymphoid tissue associated with the intestine (90, 91). Resistance to colonization is another essential feature assigned to the gut microbiota (92). Indeed, the presence of the microbiota protects the host from a potential pathogenic bacteria colonization (93). The mechanisms tend to be a combination of metabolic processes, such as short-chain fatty acid synthesis, direct competition for nutrients, and effects on the host's immune system (94). By chewing and breaking down food with enzymes from the salivary glands, gallbladder, pancreas, and intestinal wall, the food is reduced to mush. Food must first be micronized in order to move through the intestinal wall's close junctions, which act as a type of corridor between the cells. If good, these junctions are selective, allowing only digested food and microorganisms to move through (95, 96). Mucus is generated by the intestinal wall, which holds bacteria away from cell membranes (97). Maintaining the integrity of the intestinal wall is important for good health. When this dignity is compromised due to a variety of causes, we are left with a hyperpermeable disorder known as leaky gut syndrome. The leaky gut is a disorder in which the intestinal barrier's permeability is altered as a result of structural damage caused by the weakening or breaking of some of the junctions that hold the gut structure intact and functional, causing some cells to become permeable (Figure 4) (98, 99). The intestine's permeability is no longer as selective as it should be due to its lack of structural integrity. The intestine is also a massive excretory organ that removes toxins from the blood and lymph. Food particles, toxins, and microorganisms migrate into the bloodstream by permeable intestine microorganisms, causing a harmful chain reaction that would not occur if the barrier was intact and functional (100, 101). Bacteria, viruses, fungi, chemicals, and food all invade the lymphatic tissue associated with the gut. Food, in particular, may be a foe. If a person is intolerant to a food, or if the food is processed and contains harmful chemicals, the GALT will respond to prevent the food from entering the bloodstream and cause an anti-inflammatory and immunological response (102, 103). When the toxic load reaches the GALT's tolerance level, however, the GALT is perpetually alerted, triggering an inflammatory response that is quiet and unnoticed for long periods of time, but which, like a silent killer, threatens health day after day, leading to inflammatory diseases (104). Inflammation is another warning sign for the body, meaning that health will deteriorate if necessary steps are not taken right away.

Probiotics are live microorganisms that provide a health benefit to the host when provided in sufficient amounts. Both bacteria and yeasts have the ability to be probiotic. Bifidobacterium and Lactobacillus strains are examples, while Saccharomyces boulardii is the most commonly used yeast (105). Probiotics may exert their effects in the small and large intestines if they survive the acidic gastric environment and bile (106). They colonize the gut for a short time and then act by altering the colon's atmosphere in response to the persistence of ingested strains (107). Probiotics have two mechanisms for exerting their beneficial effects: one is direct, acting on the host's organs and tissues, and the other is indirect, acting on the intestinal microbiota (108). The promotion of the gastrointestinal wall's barrier function, the control of immune and systemic responses through the development of IgA and anti-inflammatory cytokines, the antagonism of pathogenic bacteria, and finally the synthesis of compounds with enzymatic activity or host beneficial metabolites are all examples of these mechanisms (Figure 5) (109, 110).

Prebiotics, on the other hand, are non-digestible components of the human body that have a beneficial impact on the host by promoting the development and activity of one or a small number of bacteria already present in the colon (111). Prebiotics include inulin, oligofructose, galactofructose, galacto-oligasaccharides, and xylo-oligosaccharides, which are non-digestible carbohydrates, oligosaccharides, or short polysaccharides (112). To be labelled as a prebiotic, a food product must not be hydrolyzed or absorbed in the upper gastrointestinal tract;

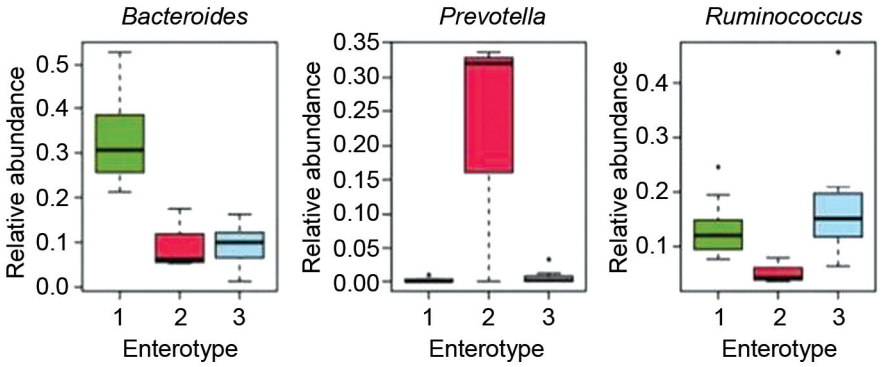

Figure 3. *The ecosystem of enterotypes.*

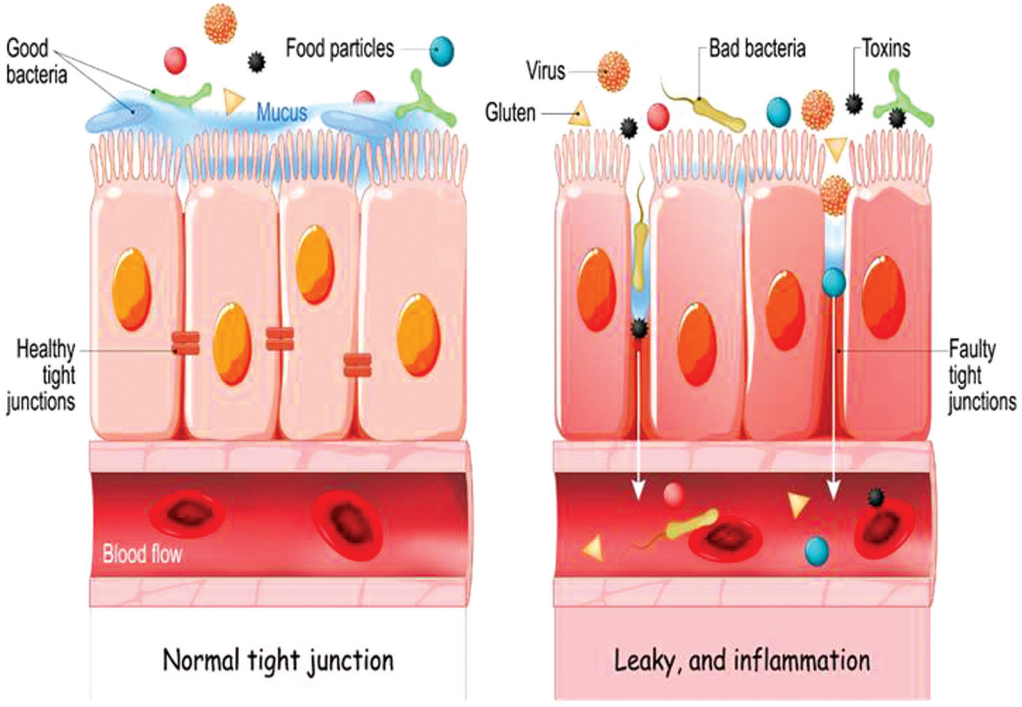

Figure 4. *The leaky intestine is a disorder in which the permeability of the intestinal barrier is affected by structural damage caused by weakening or breaking of joints, which keep the intestinal structure unchanged and functional, leading to a permeable effect on certain cells.*

instead, it must serve as a selective substrate for one or a few potentially beneficial commensal bacteria in the colon (113). Prebiotics' benefits are mediated by their ability to alter the intestinal microbiota and, more importantly, to selectively modulate the development of beneficial species already present in the colon (114). Prebiotics are directly fermented in the colon by endogenous bacteria to short-chain saturated fatty acids, with a pH reduction as a result of their chemical structure and inability to be digested by the host (115, 116). They may use this mechanism to have anti-inflammatory effects, such as stimulating the growth of regulatory T cells and lowering interferon levels (117, 118). Prebiotics may also prevent bacteria from adhering to the intestinal epithelium, stopping them from passing through (119).

Polyphenols are a form of secondary plant metabolite that has a distinct color and flavor. They've long been thought to

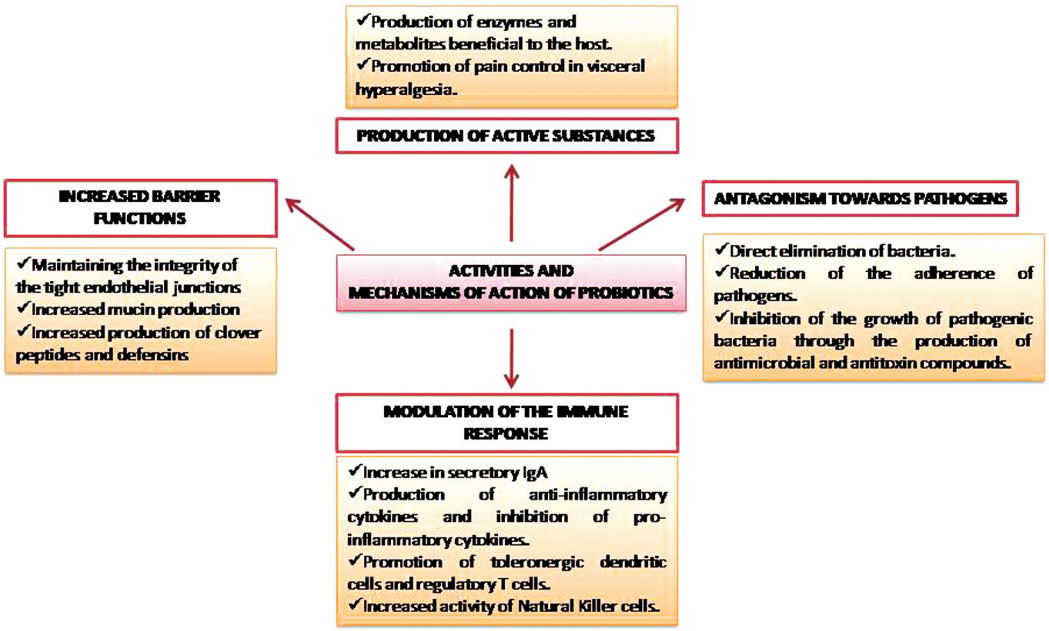

Figure 5. *Mechanisms of action of prebiotics.*

be the most likely class of food compounds capable of influencing physiological processes that protect against chronic diseases (120, 121). Food polyphenols are converted into biologically absorbable active species by the intestinal microbiota; approximately 95% of food polyphenols enter the colon (122, 123). It has recently been discovered that incorporating polyphenol extracts into the diet will help to optimize the state of eubiosis (124, 125). De-alcoholic extracts from red wine, as well as those dependent on polyphenols (resveratrol) and flavonols extracted from cocoa, are particularly important (126, 127). These extracts have been shown to change the human intestinal flora into a healthier profile, promoting wellbeing by increasing the amount of beneficial bifidobacteria and lactobacilli (128, 129).

Polyphenols (PP), the key non-absorbable flavonoids, were also shown to minimize obesity and control the expression of genes linked to lipid metabolism in mice fed a high-sugar, high-fat diet for a span of 20 weeks (130). Polyphenol treatment reduces weight gain and enhances the anti-inflammatory effects of lipopolysaccharides (which are among the causes of gut permeability) (131). PP therapy also reduces endogenous metabolites linked to insulin resistance, according to the urinary metabolic profile (132, 133). PP administration significantly decreased the Firmicutes/Bacteroidetes ratio and increased the rate of Akkermansia (a genus of bacteria that appears to have anti-obesity and waist circumference-reducing effects in humans) by eightfold, according to microbiota gene sequencing (134). These findings indicate that PP activates the intestinal flora and metabolome, resulting in metabolic homeostasis benefits.

Apples contain non-absorbable oligosaccharides and a variety of other molecules that aid the intestinal microbiota in maintaining a healthy state of dynamic equilibrium (135, 136). In reality, they have been shown to help rebalance the variability of the different microbial species that are beneficial to human health in a variety of pathological conditions (137, 138). Some studies are promising, and given the various molecules found in red apples, they can back up the old adage that "an apple a day keeps the doctor away." A recent study found that a pectin derivative of the molecules modulates the gut microbiota while also improving the gut's barrier function (139, 140). Apple polysaccharides prevent dysbiosis and chronic inflammation, as well as modulating permeability, according to the authors of a recent report (141, 142).

Physical activity. Although there is a large body of evidence supporting the effect of diet on gut microbiota, the impact of exercise has only recently become a topic of interest. Exercise has been shown to change the gut microbiota without affecting the diet. Several observational studies show that a higher ratio of Firmicutes to Bacteroidetes is associated with higher VO2 max and that women who exercised for at least 3 hours per week had higher abundance of several butyrate-producing bacteria, including Akkermansia muciniphila, which has been linked to a lean

physique (143-145). While these studies found a connection between beneficial microbiota and exercise, they were conducted in healthy people and did not account for other factors such as diet, which are known to influence gut microbiota, implying that the findings might not be due solely to exercise. More recent experimental studies in a controlled setting show that 30-60 minutes of aerobic exercise three days per week is sufficient to cause substantial changes in gut microbiota, though the changes vary in lean *versus* obese people (146). It's also true that six weeks of sedentary living after the exercise intervention helped to reverse many of the changes in the gut microbiota that were identified during physical activity, suggesting that exercise's effects are temporary and easily reversible (147).

Conclusion

The interaction of the gut microbiota with the patient's physical condition provides a potentially useful modality for influencing the onset, development, and treatment of a variety of metabolic diseases, autoimmunity disorders, and oncologic diseases. The gut microbiota can be thought of as a potential new goal for improving treatment efficacy and long-term health outcomes by retraining the patient's metabolism, molecular signaling, and immune responses in a beneficial way. Further research is required to better understand the processes affecting the intestinal microbiota and the host organism, as well as the potentials that exist between the intestinal microbiota and the sensitivity to treatments for oncological therapies or inflammatory bowel diseases. Furthermore, further characterization of the gut microbiota in relation to treatment response is required, which could lead to strategies to optimize the gut microbiota prior to treatment. It has the ability to limit the onset of multiple side effects associated with the treatment of inflammatory diseases such as cancer and chronic inflammatory bowel disease by intervening on the regulation of the intestinal microbiota, making the therapies more successful and tolerable. Diet, prebiotics, and probiotics, as well as moderate and aerobic exercise, may all be considered effective methods for improving gut microbiota pretreatment and mitigating disease-associated treatment or dysbiosis in order to improve wellness and reduce the likelihood of recurrence. By reducing the negative effects of common comorbidities including obesity, this form of intervention may also have a metabolic advantage. To find safe and efficient ways to integrate these techniques into clinical care pathways, more animal and clinical research is required. By improving our understanding of the interactions between the gut microbiota and the risk of inflammatory and metabolic diseases, we may be able to develop safe and successful gut microbiota-based treatments that will benefit the entire population.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Rosa Divella and Angelo Paradiso drafted the revision, and all the other Authors contributed in the same way.

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