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Review

Revisiting dietary effects on the gut microbiota and their implications in health and disease

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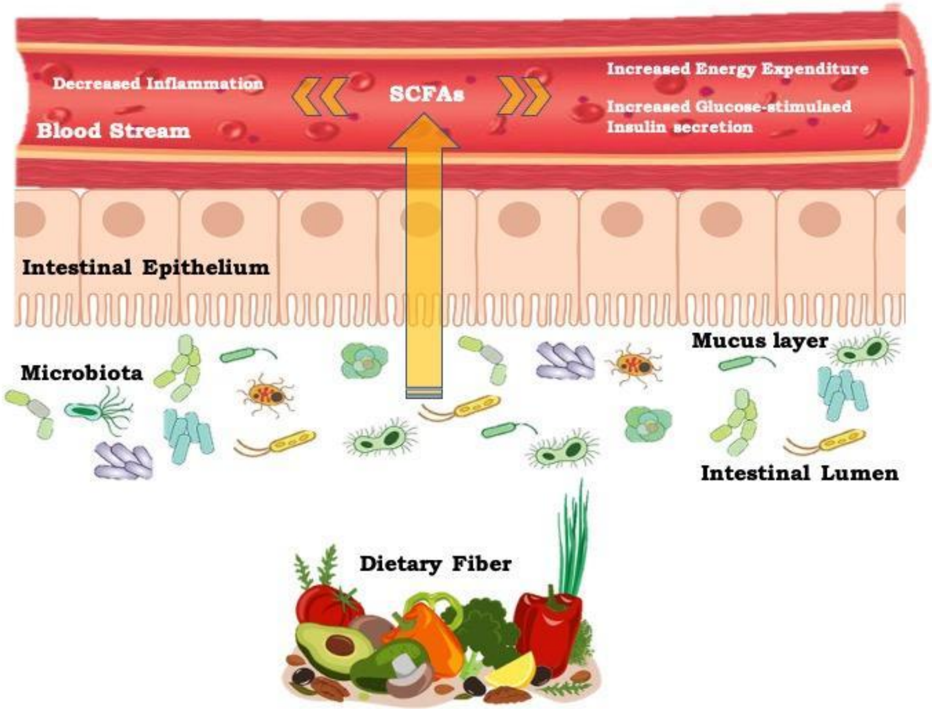
Abstract

The interaction between the gut microbiota and its mammalian host is influenced by diet. The host can absorb small metabolites produced by the microbiota, which can alter a range of physiological processes. Several types of gut microbes are linked to immunological and metabolic illnesses, as well as the host's overall health. *Bacteroides*, *Clostridium*, and *Bifidobacterium* are frequently found among these gut flora. We look at how the human intestinal microbiome is influenced by nutrition obtained from plant or animal based diet and how this can affect health and disease. Anaerobic bacteria in the colon produce short chain fatty acids (SCFAs) as the principal metabolic products of fermentation. As possible mediators, these fatty acids have been connected to the gut microbiota's influence on intestinal immune function. They've also been implicated in the treatment of inflammatory disorders such as obesity, type 2 diabetes, and heart disease. To this end, the Mediterranean diet (MD), as compared to a westernized diet, has more dietary fibre, leading to the generation of SCFAs. MD thus, has a favourable impact on the immune system and gut bacteria. As a result, the Mediterranean diet is encouraged not only as a potential aid in the treatment of numerous ailments, but also as a means of promoting global health.



Keywords

Microbiota; Diet; Inflammation; Short-chain fatty acids, Inflammatory bowel disease; Mediterranean diet

Introduction

Since the earliest times, microbes have played an important role in our biosphere. These microorganisms are also a

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significant element of the human body, that harbors trillions of microbes and is recognized as the "human microbiome." Every individual has a unique microbial flora on their skin and mucous membranes right after birth through death. These are known to have an important role in the normal functioning of multicellular organisms' vital systems (such as digestive, immunological, and neurological systems), as well as in health and disease [66, 19]. Rapid advancements in high-throughput sequencing technologies and humanized gnotobiotic models, that explore the function of the microbiome in human health and disease, have sparked interest in the human microbiome, particularly the gut microbiome, in recent decades.

The human gut microbiome contains ~ 10^{13} to 10^{14} commensal microorganisms, such as bacteria, archaea, viruses, fungi, and protists, that live in the human digestive tract [54, 84]. These microorganisms live inside an individual from conception to death, and the microbiome can alter substantially during different stages of life [22, 44]. However, when a person's diet is drastically altered, the biggest shift occurs. Dietary changes and eating habits have a significant impact on the microbiota [36, 76, 62]. Probiotics and prebiotics are the two key dietary interventions that are intended to provide health benefits. Probiotics help the host organism's immunity by replenishing the gut flora and reducing inflammation and other gastrointestinal illnesses [83]. By enhancing mucosal barrier function and increasing epithelial integrity, they may also aid to improve host health immunological function. This is accomplished by restricting mucosal passage of organisms and metabolites from the lumen and enhancing mucosal antibody production. [96]. Prebiotics, on the other hand, are dietary ingredients such as specialised plant fibres that help beneficial microbes grow and function better. They also nourish the gut's healthy microbiota, which in turn influences the bacterial composition of the gut microbiome. In a nutshell, probiotics are good bacteria, while prebiotics are good bacteria's food. *Lactobacillus* and *Bifidobacterium* are two of the most widely consumed probiotics. Probiotics are in greater demand as a result of growing public awareness of their positive effects on health. As a result, a tailored dietary intervention in the gut microbiota may be beneficial for disease management as well as healthy ageing [28, 43, 64, 74].

Role of diet in the gut microbiome health

Both intrinsic (host genetics, immunological, and metabolic reactions) and extrinsic (diet, lifestyle, and medication) variables regulate the microbiota of the human gut [75, 90, 91]. These variables are instrumental in the development of a distinct microbiome that differs from person to person. Among these key aspects, diet is a critical component that can considerably influence or alter the composition of the gut microbiota. Essentially, the bacteria in the gut have an impact on how much nutrients and energy the human host can get from their meals. The end products of the food digested as well as the undigested dietary substances are further metabolized by the resident gut flora to produce different diet derived metabolites like SCFAs or the secondary metabolites produced by microbes [36, 85].

Bacteria from two major phyla dominate the gut microbiome, accounting for approx. 95–97.7% of the total gut microbiota: gram-positive *Firmicutes*, which include the genera *Lactobacillus, Enterococcus, Clostridium, and Faecalibacterium*, and gram-negative *Bacteroidetes*, which include prominently the genera *Bacteroides* and *Prevotella* [37, 50, 65, 81]. The balance between these two major bacterial groups, Firmicutes and Bacteroidetes (F/B ratio), is commonly recognised as a key sign of gut dysbiosis. The increase in the F/B ratio i.e., a substantial increase in bacterial species like *Clostridium*, *Enterococcus, etc*. is linked to obesity and a decrease in this ratio is linked to inflammatory conditions like inflammatory bowel disease (IBD). Individual variations in gut microbiota composition due to diet have been studied extensively, and research evidence suggests that vegans and vegetarians have minimal differences amongst them [36, 42, 86]. A diet majorly based on plants appears to benefit human health by supporting the establishment of a diversified gut flora [92].

Effect of Plant based diet

A plant-based or vegan diet includes all vegetarian meals but excludes animal-derived foods, such as dairy products (included in the vegetarian diet). The vegan diet has been shown to raise *Bifidobacterium* and *Lactobacillus* populations due to its high polyphenol content. This is due to the fact that polyphenols increase the number of bacteria that can metabolise complex carbohydrates to create SCFA, which are crucial for the control of metabolism, inflammation, and illness [41]. These are vital for cardiovascular health because of their anti-inflammatory properties [50, 12, 7]. In addition, the higher fibre content of vegan meals compared to omnivore diets encourages the growth of fibre-degrading bacteria such as *Bacteroides, Prevotella, Bifidobacterium, Ruminococcus*, and *Clostridium*, etc. that can metabolise carbs and vitamins [50, 94, 72].

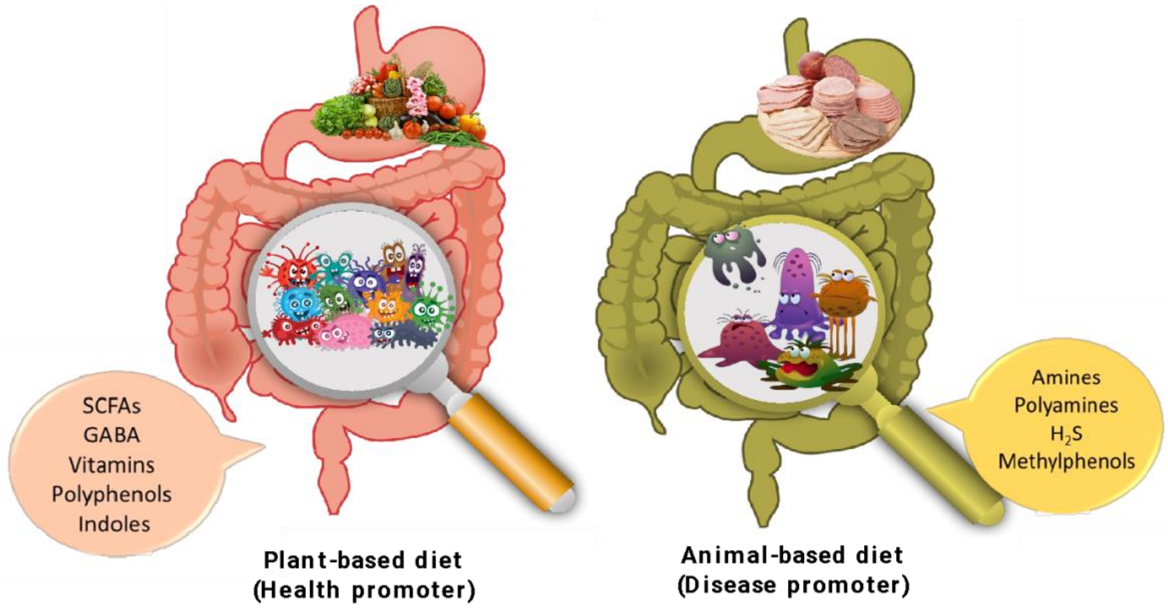

Figure 1: Long-term consumption of an animal protein-rich diet raises illness risk by creating harmful metabolites in the colon, such as amines, H_2S, and ammonia. Long term intake of plant-based diet leads to the production of SCFAs which have been linked to tumour-suppression and anti-inflammatory effects.

As a result, with fibre-rich vegetarian and vegan diets, short-chain fatty acids (SCFAs) like butyrate, acetate, and propionate, which are products of microbial fermentation, are elevated in the stomach (Figure 1). Gut microbiota also helps in breakdown of indigestible dietary fibres, polysaccharides, peptides, and sugar in the cecum and colon, that are resistant to digestion by the host enzymes. These SCFAs are colonocytes' primary energy sources, and they've been linked to a reduction in inflammatory bowel disease, type 2 diabetes, obesity, and immunological disorders. They also improve host immunity to infections and regulate key intestinal activities such as intestinal motility, and mucus formation [95, 79, 38]. Additionally, butyrate and propionate also stimulate gluconeogenesis in the liver and gut, which helps to maintain glucose and energy homeostasis. As a result, they've been suggested as promising therapeutic targets for both diet-induced obesity and disorders like Crohn's disease and ulcerative colitis [21, 46]. Further, in addition to the well-known protective function of SCFAs, proteins like flagellin, poly-galacturonase (involved in the degradation of pectic substances), and levansucrase, that are specifically associated with the diet of vegans and vegetarians, have been reported to have tumour-suppression and anti-inflammatory activities [17]. Isothiocyanates, mostly present in plants such as cruciferous vegetables, also have cytoprotective and anti-oxidant properties [86, 23].

Another important aspect of a plant-based diet that influences gut bacteria is the presence of non-digestible carbohydrates like starch and some sugars that can be fermented by gut bacteria in the large intestine, thereby providing energy and nutrients, resulting in a significant increase in lactic acid bacteria, *Ruminococcus*, and *Roseburia* species, as well as a decrease in *Clostridium* and *Enterococcus* species. Interestingly, as compared to plant-based diets, animal fat and protein-rich diets also exhibit unique alterations in gut microbial composition [18, 33, 10, 70].

Effect of Animal based diet

Animal-based diets, such as meat, cheese, and eggs, are high in protein (including dairy and meat protein) which provides the human body with roughly nine essential amino acids. Researchers found that red meat (pork and beef) provide good source of nutrients such L-carnitine, choline, B vitamins, copper, manganese, zinc, and heme iron [1, 80]. Beef led to a rise the relative abundance of *Blautia*, *Clostridium*, *Proteobacteria*, *Lactobacillus*, and *Firmicutes* in mouse, rat, and pig models while a decrease in *Bacteroidetes*, *Bifidobacterium*, and *Akkermansia* [98, 99]. This upsets the F/B ratio and may lead to obesity. In addition, the meat type and its cooking method also influences the microbial profile in human gut. Fried meat consumption, for example, reduces the amount of *Flavonifractor* as well as the beneficial faecal co-metabolites (butyric acid and valeric acid). Conversely, this increases the abundance of carnitine and melengestrol acetate, which are both harmful co-metabolites. Also, abundance of *Dialister*, *Dorea*, and *Veillonella*, all belonging to the *Firmicutes* phylum increases with consumption of fried meat [26]. It has also been discovered that following a ketogenic diet reduces the relative abundance of *Dialister*, *Eubacterium rectale* and *Bifidobacterium*. A 'ketogenic' diet mainly consists of foods rich in fats, moderate in proteins and very low carbohydrates and fibres, which includes foods like meats, poultry, fish, eggs, butter, cream, nuts and green leafy vegetables. Also, artificial and nutrition-less sweeteners may also be added in place of sugar in a ketogenic diet. The F/B ratio is also disrupted by ketogenic diets, resulting in an increase in *Bacteroidetes* and a decrease in *Firmicutes* [57, 4].

Excessive consumption of meat and meat products, particularly red and processed meat, has been associated to the development of inflammatory bowel disease (IBD), colorectal cancer (CRC), cardiovascular disease, and metabolic disorders such type 2 diabetes mellitus and obesity, according to studies [25, 47, 67, 69, 73]. The cooking and consumption of red meat not only reduces SCFAs but also causes the production of N-nitroso-compounds and heterocyclic amines, both of which raise the risk of colorectal cancer. Furthermore, animal protein consumption is associated with increases in trimethylamine N-oxide (TMAO), a molecule associated to an increased risk of heart disease [80]. By boosting platelet hyper-responsiveness to various agonists, TMAO can generate extremely high levels of vascular inflammation and pro-thrombosis, and it may be involved in the pathophysiology of cardiovascular diseases (CVDs) like atherosclerosis, hypertension, myocardial infarction, type 2 diabetes, obesity [30, 97]. Also, long-term intake of a diet rich in animal protein increases the risk of central nervous system (CNS) diseases like multiple sclerosis, by producing toxic metabolites in the colon, including amines, H_2S, and ammonia [8].

White meat diet (like fish), on the other hand, may have metabolic benefits by lowering the risk of cardiovascular disorders and Age-Related Macular Degeneration (AMD). The high quantities of n-3 polyunsaturated fatty acids (PUFAs) in the diet have been linked to the beneficial effects of fish eating. Similarly, fish oil has been associated to higher *Lactobacillus* and *Akkermansia muciniphila* levels as well as reduced gastrointestinal inflammation [48, 68]. Omega-3 PUFAs from fish can also help to reverse gut dysbiosis and boost SCFAs synthesis [13, 55, 88].

Effect of Western and Mediterranean diets

Diets vary greatly over the world due to differences in economic development, as well as agricultural and cultural practises. They also vary markedly from west to east. Americans and Europeans are the primary followers of the Western diet. Asians, Chinese, and their neighbours, on the other hand, mostly follow the Eastern diet. Residents of the same geographical zone and, in some cases, within the same country, may well have distinct eating habits depending on whether they live in urban or rural areas and whether they belong to communities with varied socio-cultural traditions. Variations in eating habits can explain the significant influence of geography on the structure of gut microbial communities [49].

Several countries have adopted the Mediterranean diet, which is a traditional dietary regime. This diet consists of an increased intake of fibres, cereals, vegetables, nuts, and fruits, as well as a low intake of fish, seafood, white meat and eggs, poultry, and dairy. While, the typical Eastern diet consists of rice or noodles, soup, and a variety of vegetable and meat dishes. The African cuisine is strikingly similar to that of Eastern countries because it is based mostly on local products as well [24]. The "Western" diet in the developed world differs greatly from that of previous generations, with the most prominent difference being a move from a mostly plant-based to a predominantly animal-based diet. A Western-style diet is characterised by calorie-dense foods high in glycemic carbs, saturated fats, animal proteins, and limited amounts of vegetables and fruits. As a result, substances that promote a pro-inflammatory environment in the colon are present in the western diet. As a result, it's unsurprising that it's being considered accountable for the rise in the frequency and severity of IBD as a primary underlying cause [71]. Furthermore, research investigations have revealed that switching to a Western diet has a negative impact on the gut microbiota [6, 77]. The western diet is poor in microbiota-accessible carbohydrates (MACs), which might reduce microbial diversity irreversibly, and lead to a substantial decrease of beneficial bacteria in the digestive system.

The Mediterranean diet is high in both complex and insoluble fibres when compared to a typical Western diet. Several studies have found that certain foods, particularly dietary fibre and proteins, have significant effects on gut microbiota composition and metabolite production, which impacts a variety of features of the host's immunological and metabolic health [9, 14, 53, 58, 63]. A high dietary fibre intake is widely perceived to support an excellent gut microbiota modulation/maintenance, with a reduced population of *Firmicutes* and a higher population of *Bacteroidetes*, resulting in high levels of SCFAs in the gut, particularly butyrate. These SCFAs maintain energy homeostasis in host immunological activities and normal gut physiology, that helps to keep the colon healthy [15]. As a result, the amount of SCFAs produced is frequently used as a measure to assess the health of microbiota. Higher levels of *Roseburia*, *Lachnospira*, and *Prevotella*, as well as enhanced SCFA synthesis, have been associated to a plant-based diet. SCFA levels in the faeces of IBD patients were shown to be significantly lower than in healthy controls, suggesting that SCFAs may be preventive towards IBD [2, 61].

Choline and L-carnitine, both of which are thought to be beneficial to heart health, are found in eggs, red meat, and cheese in a conventional Western-style diet, but in less levels in a Mediterranean-style diet. L-carnitine is delivered to microorganisms in the human intestine by eating red meat. There it is broken down by these bacteria and converted to TMAO. High TMAO levels in the urine have also been linked to poor compliance to Mediterranean diet [40, 89]. As a result, it's probable that some of the Mediterranean diet's favourable benefits on host cardio-metabolic health are mediated in part by microbiome-related mechanisms [18, 80]. Thus, the Mediterranean diet affects gut microbiota profiles (such as causing an increase in levels of *Bacteroidetes*, *Lactobacilli*, *Clostridium*, *Faecalibacterium*, and *Bifidobacteria*, or lowering the levels of *Firmicutes*) and therefore can impact the variability, features and functions of various gut microbes, enhancing healthy metabolites that may provide substantial advantages to the host [24].

Effect of Processed foods

Mediterranean diet may also contribute to the health benefits with the consumption of fewer processed foods than a Western-style diet, which has a significantly larger proportion of processed foods of plant and animal origin. While food processing has been around since the dawn of time and is necessary to assure the safety of food products, digestibility, and palatability, current socioeconomic changes, however, have led to consumption of unhealthy food products and dietary practices. Food processing scales can range from operations like packaging and freezing, which do not greatly modify the original foodstuff or its nutritional value, to processes like extreme heat-treatment, which dramatically alter both the look and nutritional value of the product. As a result, a scale must be developed to show the extent to which a food product has been treated in terms of the nutritional content that has been altered or lost [56].

Micronutrient levels in ultra-processed foods as a result of the treatments are very less than that of natural foods [20, 31, 51, 82]. A processed-food-rich diet, such as that seen in Western diets, may thereby raise the risk of vitamin or mineral deficiency. Because many micronutrients have well-known roles in the human body, micronutrient deficiency leading to altered metabolic pathways is apparent. Micronutrient insufficiency has been demonstrated to impact the gut flora. This is because micronutrients are required for optimum growth of certain bacterial processes or strains, such as vitamin B2 is required for *F. prausnitzii* to grow. A lack of vitamin A, zinc, folate, or iron, for example, has a deleterious impact on gut microbial diversity [5, 39]. Hibberd et al in 2017 used gnotobiotic mice model systems to demonstrate that acute deficiency of vitamin A drastically affects the bacterial community and leads to a profund increase in *Bacteroides vulgatus* [32].

Micronutrient deficiencies have been linked to a number of health issues such as oxidative stress, resistance to insulin, leptin secretion, increase in inflammatory markers etc. [11, 32]. By altering gut flora and their metabolism, Western eating patterns that contain a lot of processed foods may produce a digestive system imbalance [56].

Other important components of processed foods items, the food emulsifiers increase gastrointestinal inflammation, while non-nutritive artificial sweeteners, in processed foods are linked with insulin resistance in metabolic disorders. Long-term consumption of processed foods containing food emulsifiers (such as sodium sulfite and P-80) suppresses the growth of anti-inflammatory bacteria like *Faecalibacterium prausnitzii* [35]. Furthermore, research with mice have revealed that dietary emulsifiers reduce microbial diversity while increasing the number of *Gammaproteobacteria*, which has been linked to metabolic disorders, inflammation, and cancer [29, 78]. Refined carbohydrates, sugars, omega-6 polyunsaturated fatty acids, and a lack of fruits and vegetables (all trademarks of processed meals) have all been related to an increased risk of developing IBD [2, 60].

Thus a reduced intake of processed foods with calorie restriction can improve gut bacteria composition and diversity. This is achieved by protecting/fostering population numbers of various beneficial bacterial species [59].

A case study of obesity

Firmicutes and *Bacteroidetes* are the two major bacterial groups, accounting for ~60-80% and ~20-40% of the total gut microbiota, respectively. As a result, the ratio of these two bacterial groups (Firmicutes/Bacteroidetes: (F/B) ratio) is critical for maintaining normal intestinal homeostasis. Dysbiosis is defined as an increase or reduction in the F/B ratio, with a higher F/B ratio being associated with the risk of obesity and the latter with inflammatory bowel disease (IBD) (Figure 2) [27, 52, 83]. Ley et al. proposed the link between obesity and gut microbiota in 2005 [45], using 16S rRNA gene sequencing in mouse models that were of leptin-deficient, to examine the gut microbiota at the major phyla level (the leptin gene LEP produces the hormone leptin, which is implicated in body weight control). Gut microbiota from thin and obese donors were transplanted into germ-free/gnotobiotic recipient mice. Mice given microbiota from diet-induced obese donors (*ob/ob*) accumulated twice the amount of body fat as mice administered microbiota from lean donors. Furthermore, the mice with microbiota from obese vs. thin mice grew more fat tissue despite eating the same amount of calories as the latter, demonstrating that microbial communities derived from obese vs. thin mice have different effects on the energy balance of their new hosts [45]. These investigations revealed that the transplanted bacteria boosted caloric release in the host, implying that the gut microbiota is linked to obesity in the host. Furthermore, the gut microbiome has been demonstrated to alter host energetics, with transplanted gut bacteria extracting more energy from the same amount of calories as normal mice [93]. This is because the gut microbiota transferred modified host genes that affect adipocyte energy deposition [3, 87]. A link between the gut flora and obesity has even been discovered in human studies. In overweight/obese people, lower stool bacterial diversity has been linked to more prominent obesity. The F/B ratio was also shown to be higher in obese individuals, with more *Firmicutes* and about 90% fewer *Bacteroidetes* than lean ones, according to sequence analysis of faecal samples. Similarly, obese patients who were put on a low-fat or low-carbohydrate diet for at least a year had less *Firmicutes* in their colon and more *Bacteroidetes*. As a result, such research suggests that lifestyle changes, such as dietary changes, does affect gut microbiota [16, 41].

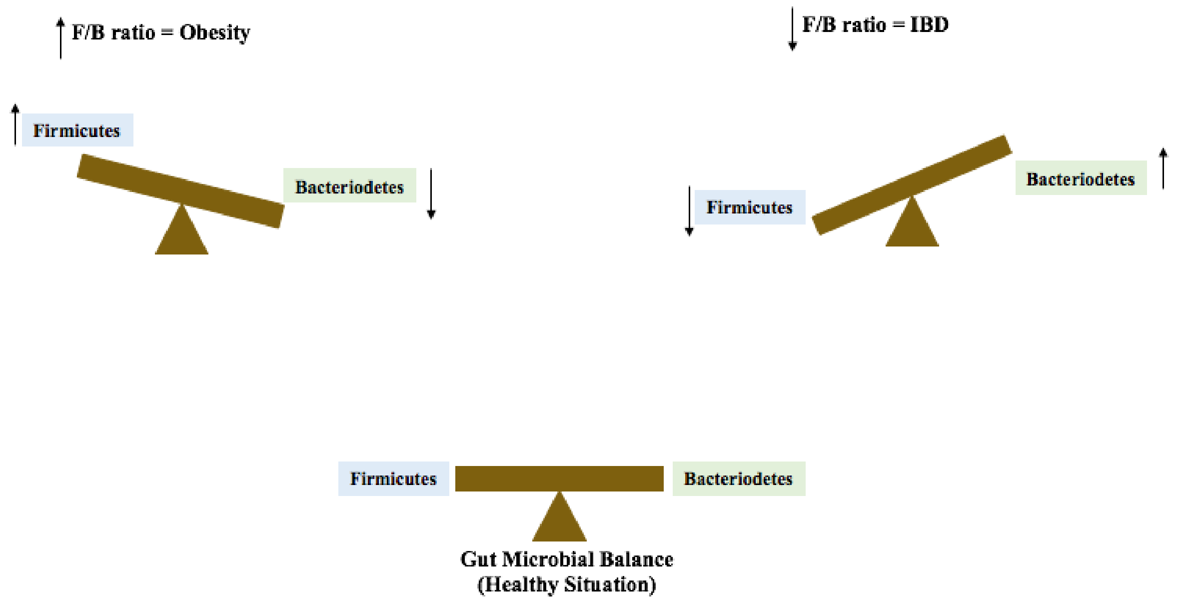

Figure 2: The ratio of the two bacterial taxa (Firmicutes/Bacteroidetes: (F/B) ratio) is critical for optimal intestinal homeostasis. A shift in the F/B ratio indicates dysbiosis, with a higher F/B ratio indicating obesity and a lower F/B ratio indicating inflammatory bowel disease (IBD)

Conclusion

Diet is one of the key players in the establishment as well as maintenance of gut microbiota of humans. The consumption of plant-based or animal-based diets can result in specific changes in the gut microbiota's composition. SCFAs or short chain fatty acids which are derived mostly from a plant-based diet have long been known to provide therapeutic effects. Alternatively, high consumption of animal-based foods may cause diseased states like IBD or cardiovascular diseases. The western diet relies heavily on foods of animal origin including processed foods, while a Mediterranean diet comprises of a 'balance' between animal and plant-based foods without compromising on the nutritional parameter. In addition to diet, different eating habits related to cooking and processing like western, eastern, ketogenic, Mediterranean, fried or well-cooked, can change the microbial composition of our gut microbiome as well as the concentrations of micronutrients in the body. Such dietary habits may also play a pivotal role in health and disease susceptibility. Thus, dietary interventions may be an effective way of causing changes in the intestinal microbiota. These are also feasible, at the same time, allowing for the repair of intestinal microbiome aberrations or imbalances and thereby improving overall health.

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Statements & Declarations

Author Contributions

The topic was conceived and designed by all authors. Yashika Thakran, Vanshi Bali, and Garima Badhan did the literature survey and wrote the first draft of the manuscript, and all authors provided feedback on prior drafts. The manuscript was critically revised and approved by the corresponding authors.

Compliance With Ethical Standards

None of the authors conducted any animal or human studies for this article.

Conflict of Interest

The authors declare that they have no competing interests that are relevant to the content of this work.

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