

# Human Gut Microbiome in Relation to Food, Nutrition, Health and Disease

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## Abstract

The role of gut microbiome in human health is important because it stimulates the immune system and protects the body from toxic food compounds and pathogenic organisms. Food and nutrition, in addition to other factors, have a profound impact on the microbial community in the gastrointestinal tract, on the intestinal microbiome, influencing human health. Dysbiosis and imbalances in gut microbial populations and their diversity can be associated with the development of many diseases, which can result from unbalanced nutrition and dietary changes. Therapeutic strategies were developed that utilize dietary modification. In this paper, the impact of different nutrients and diets on gut microbiome composition and functions is considered, as well as their potential for application as therapeutic modulators of gut microbiome in the prevention and treatment of serious diseases.

## Keywords

Gut Microbiome, Food Nutrients (Dietary Carbohydrates, Dietary Proteins, and Dietary Fats), Diets, Food Health Benefits, Diseases, Therapy

## 1. Introduction

The human microbiome, also called microbiota or microbes, consists of huge numbers of different species such as bacteria, fungi, parasites, and viruses that live in the organs of the human body or on particular parts such as the skin, gastrointestinal tract, and other organs [1] [2]. The role of microbiome in human health is important because it stimulates the immune system [3] and protects the body from toxic food compounds and pathogenic organisms that can be found in unsafe food and water that cause diseases. Various types of microbiological food contaminants, such as alimentary pathogenic bacteria, mycotoxins, molds, viruses, prions,

and parasites [4], have been linked to new occurrences of diseases with new views on the pathogenic effect of food contaminants [5].

Microbiome has multiple critical roles in human health, including synthesizing certain vitamins and amino acids [6], such as B vitamins, vitamin K, and vitamin B<sub>12</sub> [7]. The microbiome is especially important in breaking down complex carbohydrates with digestive enzymes [6]. Microbiome composition is a complex heritable trait. Many health-associated microbial taxa whose abundances were influenced by host genetics were identified. The microbiome varies genetically and biochemically and differs far more among different people than does the human genome itself [8].

Many factors can influence the microbiome, including food and nutrition, physical activities, medication, and environmental influences. Nutrition plays an important role in determining what kinds of microbiomes live in the colon [2]. Unbalanced nutrition and dietary changes can alter gut microbiome and cause serious health disorders. Diet affects gut microbiota composition and functions, having potential for application as a therapeutic modulator of gut microbiome [3].

## 2. The Effect of Different Nutrients on Gut Microbiome and Health

The human diet supplies the body with vital nutrients and influences the physiologic state of many organs, including also the life span [9]. Diet has a profound impact on the microbial community in the gastrointestinal tract, on the intestinal microbiome, influencing human health [10]. To understand the influence of diet on the gut and intestinal microbiome, research has focused on individual macronutrients, such as dietary carbohydrates, dietary proteins, and dietary fats [11].

### 2.1. Dietary Carbohydrates

Dietary carbohydrates represent a group of macronutrients that are major energy sources in the human diet with health benefits. They could be found in foods of plant origin (fruits, vegetables, edible seeds, grains, legumes, and wholegrains) and are classified according to their chemical structure, degree of polymerization (DP), and type of linkage ( $\alpha$  or  $\beta$ ). Dietary carbohydrates are divided into *digestible carbohydrates*, including monosaccharides (glucose, fructose), disaccharides (lactose, galactose) and *polysaccharides* (maltodextrin and starch) and dietary fibers (DFs).

### 2.2. Dietary Fibers (DFs)

DFs constitute a group of plant bioactive *non-digestible polysaccharides* that are naturally present in cereals, fruits, vegetables, and nuts with chemical structure and concentration that varied in sources and plant varieties [12]-[16]. DFs are important for both adult and children's health, preventing numerous diseases and improving immunity [12]. The health benefits of DF have been established for over 30 years and are numerous. Diets with higher fiber content can prevent gastroin-

testinal diseases and improve insulin sensitivity. Interest in dietary fiber intake is increasing, especially after the discovery of its impact on weight loss, lowering cholesterol reduction, reducing the risk of cardiovascular diseases such as stroke and heart disease, lowering blood sugar levels, reducing the risk of diabetes, enhancing the growth of healthy enteric bacteria, improving digestive system, improving bowel movement, reducing the risk of constipation, and reducing the risk of colorectal and breast cancer. Therefore, chemical structures, sources, classification, methods of analysis, and therapeutic functions of DF are under investigation by numerous researchers [12] [17]. Numerous AOAC Official Methods of Analysis have been adopted for the analysis of dietary fiber and its fractions [18].

DF is classified based on water solubility into *soluble dietary fiber (SDF)* and *insoluble dietary fiber (IDF)*. The ratio between these two fractions is an important factor in dietary fiber functional properties [19]. Dietary fiber is also classified based on microbial fermentation in large intestine (colon) into *fermentable dietary fiber (FDF)*, known by the name *prebiotic* and *non-fermentable dietary fiber (NFDF)*. The prebiotic definition is that indigestible fermentable fibers by enteric bacteria in the colon are converted into physiologically active metabolites such as short-chain fatty acids (SCFAs) and organic acids [20] [21]. The indigestible fermentable fibers by enteric bacteria in the colon include pectins, beta-glucans, guar gum, inulin, and oligofructose. The best sources for the fermentable fibers are beans and legumes [22]. It is important to highlight that plants such as psyllium are indigestible and non-fermented fiber by enteric bacteria in the colon, with only the function of stool regularity by retaining water [23]. DF is also classified according to chemical structure on the basis of the content of the glycosidic bonds and side chains into:  *$\beta$ -glucan, galactomannan, arabinoxylan, pectin, arabinogalactan, resistant starch, cutin, and suberin* [17]. DF influences gastrointestinal tract physiology, where it has water-holding capacity and viscosity that influence satiety, resulting in decreased food intake, improved mineral and phyto-chemical absorption, enhanced glycemic response, and reduced plasma cholesterol. It is prebiotics colonizing healthy enteric bacteria that inhibit the colonization of enteric pathogenic bacteria via a mechanism known as competitive exclusion.

Because of its health benefits, it is important to intake the right amount of fiber in the daily diet. The United States Food and Drug Administration (FDA) recommended the average value of 28 g/day for adults on a 2000-calorie diet. The recommended daily intake varies based on age and gender [24]. According to the Panel on Dietetic Products, Nutrition, and Allergies (NDA) at the European Food Safety Authority (EFSA), dietary fibre intakes should be 25 g/day for adults and 2 g/MJ for children from the age of one year [25].

### 2.3. Dietary Proteins

Dietary proteins are also essential biomolecules for both humans and animals, having significant effects on microbiome, health, and well-being at all stages of their life cycle, including DNA replication, transporting molecules, catalyzing metabolic

reactions, and providing structural support to cells [26]. Their chemical structure consists of linear chains of amino acids linked by peptide bonds, digestible by the main phyla in the distal colon [27].

Dietary protein is digested by gut microbes in the gastrointestinal tract, which is influenced by protein source, depending on the amino acid composition, accessibility, processing, and anti-nutritional content [28] [29]. Dietary protein is hydrolyzed to amino acids and small peptides by host proteases and is absorbed in the small intestine. Protein hydrolysis is affected by the amino acid composition, which influences protein chain flexibility, determining protein accessibility [27] [29] [30]. Dietary protein accessibility can also be influenced by other dietary components consumed with the protein or the matrix in which the protein resides [31]. Amino acids can be metabolized into numerous microbial metabolites that can affect host health and diseases. Composition, structure, and function of gut microbes depend on the source, concentration, and amino acid balance of dietary protein.

Several factors can influence protein fermentation, absorption, and functional properties in the gut and the composition of gut microbiome. These factors include protein source and content, dietary composition, glycation of protein, processing factors, and protein oxidation, which can affect the digestibility and bioavailability of dietary proteins [29]. Both the quantity and quality of dietary proteins digested by gut microbiome determine the balance and function of gut microbiome populations and the positive effect of dietary protein on gut microbiota and human health [31]. Therefore, it is important to know the source, structure and biological functions of dietary proteins.

There are four levels of protein structure depending on the orientations of amino acid residues in the protein structure [32]-[34]:

- 1) *Primary structure* with a linear polypeptide chain into which amino acids are arranged, only joined by peptide bonds and disulfide bonds.
- 2) *Secondary structure* arrangements of adjacent amino acids in a polypeptide chain. The most common secondary structures are alpha-helix and beta-sheet.
- 3) *Tertiary structure*, where the polypeptide chain folds into a three-dimensional space.
- 4) *Quaternary structure* with more than one polypeptide chain. Example of a quaternary structure is hemoglobin that carries oxygen in the blood and consists of four peptide chains (two alpha and two beta chains) to form a tetramer.

Proteins are also classified based on solubility to:

- 1) *Fibrous proteins*, which are insoluble in water and are mainly involved in supportive and protective functions in organisms. They are tough, strong, and linear in shape. Long, parallel polypeptide chains are cross-linked together, forming the protein, such as collagen, keratin, silk, and fibrin.
- 2) *Globular proteins*, being soluble in water and having metabolic functional roles in forming enzymes, hormones, and antibodies. The polypeptide chains are tightly folded into a sphere. The majority of proteins in the cells belong to globular proteins. Examples are DNA polymerase, RNA polymerase, and hemoglobin.

Based on structural complexity, proteins can be also classified into:

1) *Simple proteins*, with a simple structural organization and only composed of amino acid residues. They are also known as homoproteins and can be globular or fibrous proteins. Examples include keratin, elastin, albumin, collagen, and histones.

2) *Conjugated proteins*, which are complex proteins and loosely bound with one or more non-protein groups called prosthetic groups, including carbohydrates, lipids, metal ions, nucleic acid, phosphoric acid, and FAD. These proteins have globular shape and are soluble in water. Examples are nucleoproteins, metalloproteins, and lipoproteins.

3) *Derived proteins*, that are low molecular weight derivatives of protein derived from the partial hydrolysis of simple or conjugated proteins by acid, enzyme, or alkali. Examples include coagulated proteins, proteans, peptones, and peptides.

Based on biological functions, proteins are classified into [33] [34]:

1) *Structural proteins*, mostly fibrous proteins and insoluble in water, forming the components of bone, tendons, cartilage, skin, connective tissue, hair, and horn, including collagen, keratin, and elastin.

2) *Enzymes*, biological catalysts that work by reducing the activation energy of reactants, speeding up the metabolic reactions of cells. Most of them include globular conjugated proteins, such as nitrogenase, DNA polymerase, and lipase.

3) *Hormones*, protein hormones in the cells, including glucagon, insulin, and adrenocorticotrophic hormone.

4) *Respiratory pigments*, colored proteins conjugated, containing pigments (chrome) as their prosthetic group, including hemoglobin and myoglobin.

5) *Contractile proteins*, involved in muscle contraction at the expense of energy from ATP molecules, such as actin and myosin.

6) *Storage proteins*, which store metal or amino acids in the cells and are found in seeds, eggs, milk, and pulses, such as casein, gluten, and ferritin.

7) *Transport proteins*, responsible for transporting molecules or materials to their target destination and that form channels in the plasma membrane and are also involved in the formation of blood and lymph in animals. Serum albumin is an example.

8) *Defense proteins*, involved in protecting the organism from foreign microbes or materials, such as immunoglobulin (antibodies) and fibrinogen.

9) *Toxins*, including the toxic snake venoms.

## 2.4. Dietary Fats

Dietary fats are the main source of energy in the diet along with dietary carbohydrates and dietary proteins, having also a number of important biological functions such as supporting growth and development, delivering about 20% - 35% of body daily energy needs. Dietary fats and their metabolites have significant roles in the human body, including building structural components of cells and membranes.

In the diet, they are carriers for the fat-soluble vitamins A, D, E, and K, supporting their absorption in the intestine. Consuming sufficient amounts of fatty foods that contain these vitamins is essential for adequate intake of these micronutrients [35]. The gut microbiota and metabolic health are considerably influenced by dietary fat quantity and its saturation (the presence of double bonds between carbon molecules).

## 2.5. Fatty Acids

Fatty acids are necessary for the normal functioning of the body. There are two types of fatty acids: *essential fatty acids* and *non-essential fatty acids*. The body can only get essential fatty acids from food, while it can create non-essential fatty acids by converting amino acids present in the food. Essential fatty acids are involved in many physiological processes such as blood clotting, wound healing, and inflammation. Microbial species metabolize dietary fatty acids into various fatty acids [36].

Fatty acids are classified according to the presence and number of double bonds in their carbon chain into:

- 1) *Saturated fatty acids (SFAs)* that contain no double bonds.
- 2) *Monounsaturated fatty acids (MUFAs)* that contain one double bond.
- 3) *Polyunsaturated fatty acids (PUFAs)* that contain more than one double bond.

Unsaturated fatty acids in which the double bond is arranged in a *trans* configuration are *trans fats*. Consumption of *trans fats* is associated with cardiovascular diseases, diabetes mellitus, colon cancer, and others [37]. Both length and saturation of fatty acids affect the membranes in the body cells and their fluidity. Shorter chain fatty acids and those with greater unsaturation are less stiff and less viscous, making the membranes more flexible, which influences a range of important biological functions [38].

Essential fatty acids include linoleic acid (LA)—an omega-6 fatty acid, and alpha-linolenic acid (ALA)—an omega-3 fatty acid. Here also belongs omega-9 fatty acid, which is not an essential fatty acid, but one of the main MUFA found in plant and animal sources, having several health benefits such as anti-inflammatory and anti-cancer [39]. The human body cannot produce the PUFA, LA and ALA, which are essential for some vital functions. LA and ALA can be converted to longer-chain fatty acids and compounds with hormone-like or inflammatory properties. Omega-3 and omega-6 fatty acids make hormones called eicosanoids, which control the immune system, nervous system, and other hormones, thus they are necessary for the body to function correctly. Eicosanoids from omega-3 fatty acids promote heart health and can impact certain cancers and rheumatoid arthritis, while eicosanoids from omega-6 increase immune response, inflammation, and blood pressure [40] [41].

Unsaturated fatty acids are classified as “*cis*” or “*trans*” form, depending on whether hydrogen is bound on the same or on the opposite side of the molecule. Most naturally occurring unsaturated fatty acids are found in *cis* form. *Trans* fatty acids (TFAs) are divided into two groups: *artificial TFA* (industrial) and *natural*

*TFA* (ruminant). Industrial TFA is produced by humans and can be found in products containing vegetable oils/fats that have undergone a hardening process known as partial hydrogenation. TFA consumption is linked to adverse health effects [37].

Dietary recommendations for fats are issued by different international authorities, including the World Health Organization (WHO) and EFSA, as well as national governments and health authorities from a number of European countries [42].

### 3. Microbiome Dysbiosis, Health and Diseases

Under the term dysbiosis is meant a condition where the normal microbiome population structure is disturbed, generally as a consequence of many factors like medications, diet, and disease. Imbalances in gut microbial populations and their diversity can be associated with developing many diseases, including inflammatory diseases, cardiovascular diseases, obesity, type 2 diabetes, and several cancers [43]-[45]. Energy-dense diet with highly processed foods, containing emulsifiers and artificial sweeteners, can weaken the gut barrier, enabling bacteria or digested food to enter into the bloodstream. This can cause activation of the immune system, leading to many diseases [10].

#### 3.1. Inflammatory Bowel Disease (IBD)

The development of inflammatory bowel disease (IBD) is caused by a variety of factors, including environmental, genetic, immunologic or microbial factors from the digestive system [46], affecting the small and large intestines. The main types of IBD are ulcerative colitis and Crohn's disease.

#### 3.2. Crohn's Disease

Crohn's disease also affects the mouth, esophagus, stomach, and anus, targeting the mucosa and submucosa tissues. An important role in causing Crohn's disease has intestinal microbiota, increasing the abundance of Enterobacteriaceae, including *Escherichia coli* and Fusobacterium, *Serratia marcescens*, and fungal species like *Candida tropicalis*, compared to healthy patients. Metabolic changes refer to oxidative stress pathways and a decrease in basic metabolism and short-chain fatty acid production [47].

#### 3.3. Ulcerative Colitis

Ulcerative colitis occurs in the colon and distal ileum, targeting the mucosa tissue only. It causes long-lasting inflammation and ulcers in the digestive tract. It primarily affects the innermost lining of the large intestine (colon) and rectum. A higher incidence of *Enterobacteriaceae* and *Bacteroides fragilis* is evident in patients with ulcerative colitis compared to healthy patients [48].

#### 3.4. Irritable Bowel Syndrome (IBS)

Irritable bowel syndrome (IBS) affects the large intestine and symptoms include

cramping, abdominal pain, bloating, gas, diarrhea, constipation, or both [49]. The pain associated with this disease can be controlled or removed by changing the type of diet. Microbial populations are altered in patients with IBS, and it has been demonstrated that *Proteobacteria* and *Firmicutes* phyla flourish while Actinobacteria and *Bacteroidetes* are diminished compared to healthy controls. A greater abundance in the family Lachnospiraceae within the phylum *Firmicutes* has also been recorded.

A study conducted on children with IBS and healthy children by 16S ribosomal RNA gene sequencing classified different subtypes of IBS with a success rate of 98.5%, using limited sets of discriminant bacterial species. A novel Ruminococcus-like microbe was associated with IBS, indicating the potential utility of microbe discovery for gastrointestinal disorders. An increased abundance of several bacterial taxa from the genus *Alistipes* was correlated with a greater frequency of pain.

Specific microbiome signatures were associated with pediatric IBS, indicating the important association between gastrointestinal microbes and IBS in children. These approaches might be used in diagnosis of functional bowel disorders in pediatric patients [49].

### 3.5. Type 2 Diabetes

Type 2 diabetes (T2D), a metabolic disorder, is primarily caused by obesity-linked insulin resistance, with the gut microbiota playing an important role in the pathophysiology of T2D [50] [51]. Effective improvement in diabetes and obesity disorders might come from beneficial bacteria, such as butyrate producers like *Faecalibacterium* sp. and *Roseburia* [51]. Germ-free mouse models that are resistant to a high-fat diet that induces obesity (as a result of a lack of fermenting bacteria that can process complex carbohydrates) have demonstrated the association between gut microbiome and obesity.

### 3.6. Cardiovascular Diseases

Progression and pathogenesis of cardiovascular diseases (CVDs), including atherosclerosis, hypertension, and heart failure, can also be caused by microbiome dysbiosis, with a crucial role played by the production of trimethylamine-N-oxide (TMAO) as a net product derived from specific dietary nutrients [52]. A diet rich in animal proteins, including red meat and dairy products, could increase the abundance of bile-tolerant anaerobic bacteria such as *Bacteroides*, *Alistipes*, and *Bilophila*, leading to an increase of trimethylamine-N-oxide (TMAO), which plays a role in cardiovascular diseases (CVDs). L-carnitine, an amino acid in significant quantities in animal foods such as red meat, could play an essential role in the increased risk of CVD [53]-[55]. The gut microbiota can convert L-carnitine into  $\gamma$ -butyrobetaine and crotonobetaine, while each of these compounds can be converted into trimethylamine, which can then be converted to TMAO by liver enzymes [55].

It is confirmed that elevated blood TMAO levels are directly linked to patients with CVD, such as coronary artery disease and acute and chronic heart failure [53]. In patients with CVD compared to non-CVD patients with coronary risk factors, a lower abundance of the phylum *Bacteroidetes* and a higher abundance of the order *Lactobacillales*, in particular *Enterococcus* sp., has been evidenced [54]-[56].

### 3.7. Cancer

Many studies have been conducted on the involvement of the gut microbiome in the progression of cancer and acceleration of carcinogenesis, and the role of the gut microbiome in protecting host and gut homeostasis [57] [58]. The most affected organ by an alteration in gut microbes is the digestive system, with diseases of esophageal, gastric, colorectal, liver, and pancreatic cancers [59] [60]. Toxigenic *Bacteroides* and pathobionts *Fusobacterium* and *Campylobacter* are found in colorectal cancer [61] [62], and altered gut microbiome of animal models has been found to make hormone receptor-positive breast cancer more aggressive [63].

### 3.8. Neurodegenerative Diseases

Gut microbiome alterations have also been linked to many neurodegenerative diseases, including Parkinson's disease and Alzheimer's disease, as well as inflammatory central nervous system diseases [64]. The gut-brain axis interacts with intestinal cells and the enteric nervous system, as well as with the central nervous system [65]. The sympathetic nervous system can be stimulated by metabolites resulting from dysbiosis of the gut microbiome [66] [67], with adverse effects on learning and memory that lead to Alzheimer's disease [68] [69]. Certain bacteria belonging to *Bacteroidetes* (*Porphyromonas gingivalis*) in the brain may be involved in neurodegenerative disease, particularly Alzheimer's disease and periodontal disease [65] [70].

## 4. Diets in Relation to Gut Microbiome and Treating Diseases

The gut microbiome is strongly influenced by the composition [71]-[73], amount, and timing [74] [75] of its host's diet. Diets can be used to treat disease, but some of them can also have negative effects on health. Examples of diets that have positive effects on human health are Mediterranean and vegetarian diets, which are characterized as low in red meat, saturated fats, and processed foods and rich in polyphenols [76] [77]. Diet may also have indirect effects on health mediated by the gut microbiota. A diet with a negative impact on health is a Westernized diet, which is characterized by processed food rich in saturated fat, high in salt, high in processed carbohydrates, containing food additives, non-nutritive artificial sweeteners and emulsifiers, and low in fiber. This diet is correlated with the rapidly increasing incidence of obesity, metabolic syndrome, and CVD. Impacts of diet on the gut microbiota and health have been demonstrated through mechanistic studies in animal models [78].

#### 4.1. FODMAP Diet

Based on fermentable oligosaccharides, disaccharides, monosaccharides, and polyols, which are short-chain carbohydrates (sugars) that the small intestine absorbs poorly, the FODMAP diet can lead to digestive distress with symptoms including cramping, diarrhea, constipation, stomach bloating, gas, and flatulence. High FODMAP foods are recommended to be avoided in order to ease IBS and small intestinal bacterial overgrowth (SIBO) symptoms, although other therapies are often used.

#### 4.2. A Low FODMAP Diet

A low FODMAP diet can treat a variety of functional bowel disorders, such as IBS. It has been demonstrated to reduce gastrointestinal symptoms, decrease histamine and the IBS severity score while increasing p-hydroxybenzoic and azelaic acids [79] [80], reduce *Bifidobacterium* levels [80], and increase Actinobacteria richness (*i.e.*, number of species/taxonomic groups) [79]. It can also reduce the abundance of *Bifidobacterium* and increase the abundance of *Bilophila wadsworthia* [81], exerting beneficial effects on gastrointestinal symptomatology by decreasing the concentrations of unabsorbed, osmotically active short-chain carbohydrates in the intestinal lumen, which leads to a reduction in small intestinal water volume.

A healthy function of low molecular weight dietary fiber (LMWDF), such as fructo-oligosaccharides, galacto-oligosaccharides, inulin, etc., is the prebiotic property for enhancing the growth of beneficial bacteria such as lactic acid bacteria and *Bifidobacterium* in the colon [82]. These beneficial enteric bacteria ferment dietary fibers into SCFA and secrete metabolites for a healthy colon. Additionally, enteric bacteria cell wall debris enhances host immune response by activating cell immunity system of lymphocytes, including the enhancement of monocytes, macrophages, dendritic cells, natural killer and neutrophil cells.

#### 4.3. Exclusive Enteral Nutrition (EEN)

Exclusive enteral nutrition (EEN) is a completely liquid diet that can be used as a therapy to treat IBD, particularly Crohn's disease [83] [84]. It is based on the correction of nutritional deficiencies that are often associated with Crohn's disease, direct anti-inflammatory effects of EEN [85] [86], and the exclusion of a whole food diet that plays a role in Crohn's disease pathogenesis. The efficacy of EEN is reduced if some level of whole food consumption is introduced [87]. This nutrition has been demonstrated to promote significant rates of mucosal healing [88].

It has been shown that the consumption of EEN leads to a reduction in alpha diversity [83] [84], as well as the abundance of *F. prausnitzii* [83] [84] [88], *Roseburia* [88], and the *Bacteroides/Prevotella* group [83]. EEN-induced remission in Crohn's disease patients was associated with increased levels of the mucin degraders *R. gnavus* and *R. torques*, which do not produce butyrate [88], and butyrate levels are also significantly reduced on EEN [83]. Many of the gut mi-

crobiota impacts of EEN are likely due to the absence of dietary fiber in EEN [89]. Although the mechanisms are poorly understood, the positive effects of a fiber-free EEN diet in the treatment of Crohn's disease are based on strong clinical evidence.

Some studies demonstrated that long-term EEN feeding had impact on the composition of the gut microbiota, which resulted in beneficial effects on TNBS colitis through remodeling the gut microbiota and alleviating intestinal mucosal inflammation [90] [91].

#### 4.4. Very Low Carbohydrate Ketogenic Diets (VLCKD)

The ketogenic diet (KD) promotes high-fat intake, moderate protein intake, and very low carbohydrate intake, driving the body into ketosis and reliance on fat for energy. Foods that are commonly consumed on the ketogenic diet are meats, poultry, fish, shellfish, eggs, cheese, green leafy vegetables, nuts, oil, butter, mayonnaise, and cream, as well as non-nutritive sweeteners may be used to replace added sugar in the diet. Foods that contain higher amounts of carbohydrates, including grains, fruits, root vegetables, low-fat dairy, and legumes, are excluded. Therapeutic ketogenic diets are notably low in fiber.

A study in children for the treatment of intractable epilepsy examined fecal microbiota at baseline and after a KD intervention and showed decreased abundance of Firmicutes and increased abundance of Bacteroidetes. It was found that in the non-responsive group (no reduction in seizures), *Clostridiales*, *Ruminococcaceae*, *Rikenellaceae*, *Lachnospiraceae*, and *Alistipes* were enriched [92]. Elite athletes following a low-carbohydrate, high-fat KD showed increased *Bacteroides* and *Dorea*, and decreased *Faecalibacterium* [93]. In multiple sclerosis patients, a short-term decrease in diversity was observed that recovered and exceeded baseline after 6 months on the diet [94].

Study on body weight and obesity management in male and female C57Bl/6J mice revealed that long-term KD reduced body weight and fat mass only in females. This showed that gut microbiota contributes only partially to the nutritional changes in body weight and fat mass [95].

#### 4.5. Gluten-Free Diet

Celiac disease, which is an autoimmune disease with genetic predisposition and inappropriate immune response to cereal gluten, can be treated with a gluten-free diet [94] [96]. It is associated with dysbiosis [95]-[99] characterized by increased levels of *Escherichia coli* and *Staphylococcus* [97]. Celiac disease has also been associated with changes in the small intestinal microbiota, including a reduction in *Prevotella* and *Streptococcus*. Improvement in this disease was noted after treatment. Gut microbes can also modify the action of specific chemotherapeutic agents, including nonsteroidal anti-inflammatory drugs and cardiac glycosides, and outline the potential of fecal microbiota transplant as a therapeutic with a gluten-free diet [97]-[99].

## 5. Therapeutic Strategies Utilizing Dietary Modification

Diet, which contains components that provide energy to the host microbiota, plays a significant role in the maintenance of the complex microbiome. High-fat and high-sugar diets, and diets that are low in fermentable fiber, lead to dysbiosis, while diets low in fat and sugar, and high in fermentable fiber, particularly prebiotic fiber, can significantly promote proper energy homeostasis and immune response to reduce disease risk and promote overall health. In healthy conditions, dietary modification, as well as treatment with pro- and prebiotic use, can help maintain proper microbiota balance and promote proper energy and immune homeostasis.

### 5.1. Probiotics

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. They positively modulate the immune system, which leads to immunity potentiation. A number of studies prove that probiotics strengthen cognitive functions, reduce anxiety, and regulate the lipid metabolism in the human body. Probiotics used in humans are most often of the *Lactobacillus* and *Bifidobacterium* species. The effectiveness of probiotics may vary depending on treatment, disease, and strain or strains that make up the probiotic. Additionally, a probiotic may be effective in treating the disease but not in its prevention. Research to date suggests that probiotics have beneficial and multifaceted effects on human health, which encourages further experimental and clinical research. Some probiotic activities are well documented. Probiotic foods contain beneficial live microbiota that may further alter one's microbiome. These include fermented foods like kefir, yogurt with live active cultures, pickled vegetables, tempeh, kombucha tea, kimchi, miso, and sauerkraut [100].

### 5.2. Anti-Microbial Resistance and Natural Products

Microorganisms evolve resistance to antibiotics as a function of evolution. Antibiotics have accelerated bacterial resistance through mutations and acquired resistance through a combination of factors. Microorganisms that acquire resistance to chemotherapy (multidrug resistance) are a major obstacle to successful treatments. Phytochemical research was conducted in relation to the anti-microbial efficacy of selected natural product-derived compounds, as well as details of synergistic mechanisms and structures. The importance of compounds with natural origins has been emphasized, which can be used to create safer and more effective anti-microbial drugs by combating microorganisms that are resistant to multiple types of drugs [101]. Natural and biological products such as probiotics, prebiotics, herbal extracts, dietary fibers, and synbiotics have been documented for their potential to modulate gut microbiota composition and function, and clinical evidence supports their health-promoting effects and therapeutic potential [100]. Understanding the interactions between natural products and gut microbiota can provide valuable insights into their health-promoting effects and therapeutic potential. The functional

roles of the gut microbiota include anti-microbial defense, besides nutrient metabolism and gastrointestinal tract integrity [102].

Probiotic strains produce anti-microbial substances due to their high inhibitory action on Gram-negative bacteria, such as organic acids (lactic and acetic acids) and low molecular weight chemicals (bacteriocin). Entering the cell and accumulating inside the cell, they cause pH imbalance, resulting in anti-microbial activity, while bacteriocin and anti-microbial peptides exhibit a narrow activity by penetrating into cells or decreasing the cell wall synthesis of pathogens. Probiotic bacteria produce a variety of metabolic products like SCFAs, modulate the gut microbiome and improve health benefits by damaging peptidoglycan, representing a large polymer that forms a mesh-like scaffold around the bacterial cytoplasmic membrane [103].

Prebiotics that amplify the group of beneficial bacteria genera such as *Bifidobacterium* and *Lactobacillus*, as well as from other microbial taxa, also have an important role in microbiome modulation and application in anti-microbial resistance. It is due to their main characteristics: resistance to gastric pH, GI absorption and hydrolysis by enzymes; fermentation by microflora lining of the intestine and stimulation of growth/activity of the specific group of intestinal bacteria with health benefits [104] [105].

## 6. Effects of Plant vs. Animal Proteins Diet

The intake of plant-based proteins such as glycated pea proteins could increase the abundance of beneficial bacteria *Bifidobacterium* and *Lactobacillus* and decrease those of *Bacteroides fragilis* and *Clostridium perfringens* [106] [107]. In recent years, more attention has been growing towards pulses (mainly including lentils, beans, chickpeas, and peas), which could be a sustainable source of plant protein compared to animal proteins. The consumption of pulses is associated with positive gut microbial changes in rodents and humans with improved growth of genera *Bifidobacterium*, *Faecalibacterium*, *Clostridium*, *Eubacterium*, and *Roseburia*, primary producers of butyrate and acetate [105] [106].

A diet rich in plant-based proteins, such as pulses, represents a good alternative for substituting animal proteins to reduce gut inflammation-associated proteins such as methionine and cysteine. They also contain many resistant starches and bioactive compounds that are well known to positively influence gut microbial homeostasis [107] [108].

High consumption of animal-based proteins (as in a traditional Western diet) might exacerbate the growth of sulfate-reducing bacteria (SRB) such as *Desulfovibrio* spp. that produce hydrogen sulfide (H<sub>2</sub>S) from dietary inorganic sulfur and sulfated amino acids (*i.e.*, methionine, cysteine, and taurine), potentially increasing gut inflammation [109].

### 6.1. Effects of Different Fat Types

A high-fat diet (HFD), such as that with saturated fatty acids, leads to intestinal

dysbiosis with a decrease in Bacteroidetes and an increase in Firmicutes and Proteobacteria, resulting in increased insulin resistance, gut permeability, and adipose tissue inflammation [110]. High-fat diets containing milk fat with a high sulfide concentration could reduce disulfide bonds in the mucus, causing a defective mucus layer and increasing gut inflammation through the blooming of sulfate-reducing bacteria [111].

Monounsaturated fatty acids (MUFAs) (palmitoleic, oleic, and eicosenoic) could positively correlate with *Parabacteroides*, *Prevotella*, *Turicibacter* genera, and the *Enterobacteriaceae* family [112]. A MUFAs-rich diet (rich in sesame, pumpkin seeds, rapeseed, extra virgin olive oil, and peanuts) shows positive health effects with an increased gut microbiota diversity in healthy and unhealthy models, including humans at risk of metabolic syndrome.

Medium-chain fatty acids (MCFAs) contained in virgin coconut oil, human milk, and infant formulae could enhance the growth of *Bifidobacterium* and *Lactobacillus*, improving metabolic and cognitive functions [113]. Medium-chain triglycerides (MCTs) promote energy expenditure, weight loss, and lipid catabolism by improving gut microbial equilibrium and gut barrier integrity [114]. However, diets rich in coconut oil could increase levels of *Allobaculum*, *Clostridium*, *Lactobacillus*, *Staphylococcus*, and the Firmicutes to Bacteroidetes ratio, causing metabolic disorders and adipose tissue inflammation [115]. Omega-3 PUFAs exert significant positive effects on modulating the gut microbiota composition [116]. An imbalance in the Omega-6/Omega-3 ratio may contribute to a vicious cycle involving gut microbiome dysbiosis and potentially reduced Omega-3 PUFAs absorption. A high omega-6/omega-3 PUFA ratio may increase pro-inflammatory bacteria, whereas a low ratio may promote anti-inflammatory bacteria [117]. It has been hypothesized that high levels of dietary fat could lead to obesity. Although it is generally accepted that obesity is the result of a chronic positive energy balance, the homeostatic mechanisms involved in the regulation of energy metabolism discriminate between energy substrates at both the cellular and whole-body levels.

## 6.2. Personalized Nutrition

An individual's dietary plan based on the integration of life stage, current health status, and genome information forms the basis of personalized nutrition, which is made possible by nutrigenomics, a gene test-based nutrition approach. This enables improving knowledge and motivation to change eating behavior, dietary intakes, and quality of life [118]-[120].

The disclosure of genetic information and personalized nutrition interventions has been shown to effectively modify dietary behaviors. Studies have demonstrated that individuals who receive personalized genetic information are more likely to make positive dietary changes compared to those receiving general advice [118]. Web-based personalized nutrition interventions, like the Food4Me Study, have successfully influenced dietary patterns associated with the Mediterranean diet and

other beneficial eating habits [119].

The impact of genetic factors, such as the apolipoprotein E genotype, on response to personalized dietary advice has been studied, showing the potential for tailored interventions based on genetic profiles [120].

In addition to genomics, other branches of omics analysis, including proteomics, metagenomics, metabolomics, transcriptomics, lipidomics, and interactomics, encompass biochemical assays, software and databases that allow complex integrated analyses, giving data from different approaches and providing a comprehensive characterization of individual physiology, having a potential for application in personalized nutrition [121]. Multi-omics analyses and machine learning methods enable to develop biomarkers of food intake and health status. Metagenomic analyses provide accurate and quantitative description of microbial composition, including the next-generation sequencing (NGS) techniques, which enable sequencing either the whole genome (shotgun metagenomics) or a single amplicon (16S rRNA gene sequencing) [122]. As a comprehensive and rapid technique for investigation of the composition and diversity of the gut microbiome, metagenomic research is applied for the analysis and diagnosis of numerous diseases, as well as the effects of a diet on the gut microbiome and its role in metabolic diseases [123]. Personalized dietary feedback systems have been developed to deliver consistent, individualized dietary advice in multicenter studies, demonstrating the feasibility of large-scale personalized nutrition approaches [124].

## 7. Conclusions

As an external environmental factor, food is closely related to the occurrence and development of various diseases, but can also promote or restore health. An unbalanced diet or nutrient intake could enable the flourishing of pathogenic groups of the gut microbiome and a decrease in other beneficial groups, leading to various diseases. The intimate relationship between dietary components (carbohydrates, proteins, and fats) and the gut microbiome has profound implications for human health.

Dietary fibers, especially prebiotics, promote the growth of beneficial bacteria that produce short-chain fatty acids and other metabolites essential for gut health. The source and composition of dietary proteins significantly influence the gut microbiota composition, with plant-based proteins generally promoting more beneficial microbial profiles compared to animal proteins. Different types of dietary fats have varying effects on gut microbial populations, with omega-3 fatty acids generally promoting beneficial bacteria while high saturated fat diets may lead to dysbiosis.

Various dietary approaches have been demonstrated to have different effects on gut microbiome and health. Mediterranean and vegetarian diets, which are characterized as low in red meat, saturated fats, and processed foods and rich in polyphenols, have positive effects on human health. A MUFAs-rich diet (rich in sesame, pumpkin seeds, rapeseed, extra virgin olive oil, and peanuts) also shows positive

health effects with an increased gut microbiota diversity in healthy and unhealthy models, including humans at risk of metabolic syndrome. A Westernized diet, which includes processed food rich in saturated fat, high in salt, high in processed carbohydrates, low in fiber, containing food additives, non-nutritive artificial sweeteners and emulsifiers, has negative impact on health. Low FODMAP diet, EEN, very low carbohydrate ketogenic diet, and gluten-free diet have demonstrated effectiveness in managing specific gastrointestinal disorders through modulation of the gut microbiome, treating IBD, particularly Crohn's disease, multiple sclerosis and celiac disease, respectively. Dietary modification, as well as treatment with probiotics and prebiotic use, can help maintain proper microbiota balance and promote proper energy and immune homeostasis. Compounds with natural origins can be used to create safer and more effective anti-microbial drugs. On the other hand, personalized nutrition enables improving knowledge and motivation to change eating behavior, dietary intakes, and quality of life, showing the potential for tailored interventions based on genetic profiles.

Further research is needed to fully understand the complex interactions between diet, gut microbiome, and human health, and to develop more effective dietary strategies for preventing and treating microbiome-related diseases. The integration of multi-omics approaches, including metagenomics, metatranscriptomics, metaproteomics, and metabolomics, will provide more comprehensive insights into these interactions and facilitate the development of personalized dietary interventions, which will be the interest of our next paper.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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