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# The nexus of gut microbiota, diet, and health

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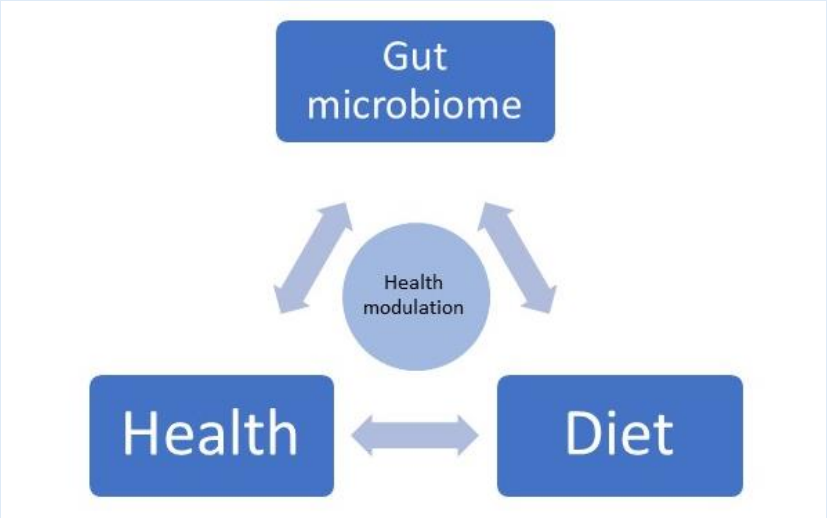
**ABSTRACT**




The gut microbiome incorporates the ecological niche specific to the totality of the microorganisms in the human gut. Unique to every individual, the blueprint of the microbiome sets up at birth and functions as a human organ and plays a significant role in digestion, detoxification, fighting pathogens, modulating the immune system, and improving health. The gut microbiota and associated health implications are influenced by factors such as birth and age, diseases, use of antibiotics and food components (e.g., complex carbohydrates and dietary fibers, plant proteins, unsaturated fatty acids, and functional compounds of natural origin such as flavones, flavonoids, polyphenols, and antioxidants). Toward this end, diet and the gut microbiome interact and govern each other's fate. Herein, gut dysbiosis, the alteration of natural state and composition of the gut microbiome, and the gut microflora diversity modulated by food constituents and associated health effects have been discussed. The gut microbiota composition and related metabolites are influenced by the diet which in turn modulates human health. The outcome is deemed to aid in developing personalized diet recommendations (based on the unique gut microbiome) toward improving human health.

**Keywords:** gut microbiome, gut microbiota, gut dysbiosis, short-chain fatty acids, metabolites, health modulation

## INTRODUCTION

The gut microbiota and its implications on human health have emerged as a critical area in health science. The intrinsic associations between food, microbiota-associated gut health and overall health are a topic of concern. This paper reviews some important aspects of these three aspects with brevity.

**Gut Microbiome**: The literature explains the gut microbiome from two different perspectives. One concept incorporates the ideology of the collective genome (pertaining to the suffix -ome that comes from the word -genome) of the micro-organisms residing in the human gut. The other one, however, incorporates the totality of all the micro-organisms, their habitat (the gut; pertaining to the suffix -biome) with unique physio-chemical properties, and all their activities inside the habitat thereby forming a unique ecological niche specific to the totality of the micro-organisms residing the habitat. Thus, the gut microbiome could be defined as (1) the collective genome of the microorganisms (bacteria, archaea, lower and higher eukaryotes and viruses) residing in the human gut [1] or (2) the total microorganisms, their habitat (the gut or gastrointestinal canal) and activities [2-3]. The appropriateness of these two perspectives is still a matter of debate but the second one appears to be more apt as it comprehensively signifies the ecological niche. The microbiome (1) is as complex as a human organ, (2) transfers to newborns and (3) shows distinct physiology and pathology [4-6]. Quoting Riccio and Rossano "*it could be considered as a kind of sensor of the variations in … relationship with environmental energy, which mainly occurs through the intake of food and the elimination of waste*" [7]. It acts as the interface between the energy obtained from food and energy needs. The microbially derived metabolites also induce epigenetic alterations in the genes responsible for disease modulation [8].

**Gut microbiota**: The human body harbors trillions of microorganisms and most of them reside in the gut [9-10]. The gut also accommodates a sparse amount of pathogenic strains (~ 0.1%) of *Escherichia coli*, *Bacteroides fragilis, Campylobacter jejuni*, *Salmonella enterica, Vibrio cholera, etc.* All the microorganisms that are part of the stable gut microecological niche are categorized as the "gut microbiota", which is the subset of the gut microbiome [11-12]. It comprises around 99.1% bacteria (e.g., Firmicutes, Bacteroidetes, Actinobacteria and Proteobacteria), 0.8% archaea (e.g., methanogens and haloarchaeal strains), and 0.1% of virus (e.g., bacteriophages), fungi (e.g., Ascomycota, Basidiomycota and Zygomycota) and protozoa (e.g., amoebozoans, flagellates, Amitochondriates, Apicomplexans and Stramenophiles) (Table 1).

**How does gut microbiota establish and form a stable niche in the human body?**: The gut is exposed to the outer environment through air, food and water. The first batch of the human gut microbiota (mainly bacteria) enter during and immediately after birth and colonize within days. The microorganisms such as *Lactobacillus* spp., *Prevotella* spp. and *Sneathia* spp. derived from the mother's vagina during natural delivery or *Staphylococcus*, *Corynebacterium* and *Propionibacterium* spp. from the mother's skin via C-section [22] dictate the overall gut microbial cohort, which later forms the micro-ecosystem within a couple of years. The gut microbiota could also colonize the unborn's gut in the uterus [23]. These prelusive bacteria develop based on nutrition availability (e.g., Human Milk Oligosaccharides) and lay the foundation for the futuristic microbial profile.

**Table 1.** Key microorganisms of human gut

| Organism | Major Phyla | Key members | References |
|---|---|---|---|
| **Bacteria** | Firmicutes | Clostridia Cluster XIVa [*Clostridium* spp., *Eubacterium* spp., *Roseburia* spp. *Blautia* spp.] and Clostridia Cluster IV [*Clostridium* spp., *Ruminococcus* spp., *Faecalibacterium* spp.] | [12-17] |
| | Bacteroidetes | *Bacteroides* spp., *Prevotella* spp., *Xylanibacter* spp. | |
| | Actinobacteria | *Bifidobacterium* spp., *Propionibacterium* spp. | |
| | Proteobacteria | *Escherichia coli* | |
| **Archaea** | Methanogens | *Methanobrevibacter, Methanobacteriales, Methanomassiliicoccales.* | [18] |
| | Haloarchaeal strains | *Haloferax miserliness and Halorubrum lipolyticum* | |
| **Virus** | Bacteriophages | - | [19] |
| **Fungi** | Ascomycota | *Candida* spp., *Cladosporium* spp., *Saccharomyces* spp. | [20] |
| | Basidiomycota | *Cryptococcus* spp., *Filobasidium* spp., *Malassezzia* spp. | |
| | Zygomycota | - | |
| **Protozoa** | Amoebozoans<br>Flagellates<br>Amitochondriates<br>Ciliates<br>Apicomplexans<br>Stramenophiles | - | [21] |

**Why is the gut microbiota a topic of significance?** The gut microbiota plays several vital roles in the human body. For example, *Lactobacillus helveticus* and *Bifidobacterium longum* alleviate anxiety and improve psychological health [24]. Herein, gut microbiota effects on (1) the immune system, (2) digestion and nutrition, (3) the integrity of the gut barrier and gastrointestinal tract, (4) detoxification and (5) antimicrobial protection have been discussed in brief.

***Immune system:*** The immune system is a composite of innate and adaptive immune systems. The innate immune system comprises monocytes, macrophages, neutrophils, basophils, eosinophils, mast cells, interleukin-10 (IL-10, an anti-inflammatory signaling protein), natural killer (NK) cells, gut-associated lymphoid tissues (GALT) along with complement and dendritic cells. On the other hand, the adaptive immune system is predominantly composed of dendritic cells and B-cells (fight against bacteria and viruses), and effector and regulatory T-cells (stimulate B-cells to make antibodies e.g., immunoglobulin A and also eradicate invaders). The gut microbiota works in close synergism with these two systems. It aids GALT in recognizing bacterial tolerance and regulating the activation of NK cells and the functionality of T-cells and B-cells [25]. It also contributes to the diversification of microbe recognition capacity of IL-10 and modulates the human immune system [26]. The gut bacteria also facilitates predicting white blood cell counts, neutrophils, lymphocytes, monocytes, eosinophils and platelets [27]. Disbalance in the gut microbial composition encourages monocyte-like macrophages (MLM) accumulation and facilitates tumorigenesis preventing apoptosis and increasing cell survival instincts [28].

***Digestion and Nutrition:*** Gut microbiota ferments carbohydrates that survive digestion and reach the colon and releases beneficial metabolites predominantly composed of short-chain fatty acids (SCFAs, e.g., butyrate, acetate, and propionate). The SCFAs (mainly butyrate) become an energy source for the host epithelial cells. The SCFAs also avert the accumulation of metabolic byproducts such as D-lactate and in turn prevent neurological disorders like delirium, ataxia, and slurred speech, to name a few. Examples of the colonic bacteria involved in the fermentation are *Bacteroides*, *Roseburia*, *Bifidobacterium* spp., *Fecalibacterium* spp., *Enterobacteria* spp. And the bacteria from Lachnospiraceae family [29]. Similarly, *Oxalobacter*, *Lactobacillus* spp. And *Bifidobacterium* spp. Process oxalate and prevent stone formation in the kidneys [30].

Gut microbiota positively influences lipid metabolism (mainly in the small intestine) and promotes the Lipoprotein Lipase (LPL) activity that aid in breaking triglycerides into fat molecules used as energy or stored in adipocytes [31]. It also regulates the colipase enzyme expression and facilitates the pancreatic lipase in lipid digestion [32]. It further deconjugates and dehydrates the primary bile acids into secondary bile acids that support fat emulsification and absorption [33]. For example, *Lactobacillus curvatus* and *Lactobacillus plantarum* digest and curb cholesterol build-up in the body [34].

Gut microbiota releases bacterial proteinases (small intestine) that act synergistically with intestinal proteases toward modulating protein digestion [35]. Furthermore, it converts amino acids into signaling molecules and antimicrobial peptides (bacteriocins) [36]. Some microbes, e.g., *Bifidobacterium, Clostridium, Lactobacillus, Escherichia* and *Klebsiella* act as amine producers too [37]. Likewise, gut microbiota (e.g., *Faecalibacterium* and *Bifidobacterium*) also metabolizes polyphenols and activates glycosylated polyphenols by hydrolyzing carbohydrate moieties [38]. Synthesis of vitamin K, components of vitamin B and conjugated linoleic acid (CLA) are other important attributes [29].

***Integrity of the Gut barrier and Gastrointestinal Tract:*** Gut microbiota maintains the gut barrier integrity as well as structural and functional aspects of the gastrointestinal tract. It helps to minimize stress-induced gastrointestinal damage via induction of the epithelial heat-shock proteins (*in vivo* study), restoration of the tight junction protein structure (human colonic epithelial cell line study), up-regulation of the mucin genes, secretion of defensins (mice study), regulation of NFxB signaling pathway and competitive inhibition of pathogens, to name a few. For example, through mucin synthesis, TJ reassembly, or 25ccluding and ZO-1 up-regulation (mice study), the butyrate produced by the gut bacteria improves gut barrier permeability (human colonic epithelial cell line study) [38], *Lactobacillus rhamnosus* prevents cytokine-induced apoptosis of the intestinal cells (intestinal epithelial cell model) [39] and *Akkermansia muc*iniphila helps to increment the endocannabinoids that can decrease the metabolic endotoxemia and control the gut barrier functions (mice study) [40]. Similarly, gut microbiota maintains tight junctions between cells through TLR2 mediated signaling (mice study) [41]. It also induces the transcription factor angiogenin-3 which is essential during microvasculature development in the intestine. The absence of microvasculature developed lowers the intestinal surface area, the thickness of the intestinal villi, curtails the peristalsis, increases the cell-cycle time and in turn impairs nutrient digestion and absorption [42]. The disbalance in the gut microbiome also leads to a situation called leaky gut where the disrupted gut barrier allows the translocation of the bacteria to the liver through the gut-liver axis that plays role in liver disease development and progression.

***Detoxification:*** Metals in the elemental, inorganic and/or organic form of ingested food undergo absorption, distribution, biotransformation and elimination. Organic forms readily absorb due to their fat solubility and better membrane diffusivity. However, heavy metals (e.g., lead, arsenic, and cadmium) cause metal toxicity but gut microbiota mitigates metal toxification through biotransformation. For example, *Lactobacillus* aids in intestinal lead sequestration [43] and *Faecalibacterium* protects against acute arsenic toxicity [44]. Gut microbiota also absorbs and utilizes metals for its own needs. For example, *Bacteroides*, *Butyricimonas*, *Dorea* and *Lactobacillus* could consume arsenic, *Coprococcus* and *Lactobacillus* cadmium and lead by *Desulfovibrio*, *Prevotella* and *Roseburia* [45].

***Antimicrobial Protection:*** Healthy gut microbiota is essential for normal homeostasis. It creates, however, a challenging scenario for the gut epithelial linings to accept commensal microbiota and reject harmful ones (e.g., through nutrition competition, variation in the oxidative stress, redox potential, and production of bacteriocins). Unlike the large intestine, wherein the two-layered mucus membrane prevents microbial access to the gut epithelial cells, the small intestine, possessing discontinuous and inadequate mucus layer, precludes harmful microbial invasion with its antimicrobial proteins (AMPs) and gut microbiota assistance [46-47]. The gut microbiota induces the Paneth cells to synthesize AMPs such as cathelicidins, C-type lectins, and (pro)defensins through the pattern recognition receptor (PRR) mediated mechanism. The PRR gets activated by organism-specific microbe-associated molecular patterns (MAMPs). Interactions between PRR and MAMPs trigger signaling pathways that promote the production of AMPs, mucin glycoproteins and Immunoglobin A (IgA), which in turn enhance the mucosal barrier functionality [48]. The AMPs production is driven by healthy gut microbiota, and bacteria such as *Bacteroides theataiotaomicron* and *Lactobacillus innocua* are essential in this process. The SCFAs produced by the microbiota also induce the AMPs fabrication.

Gut microbiota also stimulates local immunoglobulins production. Gram-negative bacteria such as *Bacteroides* help to activate the intestinal dendritic cells (DCs), which in turn fuels plasma cells to produce secretory IgA (sIgA). The sIgA coats the gut microbiota and resists degradation by by the mesenteric lymph nodes, ensuring that the bacterial proteases [49]. Moreover, DCs loaded with gut microbiota are restricted to the mucosal layers systemic immune system remains unaffected by the immune responses around the gut microbiota [50].

**Gut Dysbiosis:** Every human body has a unique stable gut microbiome (which varies over time due to various factors discussed later), and the relative proportion of specific taxonomic groups vary greatly. Once the stable gut microbiota establishes, the core composition shapes futuristic bacteria in conjunction with factors such as food and prevalent diseases. However, any substantial alteration leads to gut disbalance known as gut dysbiosis resulting in health aberrations such as obesity, cardiovascular diseases, hypertension, diabetes, and inflammatory bowel disease. On the other hand, the increment of certain bacteria is good for cardiovascular health. For example, domination from some bacteria from Firmicutes phylum such as *Lactobacillus reuteri* is linked with increased High-density Lipoproteins is good for health [51], and *Akkermansia muciniphila* and *Phascolarctobacterium* have been linked to fat deposition [52]. Likewise, increased *Bacteroides fragilis, Fusobacterium nucleatum, Porphyromonas asaccharolytica, Parvimonas micra, Prevotella*

*intermedia, Alistipes finegoldii* and *Thermanaerovibrio acidaminovorans* have been linked to colorectal cancer [53]. Similarly, reduced *Faecalibacterium prausnitzii, Erysipelotrichales, Bacteroidales* and *Clostridiales* link to Corhn's disease [54]. Decreased *Bifidobacterium* and increased *Bacteroides* and *Enterococci* might hint the Inflammatory Bowel Disease (IBD) [55]. The gut microbiota also plays roles in the gut-brain axis in a bi-directional fashion through neural, endocrine, immune and humoral pathways. For example, alteration of healthy gut bacteria profile has been linked with central nervous disorders such as autism and depressive behaviors and gut-related issues such as IBD. Gut dysbiosis associated with a couple of health implications is highlighted in Table 2.

**Table 2.** Decrement in some gut bacteria proportion during diseases

| Disease | Gut bacteria | References |
|---|---|---|
| **Autism** | Firmicutes<br>*Actinobacteria* | [21, 56, 57] |
| **Celiac Disease** | *Bifidobacterium* | [21] |
| **Clostridium difficile infection** | *Clostridium scindens* | |
| **Colorectal cancer** | *Prevotella*<br>*Ruminococcus spp.*<br>*Pseudobutyrivibrio ruminis* | [21, 56, 58] |
| **Crohn's disease** | *Bacteroides*<br>*Bifidobacteria* | [21, 56, 59] |
| **Depression** | *Prevotella, Dialister* | |
| **HIV** | *Clostridia*<br>*Bacteroidia*<br>*Lactobacilli*<br>*Bifidobacteria* | [21, 56, 60-62] |
| **Hypertension** | Acetate and butyrate producers | [21] |
| **Irritable bowel syndrome** | *Clostridium laptum, Bifidobacteria* | [21] |
| **Obesity** | *Bacteroides* | [21, 56, 63] |
| **Rheumatic arthritis** | *Bifidobacteria*<br>*Bacteroides fragilis* | [21, 56, 64] |
| **Type-1 diabetes** | *Lactobacillus*<br>*Bifidobacterium*<br>*Blautia coccoides*<br>*Eubacterium rectale*<br>*Prevotella*<br>*Actinobacteria*<br>Firmicutes | [21, 56, 65] |
| **Type-2 diabetes** | *Clostridium coccoides*<br>*Firmicutes, Prevotella, Atopobium* | [21, 56, 66] |
| **Ulcerative colitis** | *Lactobacilli*<br>*Runinococcus hominis*<br>*Faecalibacterium prausnitzii* | [21,67-69, 56] |

**Factors affecting the gut microbiome:** Genetics, food, age, diseases and the use of medicines and antibiotics are some of the influencing factors that modulate the gut microbiota cohort throughout human life. A few of them are selected for further elaboration in the following sections.

### *Host interior factors*

***Birth and Age:*** The first meconium loaded with a few gut microbiota species suggests that the blueprint of the gut microbiome on sets at birth. Indeed, the mode of delivery lays the foundation for the futuristic microbiota composition. The initial inoculum, however, is not necessarily stable and diverse, but manifests into established composite by 3 years and resembles 40-60% of the adult microbiota profile; however, varies significantly with age [70]. It reaches a stable state at around 30 years but continues to stabilize up to 70 years [71] and is predominantly influenced by environmental exposure, diet, life events, contraction of diseases and consumption of antibiotics. Human milk oligosaccharides (HMOs) consumed during lactation might not necessarily be present in the adult diet. Therefore, infants have an abundant presence of certain *Bifidobacterium* species such as *Bifidobacterium breve, Bifidobacterium bifidum, Bifidobacterium longum* subsp*. longum (Bifidobacterium longum), Bifidobacterium longum* subsp*. infantis (Bifidobacterium infantis), Bifidobacterium pseudocatenulatum* etc. compared to adults [72]. The *Bacteroides* and *Bifidobacterium* in young children and adolescents differ significantly from adults. The *E. coli*, *Proteobacteria* and *Staphylococcus* proliferate with age, whilst *Bifidobacteria,* Firmicutes and *Faecalibacterium prausnitzii* decline [73]. Such dynamics negate an individual's ability to synthesize vitamin B12, increase the host's tendency for DNA alterations and weaken the immune system in addition to a host of other health anomalies [74].

### *Non-dietary factors*

***Antibiotics:*** Gut microbiota contains a pool of genes that express antibiotic resistance. However, upon antibiotics administration, bacterial species with resistant genes competitively flourish over non-resistant bacteria resulting in altered microbial diversity and instability in the overall gut microbiota profile. Such resistant genes can also be transferred to the pathogenic strains. This phenomenon further compromises microbial recognition capacity of the immune system leading to several health issues. It further modifies the metabolome (collection of metabolites), increases antibiotic resistance, and impairs the competitive inhibitory effect on the external pathogens. The mechanisms by which the antibiotic affects the gut bacteria include inhibition of cell wall synthesis, protein synthesis, nucleic acid synthesis, membrane disruption, etc. In this regard, different antibiotics act distinctly. For example, meropenem, gentamicin, and vancomycin administration reduces the *Bifidobacterium* and butyrate-producing species and promotes *Enterobacteriaceae*. Likewise, Vancomycin/imipenem diminishes *Lachnospiraceae* and *Ruminococcaceae* bacteria that are responsible for the conversion of arabinitol to pentose sugars [75].

***Dietary factors:*** Interactions between gut microbiota and diet significantly influence the metabolic response to nutrition and in turn human health. In general, fruits, vegetables, fibers, and whole plant-based foods promote

the richness and diversity of gut microbiota compared to animal-based and/or processed foods [76] and aid in the prevention of chronic non-communicable diseases including cancer. Modulating human health through personalized diet recommendations for individuals (with their unique gut microbiome) is deemed to emerge as a new area of diet therapy. Herein, interactions between food classes and gut microbiota, and resultant health effects are highlighted.

***Carbohydrates:*** Gut microbiota interacts with (1) dietary fibers, (2) digestible but undigested carbohydrates by the gut from diet and (3) endogenousglycans from the mucus of the host. In this set, dietary fibers are the major energy source for the gut microbiota, known as microbiota accessible carbohydrates (MACs), for brevity. The fibrinolytic (fiber digesting) community includes *Roseburia, Ruminococcus, Bacteroides* and *Bifidobacterium*, etc. Likewise, the glycolytic (that digest the gut-digestible carbohydrates, but somehow skip the digestion in the gut) cohort includes *Lactobacillus, Enterococcus, Staphylococcus, E. coli*, etc. These microbes ferment complex fibers, sugars, and endogenous carbohydrates resulting in SCFAs (acetate, propionate, butyrate), carboxylic acids (e.g., lactate, succinate, and formate) along with various gases namely $CO_2$, $H_2$, $H_2S$ and $CH_4$, which could further get interconverted. SCFAs are the energy source for the intestinal epithelial cells (colonocytes). Butyrate in particular will be utilized by colonocytes, whereas acetate and propionate in the gluconeogenesis process by the liver as well as transported through the bloodstream to the brain and heart [77]. Consequently, reduction in fiber consumption impacts SCFAs products that concomitantly influence the gut microbial diversity that further resulting in a host of health issues.

Among the several available MACs (Table 3), resistant starch (RS) increases *Lactobacilli, Bifidobacteria, Roseburia, Eubacteria* and *Ruminococcus* species; RS2 *Ruminococcus bromii* and *Eubacterium rectale*, RS3 *Faecalibacterium prausnitzii* and RS4 *Bifidobacterium adolescentis* and *Parabacteroides distasonis* [78]. Pectin boosts the relative abundance of *Bacteroides, Anaeroplasma, Anaerostipes* and *Roseburia*, but decreases *Alistipes* and *Bacteroide*. Likewise, cellulose promotes *Clostridium, Eubacterium, Ruminococcus, Bacteroides,* etc., whilst Inulin upsurges *E. rectale*, *Roseburia intestinalis* and *Anaerostipes caccae* and xanthan gum fosters *Roseburia, Ruminococcus, Bacteroides* and *Bifidobacterium* with an increase in the overall SCFAs production along with resistance against diarrhea-causing *Clostridioides diff*icile [79]. Similarly, arabinoxylans rise the butyrate-producing species such as *Bifidobacterium* [80] and xylan fermenting species such as Bacteroidetes [81]. Diets with low MACs promote mucus degrading bacteria e.g., *Akkermansia muciniphila* and *Bacteroides cacc*ae, that impair the first line of defense in the human gut leading to gut dysbiosis [82], decreased epithelial integrity and modification of epithelium cytokine expression [83-84]. Diets rich in glucose, fructose, sucrose, and lactose promote *Bifidobacteria* and decrease *Bacteroides* [85-86]. Likewise, lactose blooms *Lactobacilli* but tapers *Clostridia*. Artificial sweeteners (e.g., saccharin, aspartame) decrease *Lactobacilli* and *Clostridia* [87].

**Table 3.** A few carbohydrates and artificial sweetener fermented by some gut microbiota

| Fermenting organism | Carbohydrate | References |
|---|---|---|
| ***Bacteroides uniformis*** | Agarose | [13] |
| ***Bifidobacteria, Bacteroides xylanisolvens, Bacteroides thetaiotaomicron, Bacteroides ovatus*** | Alginate | [15, 88] |
| ***Bifidobacterium, Anaerostipes, Prevotella*** | Bacterial polysaccharides | [13] |
| ***Bifidobacterium, Lactobacillus, Bacteroides*** | Beta-glycan | [88] |
| ***Bacteroides xylanisolvens, Escherichia coli*** | Carrageenan | [89] |
| ***Ruminococcus, Bacteroides*** | Cellulose | [13] |
| ***Bacteroides, Roseburia, Faecalibacterium, Bifidobacterium*** | Fructans (inulin and FOS) | [13] |
| ***Bifidobacterium, Lactobacillus, Bacteroides*** | Fructooligosaccharide | [88] |
| ***Bifidoacterium, Roseburia*** | Fructose | [13] |
| ***Akkermansia*** | Fucoidan | [88] |
| ***Bifidobacterium*** | Galacto oligosaccharide | [88] |
| ***Bifidobacterium, Roseburia, Eubacterium rectale*** | Guar gum | [88] |
| ***Bifidobacterium, Lactobacillus*** | Gum acacia | [88] |
| ***Clostridial cluster XIVa, Bifidobacterium*** | Hemicellulose | [88] |
| ***Lactobacillus. Bifidobacterium*** | Lactose | [13] |
| ***Bifidobacterium*** | Milk oligosaccharides | [13] |
| ***Akkermansia, Bacteroides*** | Mucin and mucopolysaccharides | [13] |
| ***Peptostreptococcus, Fusobacterium, Bifidobacterium*** | Nutriose | [90] |
| ***Bacteroides, faecalibacterium*** | Pectin | [13] |
| | | |
| ***Eubacterium rectale, Bacteroidetes, Ruminococcus bromii, Bifidobacterium, Akkermansia, Allobaculum*** | Resistant starch II | [88] |
| ***Eubacterium rectale, Ruminococcus bromii, Oscillibacter, Atopobium spp., Bifidobacteria spp.*** | Resistant starch III | [88] |
| ***Eubacterium oxidoreducens, Ruminococcus lactaris, Parabacteroides distasonis, Eubacterium rectale, Rumminococcus bromii*** | Resistant starch IV | [88] |
| ***Bacteroidetes*** | Saccharin (artificial sweetner) | [91] |
| ***Lactobacillus, Escherichia*** | Sugar-alcohols | [13] |
| ***Roseburia, Bacteroides, Prevotella*** | Xylan and arabinoxylan | [13] |

***Proteins:*** Microbial proteinases digest proteins, in association with proteinases and peptidases, and aid in protein metabolism. The gut microbiota also converts amino acids to signaling molecules and antimicrobial

peptides [92]. The presence, absence, or type of protein in conjunction with the levels of oxygen and carbohydrate significantly affect the gut microbial profile. For example, animal proteins increase *Alistipes, Bilophila* and *Clostridia* along with subtle increment in *Eubacterium rec*tale and *Bifidobacteria*, which could promote bile-tolerant anaerobes and subsequent reduction of SCFAs along with increment in the production of Trimethylamine N-oxide (TMAO) thereby increasing the risks of cardiovascular diseases and Inflammatory Bowel Diseases [93]. On the other hand, the consumption of plant-based proteins appears to be favorable [94]. Whey protein discourages the growth of Bacteroi*de*s and *Clostridia* but increases *Bifidobacteria* and *Lactobacilli* [95]. The *Bifidobacterium*, *Lactobacillus* increment with concomitant *Bacteroides* and *Clostridium* spp. Reduction augments SCFAs production, which reduces inflammation and improves gut barrier and production of Tregs regulatory cells [96].

***Fats:*** Gut microbiota positively impacts lipid metabolism by promoting Lipoprotein Lipase (LPL) activity and colipase expression [97]. However, fat type and amount influence the microbial cohort. Consumption of lower amounts of fat increases the *Bifidobacterium* spp. while higher quantities proliferate anaerobic microbes and *Bacteroides* [98]. Likewise, diets rich in saturated fats enhance *Faecalibacterium prausnitzii*. On the other hand, monounsaturated fats aid to reduce the overall bacterial load. Lard promotes *Bacteroides* and *Bilophila* growth whilst *Bifidobacteria*, *Adlercreitzia*, *Lactobacillus*, *Streptococcus* and *Akkermansia muciniphila* by fish-oil [99]. Mice studies hint at increased systemic TLR stimulation, inflammation of the adipose tissues and decreased insulin sensitivity compared to fish-oil consumption suggesting some relationship between developed gut microbiota and health issues [96]. However, further research is warranted to understand the root cause.

***Natural compounds:*** A variety of natural food systems such as vegetables, fruits and herbs contain health-promoting and disease-preventing compounds (e.g., catechins, flavonols, flavones, anthocyanins, proanthocyanidins, phenolic acids and polyphenols) and gut microbiota plays important role in metabolizing these compounds. Gut microbiota transforms these natural compounds to a more active and absorbable form via esterase, glucosidase, demethylation, dehydroxylation and decarboxylation [100]. For example, polyphenols that are naturally present as glycosides are transformed to aglycones by the gut microbiota glycohydrolases, which are better absorbed in the intestine. Gut microbiota is also essential to produce active isoflavone metabolites with oestrogen-like activity that display various anti-inflammatory properties. For example, quercetin derived through microbial digestion possesses improves anti-inflammatory properties than the glycosylated form [101].

The presence or absence of these beneficial compounds modulates the gut microbial composition. Flavonol-rich foods promote healthy gut bacteria [102]. Polyphenols from tea, wine and cocoa prosper the *Bifidobacteria* and *Lactobacillus* species with a concomitant reduction in the pathogenic strains such as *Staphylococcus aureus*, *Salmonella typhimurium*, Clostridium *perfringens*, Clostridium *Histolyticum, Bacteroides, Salmonella typhimurium* and *Staphylococcus aureus* [103]. Tea phenolics reduce *Bacteroides* spp., *Clostridium* spp., *E. coli* and *Salmonella typhimurium* [104]. Wine resveratrol promotes the growth of *Bifidobacterium* and *Lactobacillus* [105]. Anthocyanins from berries inhibit pathogens such as *Staphylococcus, Salmonella spp., Helicobacter pylori* and *Bacillus cereus* [106]. Tea catechins modify the intestine

mucin layer toward modulating adhesion and colonization of the bacteria in the gut [107].

## CONCLUSION

The gut microbiome, the ecological niche formed by the gut microbiota, is influenced by factors such as birth, age, antibiotics, diseases, food, etc. It interacts with the outer environment through food, water, and air. More importantly, food and water are the major influencing factors through which the gut microbiome could get modified and in turn modulate human health. For example, consumption of an animal-protein-rich diet appears to reduce *Roseburia* and *Eubacterium rectale* which are associated with increased risks of IBD. On the other hand, the presence of MACs increases *Lactobacillus*, *Ruminococcus*, *Eubacterium rectale* and *Roseburia* and the overall SCFA production. Probiotics and polyphenols favor beneficial *Bifidobacterium* and lactic acid bacteria and reduce the enteropathogenic *Clostridia* species. The metabolites formed during this process also play critical roles in antimicrobial protection and immunomodulation. This brief review provides a synopsis of the gut microbiota and its interplay with diet and health. Diet-induced health modulation could hold a promising future via the pathway of inter-dependent micro-ecosystem of food, gut microbiome and human health toward improving human health.

**List of Abbreviations:** IBD: inflammatory bowel diseases, MAC: microbiota accessible carbohydrates, SCFA: short-chain fatty acids, LPL: lipoprotein lipase, TMAO: Trimethylamine N-oxide, RS: resistant starch, HMO: human milk oligosaccharides, DNA: deoxyribonucleic acid, DC: dendritic cells, AMP: antimicrobial proteins, MAMP: microbe-associated-molecular patterns, NFxB: nuclear factor kappa-light-chain-enhancer of activated B cells, CLA: conjugated linoleic acid, MLM: monocyte-like macrophages, IL: interleukin, NK: natural killer, GALT: gut-associated lymphoid tissue

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