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Review

Gut microbiota compositions and metabolite abundance

Rina Triana[1,2,*], Keri Lestari[1], Mas Rizky A. A. Syamsunarno[3] and Indriyanti Rafi Sukmawati[1,2]

[1]Faculty of Pharmacy, Padjadjaran University, Jl. Eijkman No. 38, Bandung, Indonesia; [2]Prodia Clinical Laboratories, Jl. Kramat Raya No. 150, Jakarta, Indonesia; [3]Department of Biomedical Sciences, Faculty of Medicine, Padjadjaran University, Jl. Eijkman No. 38, Bandung, Indonesia.

ABSTRACT

Human gastrointestinal (GI) tract harbors a complex population of microorganisms, the gut microbiota, which influence the host during homeostasis and disease. Multiple factors contribute in the composition of human gut microbiota during infancy. Diet is considered as one of the main drivers in modifying gut microbiota across a lifetime. Microbial metabolites can be the mediators for diet-induced host-microbial crosstalk, which is important for health. This review provides an overview about gut microbiota compositions and its metabolite function due to their significant impact on human wellbeing. Gut microbiota can be classified into 12 phyla and three enterotypes. The microbiota compositions can be affected by several factors such as delivery method, diet, geographic location, antibiotics, and host factors. Gut microbiota absorbs nutrients from the host and diet to support their growth and release metabolites, which are produced through fermentation. These diet-derived metabolites consist of short-chain fatty acids, secondary bile acids, microbial tryptophan metabolites, and trimethylamine N-oxide. Each individual has a unique gut microbiota composition that influences host nutrient metabolism, physiology, and immune system development. Microbial metabolites were generated through microorganism–microorganism, and host–microorganism interactions, and there is a growing appreciation for the role of this metabolic interaction in human health and disease. Understanding the role of gut microbiota in some diseases is fundamental for developing ultimate appropriate therapeutic approaches. Targeting specific metabolites of gut microbiota will potentially contribute to improve our health.

KEYWORDS: gastrointestinal, gut microbiota, composition, metabolites.

1. Introduction

The human gastrointestinal (GI) tract represents one of the largest interfaces (250–400 m^2) between the host, environmental factors, and antigens in the human body. In an average lifetime, around 60 tonnes of food pass through the human GI tract, along with an abundance of microorganisms from the environment, which impose a significant threat on gut integrity [1]. The human GI tract harbors a diverse and complex microbial community that plays a central role in human health, called gut microflora or gut microbiota. Gut microbiota is an assortment of microorganisms that inhabit the length and width of the mammalian gastrointestinal tract. The composition of this microbial community is host-specific, evolving throughout an individual's lifetime and is susceptible to both exogenous and endogenous modifications. The gut microbiota comprise of all the bacteria, both commensal and pathogenic bacteria [2-4].

It has been estimated that the human gut comprises 1000 bacterial species, 10^{14} bacterial cells, and also 100-fold more genes than found in the human genome [2, 5, 6]. This community comprises a complex ecosystem with functions that significantly contribute to our systemic metabolism and have

*Corresponding author: rina.triana@prodia.co.id

an impact on health and disease, including host's metabolism, physiology, nutrition, and immune function. The changes to this population can have significant consequences, both beneficial and harmful, for human health. Perturbation of the gut microbiota (or dysbiosis) can lead to pathological intestinal conditions such as obesity, diabetes, metabolic syndrome, nonalcoholic fatty liver disease [7-9], malnutrition [10], inflammatory bowel disease, encompassing ulcerative colitis and Crohn's disease [11]. This review provides an overview of the gut microbiota composition and its metabolite function due to their immense impact on human wellbeing.

2. Composition of the human gut microbiota

Each individual has a unique gut microbiota composition that plays roles in many specific functions such as host's nutrient metabolism, maintenance of structural integrity of the gut, immunomodulation, and protection against pathogens. Gut microbiota is composed of different bacteria species taxonomically classified by genus, family, order, and phyla. Each human's gut microbiota is formed in early life, as their composition depends on infant transitions (birth, type of delivery, methods of milk feeding, weaning period), and external factors such as antibiotic use [12].

Around a decade ago, most knowledge about the composition of adult human gut microbiota stemmed from labor-intensive culture-based methods. These approaches have become less popular because just 10–50% of the gut bacteria are culturable [1, 2]. Nowadays, the ability to study microbial communities has been greatly improved due to the advent of culture-independent approaches such as high-throughput and low-cost sequencing methods, by targeting of the bacterial 16S ribosomal RNA (rRNA) gene. The 16S rRNA is present in all bacteria and contain nine highly variable regions (V1–V9), which allow different taxa to be easily distinguished [13].

In recent years, many large funding initiatives were undertaken to understand the complexity of the human microbiome. The European Metagenomics of the human intestinal tract (MetaHIT) [5, 14] and the US Human Microbiome Project (HMP) [15, 16] worked through a large-scale sequencing, for establishing the baseline healthy gut microbiota and how they are altered in a pathologic state.

Combined data from the MetaHit and the Human Microbiome Project have provided the most comprehensive view of the human-associated microbial repertoire to date. Compiled data from these studies identified 2172 species isolated from human beings, classified into 12 different phyla, of which 93.5% belonged to Proteobacteria, Firmicutes, Actinobacteria, and Bacteroidetes [17, 18]. The Firmicutes phylum is composed of more than 200 different genera such as *Bacillus*, *Lactobacillus*, *Clostridium*, *Ruminicoccus*, and *Enterococcus*. *Clostridium* genus represents 95% of the Firmicutes phyla. Bacteroidetes consist of predominant genera such as *Bacteroides* and *Prevotella*. The Actinobacteria phylum is proportionally less abundant and mainly represented by the *Bifidobacterium* genus [14].

Network analysis of the fecal colony at the genus level has suggested that the microbial ecosystem conforms to a steady microbial symbiotic state driven by groups of co-occurring genera. Analysis of samples from European, American, and Japanese subjects showed that all individual samples congregated around three robust clusters conforming to their composition similarity. Clustering was not driven by sex, age, nationality, or body mass index. These clusters were designated as "enterotypes": Bacteroides (enterotype 1), Prevotella (enterotype 2), and Ruminococcus (enterotype 3) [14, 19]. Enterotypes should be considered as a way to simplify the gut microbiota complexity rather than as distinct clusters [14].

Wu G. D. *et al*. identified the long-term dietary habits in subjects, and reported that the enterotypes are associated with long-term diets, particularly the Bacteroides enterotype (animal fat and protein diet) compared to the Prevotella enterotype (carbohydrates diet). Ruminococcus was an ambiguous enterotype [20]. There were two other studies that reported that Ruminococcus could not be classified in their datasets, and Firmicutes was identified as the dominant species in those studies [21, 22]. Liang C. *et al.* studied the enterotype from the fecal samples in the Asian population. They reported the primary bacteria in the enterotypes identified were Bacteroides, Prevotella, and Enterobacteriaceae, and confirmed their correlation with dietary habits. Another finding was, Enterobacteriaceae, the predominant subtype, could

be a new subtype of enterotypes in the Asian population [23]. Murry *et al*. suggested that children with type 1 diabetes tend to have the Bacteroides enterotype, while their healthy counterparts have the Prevotella enterotype [24].

3. Factors that modify the gut microbiota composition

The microbial colonization process promotes short- and long-term health benefits. Different factors modify the gut microbiota compositions [25].

3.1. Delivery method

Colonization of gut by microbes begins immediately at birth. First postnatal microbial exposure occurs during and shortly after birth. The mode of delivery heavily influences the early colonization pattern of gut microbiota. Naturally delivered infants are first exposed to maternal vaginal and fecal bacteria, and hence Lactobacillus, Prevotella, Atopobium are prevalent in their gut. In contrast, the microbiota of cesarean section babies are more similar to the skin communities of the mothers, with an abundance of *Staphylococcus* spp. Microbial colonization of the gut in infants delivered by cesarean section is delayed compared to naturally delivered infants. Infants born through cesarean section have lower numbers of Bifidobacterium and Bacteroides, whereas they are more colonized by *Clostridium* spp., in comparison with vaginally born infants [26, 27].

The first three years of life define the most critical period for dietary interventions due to the development and improvement of child growth. In this period, intestinal microbiota, which are a vital asset for neurodevelopment and health, are established, and their change during this period, has the potential to affect host health and development profoundly [28].

3.2. Diet

Diet composition affects the composition and abundance of gut microbiota. Breastfeeding is a major influence on gut microbiota development followed by the dietary composition of macronutrients carbohydrates, protein, and fat. A major contributor to the changes in the microbial content is the ingestion of dietary, soluble, fermentable fiber, including fruits, vegetables, and other plants. Proportions of the four main phyla are altered among populations from different regions of the world, depending on the typical intake of macronutrients [29].

The route of feeding also plays an important role in the development of and changes in the gut microbiota. Enterally fed patients have altered gut microbiota patterns that are associated with decreased short-chain fatty acid (SCFA) profiles. Parental feeding due to intestinal failure and inability to survive solely on oral intake or enteral feeding, is associated with decreased microbial diversity which contributes to weakened epithelial mucosal barrier and alterations in gut immune regulation [30].

3.3. Geographic location

The composition of gut microbiota can be differentiated by ethnicity and geographic location. Phylogenetic variances in the microbial composition were noted in subjects from different countries. Prideaux *et al*. reported that diversity of microbial composition was seen between subjects of Caucasian and Chinese ethnicity within the same country and varied from the composition of microbes of subjects from Hong Kong [31].

3.4. Antibiotics

Antibiotics destroy both pathological and beneficial microbes indiscriminately. It allows the loss of gut microbiota and the growth of undesired microbes. However, it disrupts the basic property by which microbiota eliminates pathological microbes. This disturbance drives the growth of other pathogens, for example *Clostridium difficile* [32]. Studies have reported that clindamycin, clarithromycin, metronidazole and ciprofloxacin influence the microbiota structure for a long time [33-35]. Vancomycin therapy also causes depletion of many gut microbiota, such as Bacteroidetes. Vancomycin is related to the increases in *Proteobacteria* species and the decreases in *Bacteroidetes, Fuminococcus,* and *Faecalibacterium* [36, 37].

3.5. Host factors

There are specific and nonspecific factors that affect the host's gut microbiota. The host prefers microbes which are able to colonize in its intestines and release other microbes from the body [32]. The host produces several molecular specific signals

through the intestinal epithelial cells (IECs) which maintain the structure of the surfaces colonized by microbiota, and hence influence its composition. These are molecules of mucus, antimicrobial peptides (AMPs), and immunoglobulin A (IgA). In the large intestine, mucus plays a key role in preventing the microbes from approaching IECs. The inner layer of mucus does not contain any microorganisms. Meanwhile, the outer layer loads soluble mucins, which include nutrient-rich O-glycans and become the binding site for gut microbiota. Both mucus and mucin O-glycans are important in building the gut microbiota and choosing the most appropriate microbial species for the host's health [38, 39]. Gut microbiota encode their genes of glycoside hydrolases and polysaccharide lyases to utilize the mucin [40].

AMPs play a role in shaping gut microbiota since there is less mucus in the small intestine. AMPs that were produced by the host have a significant role in determining whether the bacteria are beneficial or pathogenic. The AMP production was induced *via* Paneth cells through a mechanism helped by the pattern recognition receptor (PRR). In contrast, microbial components, such as flagella and lipopolysaccharide, activate the PRRs in a system called microbe-associated molecular patterns (MAMP). IEC releases AMPs as the primary line of defense against any attacks, and they have massive impacts which directly destroy bacteria, viruses, yeast, fungi, and even cancer cells. Bacteroides, which are the biggest gram-negative genus among the gut microbiota, are resistant to AMPs [41].

Some plasma cells in the intestinal mucosa produce secretory immunoglobulin A (SIgA) which covers the bacteria and locally maintains its numbers. SIgA is important in the formation of bacterial biofilm, since it binds to SIgA receptors on bacteria. The presence of gut microbiota activates dendritic cells, inducing plasma cells to generate IgA. Increases in segmental filamentous bacteria in mice happens when IgA does not exist. It causes IgA-deficient mice, indicating that the increase in secretory IgA production depends on the diverse types of gut microbiota [32].

The other host factor that can affect gut microbiota composition is miRNAs. miRNAs are formed in the nucleus, and then mobilized to the cytoplasm for gene silencing process, by hybridizing the 3′ untranslated region of the target gene. This process will end up increasing mRNA degradation or inhibition of translation [42]. One miRNA can target different mRNAs, and it has been proven that miRNAs circulate through bodily fluids [43-45]. miRNAs are considered as potential markers to indicate intestinal malignancy in intestinal contents and feces miRNA impacts the gut microbiota composition. Several miRNAs penetrate the gut bacterial cells and control their growth and gene expression [46, 47].

4. Gut microbiota metabolites

The gut microbiota is related to both good health and risk of disease. Gut microbiota absorb energy from the host and the diet to support their growth, and release metabolites produced through fermentation. The gut microbiota synthesizes, modulates, and also releases a number of metabolites. Gut microbiota has become the functional complement for host metabolism, specifically for the unmetabolized dietary components. The gut microbiota produces a wide range of metabolites *via* fermentation of undigested dietary components in the large intestine. Gut microbiota also generate endogenous compounds through the microbial communities [48-50].

Most metabolites come from diet-dependent or diet-independent microbial products. Metabolites from diet-dependent microbial products are directly related to diet or digestion. Short-chain fatty acids (SCFAs), indole, indole derivatives and secondary bile acids are examples of the diet-dependent products (Figure 1). Gut microbes synthesize metabolites from diet-independent microbial products through *de-novo* mechanisms. Peptidoglycans and lipopolysaccharides are the examples of the diet-independent products [51]. In the following sections, we describe the bacteria-derived diet-dependent metabolites.

4.1. Short-chain fatty acids (SCFAs)

Nondigestible carbohydrates and soluble dietary fibers, such as cellulose, are an integral component of the human diet. Humans are short of the enzymes that degrade such polysaccharides, but anaerobic commensal bacteria in the large intestine can ferment these fibers. SCFA, a volatile fatty acid which has

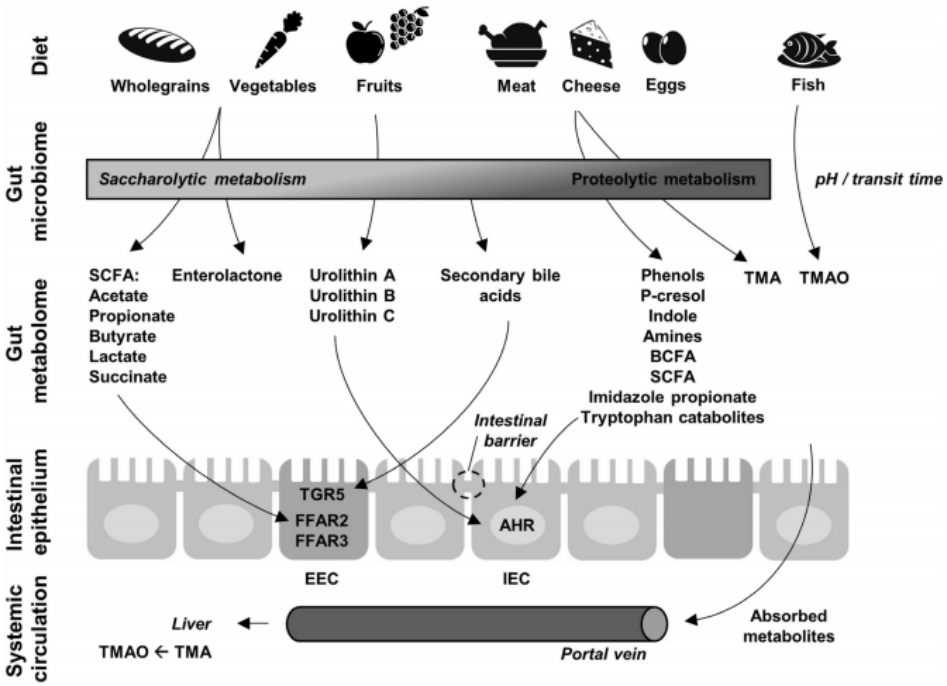

Figure 1. Overview of metabolites from diet-dependent microbial products and their related effects on health. (Adapted from [48] with permission from John Wiley and Sons).

1–6 carbon atoms backbones, is the outcome of dietary fiber fermentation. Acetate, propionate, and butyrate are the main products of SCFA. Meanwhile, SCFAs produce lactate and succinate in a lesser amount [48, 52]. Butyrate is mostly produced by Firmicutes, while acetates and propionates are mostly produced by Bacteroidetes [50]. Upon synthesis by gut microbiota, butyrate has local effects as the primary energy source for gut mucosal cells while propionate activates intestinal gluconeogenesis through distinct mechanisms [53].

In some abdominal bacteria, acetate, which is the most profuse SCFA in the colon, is produced as the secondary product of undigested polysaccharide fermentation. Acetogenic bacteria, such as *Blautia hydrogenotrophica* are the source of nearly one-third of acetate in the GI tract. These bacteria use the combination of H_2 and CO_2 or formic acid to synthesize acetate through the Wood-Ljungdahl pathway [54].

There are three pathways of propionate production by gut bacteria, namely succinate pathway, acrylate pathway, and propanediol pathway. Bacteroidetes use succinate pathway to form propionate as a substrate. For the families Veillonellaceae and Lachnospiraceae, lactate is converted to propionate by the acrylate pathway *via* several enzymatic reactions [55]. In Lachnospiraceae bacteria and Proteobacterium *Salmonella enterica* serovar Typhimurium., the conversion of deoxy-sugars (rhamnose and fucose) to propionate is synthetized using the propanediol pathway [50].

There are two pathways that can be used in the production of butyrate, namely acetate CoA-transferase pathway and butyrate kinase pathway. Through butyrate kinase pathway, the butyryl-CoA is converted into butyrate using butyrate kinase and phosphotransbutyrylase. Only some members of Coprococcus, such as *Coprococcus eutactus* and *Coprococcus comes,* use this pathway [55]. While most known butyrate-producing gut strains such as *Roseburia spp., Eubacterium rectangle, Coprococcus cactus, Faecalibacterium prausnitzii, Anaerostipes* spp. and *Eubacterium hallii* use the route of butyryl-CoA and acetate CoA-transferase pathway [50].

G protein-coupled receptors (GPCRs) will be activated once it is bound to SCFA. Those GPCRs

include GPR41 (FFAR3), GPR43 (FFAR2), and GPR109A (HCAR2), which are mainly expressed in adipose tissue, gut, and immune cells [53, 56]. The activation can affect satiety and intestinal transit through the release of peptide YY (PYY) and glucagon-like peptide-1 (GLP-1) from enteroendocrine cells [57]. SCFAs also regulate immune cell functions *via* the activation of GPR41, GPR43, and GPR109A [50] or by histone deacetylase inhibition [58].

4.2. Tryptophan metabolites

Tryptophan is an essential amino acid that participates in many physiological functions in the human body. It is necessary for the synthesis of proteins, but gut microbiota can directly use tryptophan to produce a lot of immunologically important metabolites, such as indole, indolic acid derivatives, and tryptamines. The other final products are metabolized from indole and indolic acid derivatives (Figure 2) [50, 59]. Multiple catalytic reactions are involved in the metabolism of tryptophan by gut microbiota, such as *Bacteroides* spp., *E. coli, and Clostridia.* Tryptophans are converted into indole and tryptamine by *Bacteroides* spp. and *E. coli*, while they are converted into indole pyruvic acid and then into indole-3-acetic acid by *Clostridia* [50]. As the main bacterial tryptophan metabolite, indol is considered as a necessary interspecies and interkingdom signaling molecule for the regulation of bacterial motility and resistance against nonindole-producing species invasion, such as *Salmonella enterica* and *Pseudomonas aeruginosa johnsonii* [60].

4.3. Trimethylamine N-oxide

Eggs, milk, red meats, poultry and fish contain a lot of phosphatidylcholine. Dietary lipid phosphatidylcholine has two kinds of metabolites, *i.e.* choline and trimethylamine N-oxide (TMAO). Gut microbiota converts choline, phosphatidylcholine, and carnitine into trimethylamine (TMA). TMA is later metabolized into TMAO by hepatic flavin monooxygenase. Also, c-butyrobetaine has been

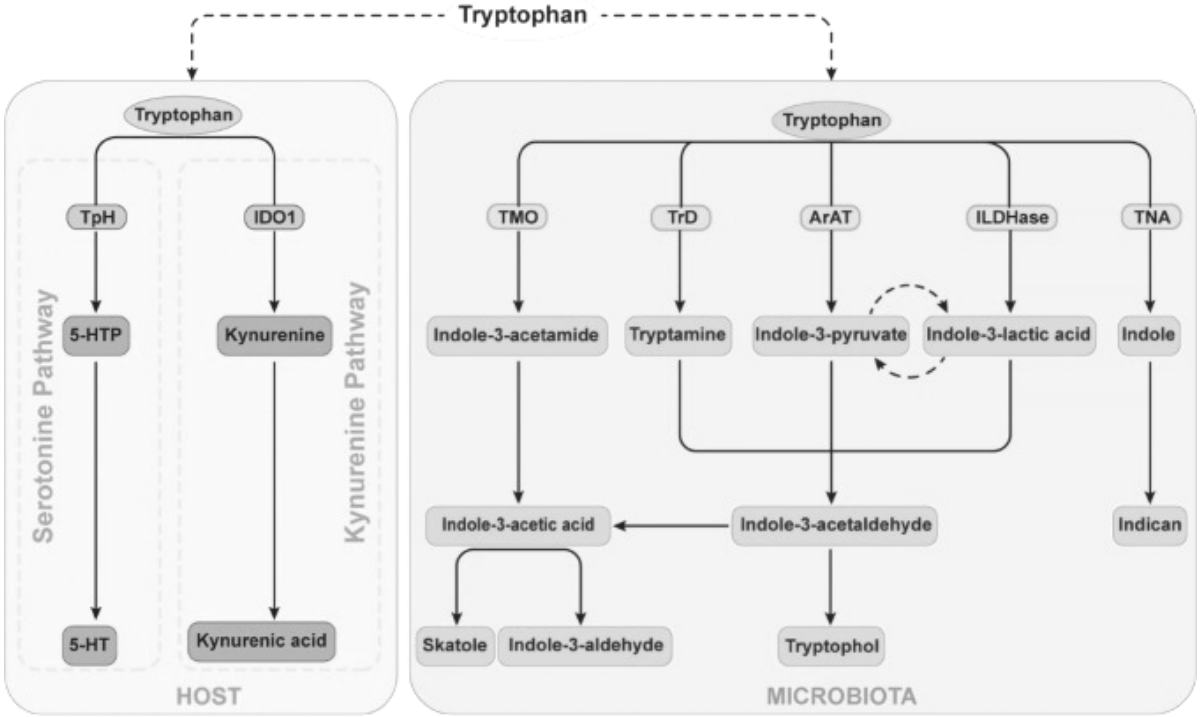

Figure 2. Tryptophan metabolic pathways in host and microbiota [50]. Trp: tryptophan, TpH: tryptophan hydroxylase, 5-HT: serotonin, 5-HTTP: 5-hydroxy tryptophan, TMO: tryptophan decarboxylase, IDO1: indoleamine 2,3-dioxygenase, TrD: tryptophan decarboxylase, ArAT: aromatic amino acid aminotransferases, ILDHase: indole-3-lactic acid dehydrogenase, TNA: tryptophanase (Adapted from [50] with permission from Springer).

found to be an intercessor in the metabolism of carnitine into TMAO [61]. The concentration of blood TMAO was found to be related with thrombosis risk, type 2 diabetes, mortality risk in chronic kidney disease, and rising risks of major adverse cardiovascular events [62-65].

4.4. Secondary bile acids

To help the dietary lipid and lipid-soluble vitamin absorption, bile acids that are released after a meal reach the duodenum. The gut microbiota metabolize bile acid into secondary bile acids through deconjugation, dehydrogenation, dehydroxylation, and epimerization. The secondary bile acids modulate the signaling properties through the nuclear farnesoid X receptor (FXR) and G protein-coupled bile acid receptor 1 (TGR5) [66].

Primary bile acids activate mostly FXR which affects bile acid homeostasis, glucose, lipid homeostasis, immune responses, and insulin signaling [66, 67]. Secondary bile acids activate TGR5 which affects energy homeostasis, thermogenesis, insulin signaling, inflammation, and bile acid homeostasis. Bile acids have an important role in facilitating the uptake of nutrients and regulating host metabolism. Hence, it is obvious that diet-induced alteration of the gut microbiota may regulate the host metabolism through alterations in the bile acid [66].

4.5. Polyphenol-derived microbial metabolites

Polyphenols are phytochemicals that originate from tea, fruit, grains and vegetables which contain phenolic acids, flavonoids, ellagitannins, and lignans. A wide proportion of dietary polyphenols undergoes modifications by gut microbiota as they penetrate the colon [48]. Hippuric acid is a polyphenol-derived microbial metabolite which is related to gut microbiota [68, 69]. Urolithin A, an example of ellagitannin-derived microbial metabolite is correlated with potential anti-oxidative, anti-inflammatory, and anti-aging activities [70, 71].

5. Conclusion

Human gut microbiota plays a pivotal role in human health and disease. Each individual has a unique gut microbiota composition which influences host nutrient metabolism, physiology, and immune system development. At the same time, the perturbation of the microbial community can result in many diseases. Microbial metabolites are generated through microorganism–microorganism and host–microorganism interactions, and there is a growing appreciation for the role of this co-metabolism in human health and disease. The revolution in molecular technologies provided equipment that are necessary for a more accurate study of gut microbiota; thus the relationships between the gut microbiota and several diseases could be more precisely elucidated. Understanding the roles microbial populations play in some diseases is fundamental for developing ultimate appropriate therapeutic approaches. Targeting the specific metabolites of gut microbiota will potentially contribute to improve our health.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest.

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