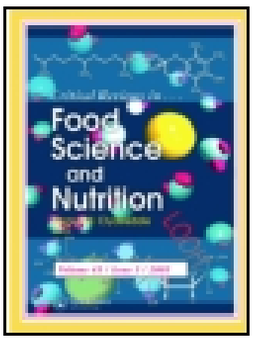

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REVIEW

Gut microbiome responses in the metabolism of human dietary components: Implications in health and homeostasis

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ABSTRACT

The gut microbiome and its link with human health and disease have gained a lot of attention recently. The microbiome executes its functions in the host by carrying out the transformation of dietary components and/or *de novo* synthesis of various essential nutrients. The presence of complex microbial communities makes it difficult to understand the host-microbiome interplay in the metabolism of dietary components. This review attempts to uncover the incredible role of the gut microbiome in the metabolism of dietary components, diet-microbiome interplay, and restoration of the microbiome. The *in silico* analysis performed in this study elucidates the functional description of essential/hub genes involved in the amino acid degradation pathway, which are mutually present in the host and its gut microbiome. Hence, the computational model helps comprehend the inter-and intracellular molecular networks between humans and their microbial partners.

KEYWORDS

amino acid degradation; CAZymes; hub genes; probiotics; short chain fatty acids; trimethylamine

Introduction

The gut is known to be a vital organ, as it comprises diverse microbial communities, which involve in nutrient absorption, homeostasis, and host immune response (Anwar et al. 2019; Wu and Wu 2012). The microbiome interacts with the host via several metabolic and immune signaling molecules that connect the brain, muscles, gut, and liver (Nicholson et al. 2012). The term microbiome is briefly defined as "a characteristic microbial community occupying a reasonable, well-defined habitat with distinct physicochemical properties" (Berg et al. 2020). The gut microbes conduct a multitude of biochemical reactions and are a dynamic ecosystem influenced by various factors, including growth stage, geographic area (Rajeev et al. 2021), exposure to pathogenic microorganisms (Machiavelli et al. 2019) and other disease conditions, use of chemotherapeutics such as antimicrobials (Sanidad, Xiao, and Zhang 2019), physical exercise (Dalton, Mermier, and Zuhl 2019), lifestyle and diet (Nicholson and Wilson 2003). Hence, it is challenging to consider a particular collection of the microbial community as healthy microbiome (Rajeev et al. 2021).

The metabolic phenotype is influenced by the host's genetic makeup and the gut microbiome. However, the influence of host genetics in molding the gut microflora and its impact in shaping the host phenotype lacks clarity (Goodrich, et al. 2014). Dysbiosis predisposes to metabolic syndrome, obesity, inflammatory bowel disease, irritable bowel syndrome (IBS), celiac disease, cardiovascular disease, allergy, and asthma (Carding et al. 2015). The study of metabolic functions performed by the gut microbial community may provide a better understanding of whether a change in population induces disease (Rajilić-Stojanović 2013). Systems biology approaches can aid in establishing the interlink between genetic variation and disease progression, hence, the genomic knowledge can be utilized in drug discovery (Nicholson and Wilson 2003). This review consolidates the functions of the gut microbiome in metabolizing different dietary components and the role of such microbial metabolites in maintaining the homeostasis of the host. The influence of dietary components on the metabolic functioning of the gut microbiome and the role of microbiome-mediated treatment strategies are also discussed here. With the rapid advances in bioinformatics, and systems biology is considered a promising approach toward more cost-effective drug development due to its ability to reveal the underlying complex association between multi-components and multi-targets during diseases. Here, we demonstrate insights into *in silico* analysis to explicate the mutually present essential/hub genes in both humans and gut microbes involved in the amino acid degradation pathway. Thus, the computational platform helps comprehend the complex human-microbiome metabolic networks and their impact on dietary metabolism.

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Metabolism of various dietary components by the gut microbiome

The cross-talk between diet and the microbiome components to execute a metabolic pathway plays a central role in the host's health status (Table 1). The microbial partner manipulates the dietary nutrients to synthesize various metabolites (Ezra-Nevo, Henriques, and Ribeiro 2020) utilized by the host, influencing the host physiology (Chatterjee, et al. 2020). The microbial consortia can metabolize the undigested dietary components and make nutrients available to the host; however, a competition for the nutrient present in the diet is also reported among the microbes (Ezra-Nevo, Henriques, and Ribeiro 2020). The microbes produce different metabolites based on the type of dietary components present, and each metabolite has critical roles in maintaining the host health (Figure 1).

Carbohydrates

The digestion of food starts from the oral cavity, where the microbes breakdown the dietary fibers (Kumar, Rani, and Datt 2020; Cantarel, Lombard, and Henrissat 2012) by producing various enzymes such as cellulases, hemicellulases, pectin hydrolases (Cantarel, Lombard, and Henrissat 2012), etc. The oral microbiome also initiates the degradation of digestible carbohydrates such as sucrose and starch, which are converted into dextran and fructans, involved in biofilm formation, thereby stabilize the oral microbiota (Cantarel, Lombard, and Henrissat 2012). An individual's gut comprises microbes capable of fermenting dietary fibers into short-chain fatty acids (SCFAs), which have health benefits (Chen et al. 2017). The dietary fibers are digested by microbial enzymes and then anaerobically fermented by the colonic microbiota, which results in the production of SCFAs as end products (Wang et al. 2019). A diet formulation comprising 50% raw potato starch and 50% chitin-glucan enhanced the abundance of SCFA producing microbes such as *Bifidobacterium* sp., *Anaerostipes,* and Lachnospiraceae unclassified (Bishehsari et al. 2018). The modern Western dietary habits have led to a 'fiber gap' or a reduced amount of fiber that eventually reduced the beneficial members of the gut microbiome and their metabolites and decrease the rate of eubiosis (Han et al. 2017; Tanes et al. 2021). Dietary fibers confer protection from metabolic and lifestyle diseases, thereby maintaining the overall health and well-being of an individual (Pyryeva and Safronova 2019).

Plant-based carbohydrates

Vegetables, fruits, and cereals provide carbohydrates and fibers to the host. The gut commensals encode a group of enzymes called "CAZymes," which hydrolyzes oligosaccharides, glycoconjugates, and polysaccharides into monomeric units (El Kaoutari et al. 2013). CAZymes specific to the degradation of plant-based polysaccharides and xylans are produced by *Prevotella* spp. which includes Xylan-1,4-β -xylosidase of the GH3 family, α-l-arabinofuranosidase of GH51 family, β-xylosidase of GH43, GH28-family endopolygalacturonase, and starch hydrolyzing enzymes of the GH13 family (Aakko et al. 2020). After enzymic action, a considerable quantity of undigested starch remains, which are degraded by the microbial enzymes belonging to the GH13 family (El Kaoutari et al. 2013). Gut commensals such as *Bifidobacterium adolescentis* and *Ruminococcus bromii* play a pivotal role in starch degradation (Ze et al. 2012). In addition, *Ruminococcus champanellensis* is involved exclusively in metabolizing cellulose, cellobiose, and xylan, thereby producing succinate and acetate with minor amounts of ethanol, formate, and lactate (Chassard et al. 2012). *Ruminococcus flavefaciens* and *Ruminococcus albus* degrades cellulose without producing succinate (Chassard et al. 2012). This suggests that species-level variation exists amongst cellulolytic gut commensals of mammals. Due to cross-feeding, the different microbial metabolic end-products might contribute to the colonization of different microbes. *Phascolarctobacterium succinatutens*, and genus *Negativicutes* and *Bacteroidetes* could utilize succinate for propionate synthesis (Watanabe, Nagai, and Morotomi 2012; Ríos-Covián et al. 2016), while succinate can be utilized by the members of *Prevotellaceae* for butyrate synthesis (Esquivel-Elizondo et al. 2017). Acetate present exogenously can be transformed into butyrate by *Faecalibacterium prausnitzii* and *Roseburia* spp. (Duncan et al. 2004) (Figure 2). Propionate, butyrate, and acetate derived from the gut microbiome regulates the metabolism and immune response of the host.

Breast milk-based carbohydrates

Breast milk contains structurally diverse sets of Human Milk Oligosaccharides (HMO) serving as a prebiotic for infants (Wu et al. 2010; Jena et al. 2018). *Bifidobacterium bifidum* from the infant's intestine secretes extracellular enzyme Lacto-N-biosidase to degrade milk glycan, Lacto-N-tetraose into lactose, and lacto-N-biose. These components are further degraded inside the microbial cells to galactose and N-acetylglucosamine mediated by the enzyme lacto-N-biose phosphorylase (Sela and Mills 2010). *Bifidobacterium longum* subsp. *infantis* deploys intracellular enzymes fucosidases, sialidases, or galactosidases to cleave HMOs into monomeric units (Marcobal and Sonnenburg 2012), whereas *Bifidobacterium breve* relies on other bacterial species to procure monosaccharides (Sela and Mills 2010), due to their incapability of hydrolyzing intact HMOs (Ward et al. 2007). The catabolic end products of HMOs can be expected to metabolically cross-feed other gut commensals or enter host metabolic pathways. Galactose in the infant's gut can get converted to tagatose due to the activity of *Lactobacillus crispatus* (Kirtzalidou et al. 2011), *Enterococcus faecalis* and *Anaerococcus prevotii* (Brooks et al. 2014; Ibrahim and Anishetty 2012). Fermentation of tagatose produces SCFA by *Enterococcus faecium*, *E. faecalis*, some *Lactobacillus* strains (Albesharat et al. 2011; Bertelsen, Andersen, and Tvede 2001), and *Haloimpatiens massiliensis* (Anani et al. 2020). Furthermore, a recent study has found a positive correlation of HMOs with SCFA levels and their role in infant weight gain (Pekmez, et al. 2020). This indicates that the gut

Table 1. Various functional roles of gut microbiome.

Gut microbiome functions	Bacteria involved	References
Digestion of plant-based polysaccharides	*Prevotella* spp.	Aakko et al. (2020)
Digestion of starch	*Bifidobacterium adolescentis Ruminococcus bromii*	Ze et al. (2012)
Digestion of xylan, cellobiose and cellulose	*Ruminococcus champanellensis*	Chassard et al. (2012)
Digestion of cellulose	*Ruminococcus flavefaciens Ruminococcus albus*	Chassard et al. (2012)
Degradation of succinate to propionate	*Phascolarctobacterium succinatutens*, *Negativicutes* and *Bacteroidetes*	Watanabe, Nagai, and Morotomi (2012) Ríos-Covián et al. (2016)
Bioconversion of acetate to butyrate	*Faecalibacterium prausnitzii* and *Roseburia* spp.	Duncan et al. (2004)
Digestion of Lacto-N-tetraose in breastmilk into lactose and lacto-N-biose.	*Bifidobacterium bifidum*	Sela and Mills (2010)
Degradation of HMOs into monomeric units	*Bifidobacterium longum* subsp. *Infantis*	Marcobal and Sonnenburg (2012)
Digestion of galactose into tagatose	*Lactobacillus crispatus*, *Enterococcus faecalis* and *Anaerococcus prevotii*	Kirtzalidou et al. (2011) Brooks et al. (2014) Ibrahim and Anishetty (2012)
Fermentation of tagatose into SCFAs	*Enterococcus faecium E. faecalis* Some *Lactobacillus* strains and *Haloimpatiens massiliensis*	Albesharat et al. (2011) Bertelsen, Andersen, and Tvede (2001) Anani et al. (2020)
Digestion of proteins	*Klebsiella spp.* *Escherichia coli* *Mitsuokella spp.* *Succinivibrio dextrinosolvens*, *Streptococcus spp*, *and Anaerovibrio lipolytica*.	Fan et al. (2017); Zhao et al. (2019)
Digestion of proteins into SCFAs, BCFAs, amines, ammonia, indoles, phenols and hydrogen sulfide	*Bacteroides* *Propionibacterium* *Clostridium* *Streptococcus* *Lactobacillus* and *Fusobacterium*	Diether and Willing (2019) Portune et al. (2016) Macfarlane et al. (1992) Dalmasso et al. (2008) Ma and Ma (2019)
AAs to propionate and succinate	*Bacteroidetes* *Propionibacterium* *Roseburia sp*. and *Clostridium* clusters	Ma and Ma (2019)
Production of Serotonin and GABA from AAs	*Bifidobacterium* and *Lactobacillus* spp	Strandwitz (2018)
Synthesis of A.A. from lactate.	*Acetobacter pomorum*	Henriques, et al. (2020)
De novo synthesis of vitamins	LAB and *Bifidobacterium spp.*	LeBlanc et al. (2013)
Synthesis of Vitamin B1	*Bacteroides fragilis*, *Fusobacterium varium*, *Clostridium difficile* *Lactobacillus* sp. *Prevotella copri* *Bifidobacterium* sp. and *Ruminococcus lactaris*	Magnúsdóttir et al. (2015) Costliow et al. (2017)
Synthesis of Vitamin B2	*B. fragilis* *F. varium* *C. difficile* *Lactobacillus* sp. *P. copri* *Bifidobacterium* sp. *R. lactaris* *Lactobacillus plantarum* and *L. fermentum*	Magnúsdóttir et al. (2015) Costliow and Degnan (2017) Yoshii et al. (2019)
Vitamin D activation	*Streptomyces griseolus* and *Sebekia benihana*	Szaleniec et al. (2018)
Regulation of expression of diacylglycerol O-acyltransferases 2 involved in lipid esterification.	*Clostridium bifermentans*	Martinez-Guryn, et al. (2018)
Sphingolipids synthesis	*Bacteriodes*	Brown, et al. (2019)
Glycosphingolipid GSL-Bf717 synthesis	*B. fragilis*	An et al. (2014)
Cholesterol reduction in humans	*Bacteroides spp* strain D8	Gérard et al. (2007)
Conversion of cholesterol to coprostanol	Cluster IV *Clostridium*	Kenny, et al. (2020)
Primary deglycosylation of secoisolariciresinol diglucoside	*Bacteroides ovatus* *Bacteroides distasonis* *Clostridium cocleatum Bacteroides fragilis* and *Clostridium saccharogumia*	Rowland, et al. (2018)
Degradation of plant-based polyphenols	*Bacteroides ovatus* *Bacteroides distasonis* *Clostridium cocleatum* *Bacteroides fragilis* *Clostridium saccharogumia*. *Eubacterium callanderi* *Peptostreptococcus productus* *Butyribacterium methylotrophicum* *Blautia product* *Eubacterium limosum Clostridium scindens Eggerthella lenta* and *Lactonifactor longoviformis*	Rowland, et al. (2018) Clavel et al. (2006) Clavel et al. (2007) Quartieri et al. (2016)
Deconjugates bile acids to unconjugated bile acid and glycine/taurine	*Bifidobacterium* spp and *Lactobacillus* spp.	(Gilliland and Speck 1977)
TMA synthesis from choline, L-carnitine, and their derivatives	*Lactobacillus*, *Clostridium*, *Proteus*, *Desulfovibrio*, and *Collinsella*	Onyszkiewicz, Jaworska, and Ufnal (2020)

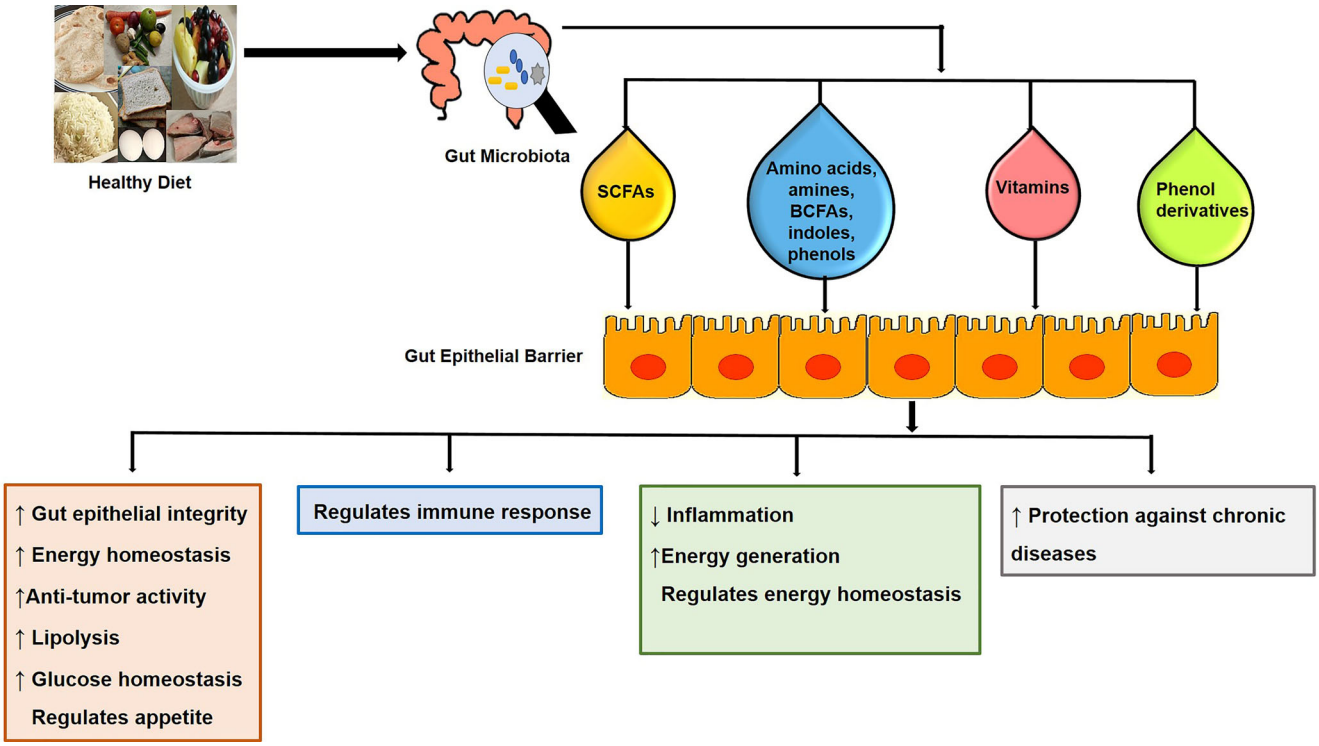


Figure 1. Degradation of dietary components by the gut microbiome and their positive effects. This illustration represents an overview of various beneficial aspects of gut microbial degradation of dietary components.

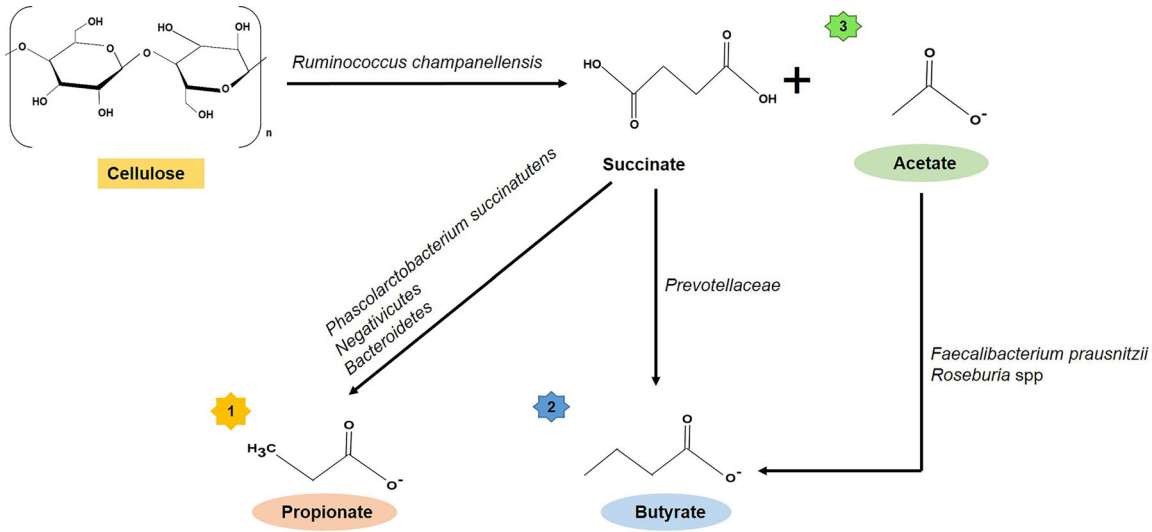


Figure 2. Cellulose degradation by the gut microbiome. The microbial community of the intestine mediated the conversion of cellulose to various SCFA such as propionate, butyrate, acetate and intermediate metabolites include succinate.

microbiome helps in the utilization of complex breast milk components and microbial metabolites that influence neonatal health (Figure 3).

Proteins and amino acids

The gut microbiome produces metabolites and proteinogenic amino acids (A.A.) by the fermentation of dietary proteins (Diether and Willing 2019). Aromatic A.A.s such as tyrosine, phenylalanine, histidine, tryptophan (Rahim et al. 2019), isoleucine, arginine, valine, could be utilized by the gut microbes (Dai et al. 2010; Dai et al. 2012). *Klebsiella* spp., *Escherichia coli, Mitsuokella* spp., *Succinivibrio dextrinosolvens, Streptococcus* spp, and *Anaerovibrio lipolytica* help in protein degradation in the small intestine (Fan et al. 2017; Zhao et al. 2019). A diet with 13% crude protein (moderate dietary protein restriction) enhances the colonization of beneficial microbes in both ileum and colon, thereby improves gut barrier function (Fan et al. 2017).

The gut microbes can either utilize the A.A.s for protein synthesis or as energy sources to produce certain other metabolites. Under aerobic conditions, A.A.s are converted into ketoacids or saturated fatty acids through transamination/deamination and are oxidized as energy sources in the

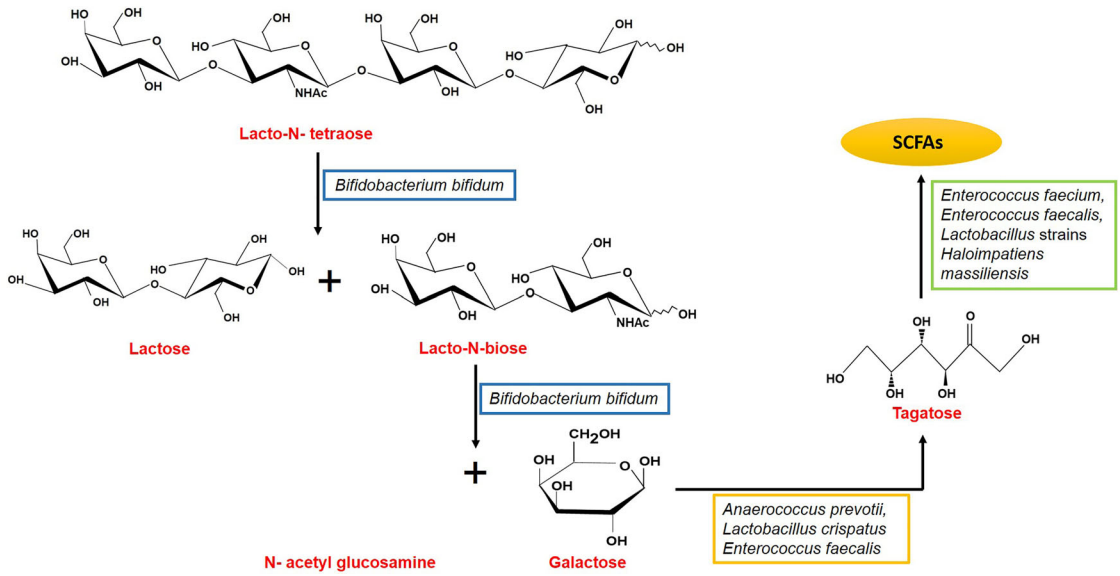


Figure 3. Lacto-N-tetraose degradation by the gut microbiome. The metabolic pathways and intermediate metabolites involved in the production of SCFA due to cross-feeding of metabolites amongst various microorganisms of the infant's intestine.

tricarboxylic acid (TCA) cycle (Portune et al. 2016). The fermentation of the dietary proteins is mainly carried out by the gut microbiome comprising of *Bacteroides*, *Propionibacterium*, *Clostridium*, *Streptococcus*, *Lactobacillus,* and *Fusobacterium* (Dalmasso et al. 2008; Ma and Ma 2019), which yields SCFAs along with amines, ammonia, branch-chained fatty acids (BCFAs), phenols, hydrogen sulfide, and indoles (Macfarlane et al. 1992; Diether and Willing 2019).

The gut microbiome also catabolizes A.A.s through deamination and decarboxylation (Fan et al. 2015). *Bifidobacterium* and *Lactobacillus* spp. produce neurotransmitters like serotonin and gamma aminobutyric acid (GABA) from A.A. (Strandwitz 2018). The consumption of GABA-producing probionts was found to alleviate depression and metabolic dysfunctions in mice (Patterson, et al. 2019). Protein lysine acetylation is a crucial metabolic pathway carried out by the SCFA producing Firmicutes in the gut, which is interrupted in patients suffering from Crohn's disease (Zhang et al. 2020). Tyrosine metabolism leading to the production of 3-(4-hydroxyphenyl) lactate observed in members of phyla Bacteroidetes, Firmicutes and Proteobacteria have been linked to nonalcoholic fatty liver disease (Caussy, et al. 2018).

Human subjects under an experimental diet consisting of iso-nitrogenous quantities of ^{15}N isotope bearing urea and $NH_{14}Cl$ exhibited isotope bearing lysine in the plasma proteins (Metges, et al. 1999). The bacterium *Acetobacter pomorum* utilizes lactate produced by *Lactobacillus plantarum* to synthesize essential A.A.s and improves egg-laying in malnourished *Drosophila melanogaster* (Henriques, et al. 2020). Whether the microbially derived A.A.s in hosts is sufficient to meet the body's nutritional demands needs further investigation (Karasov and Carey 2009).

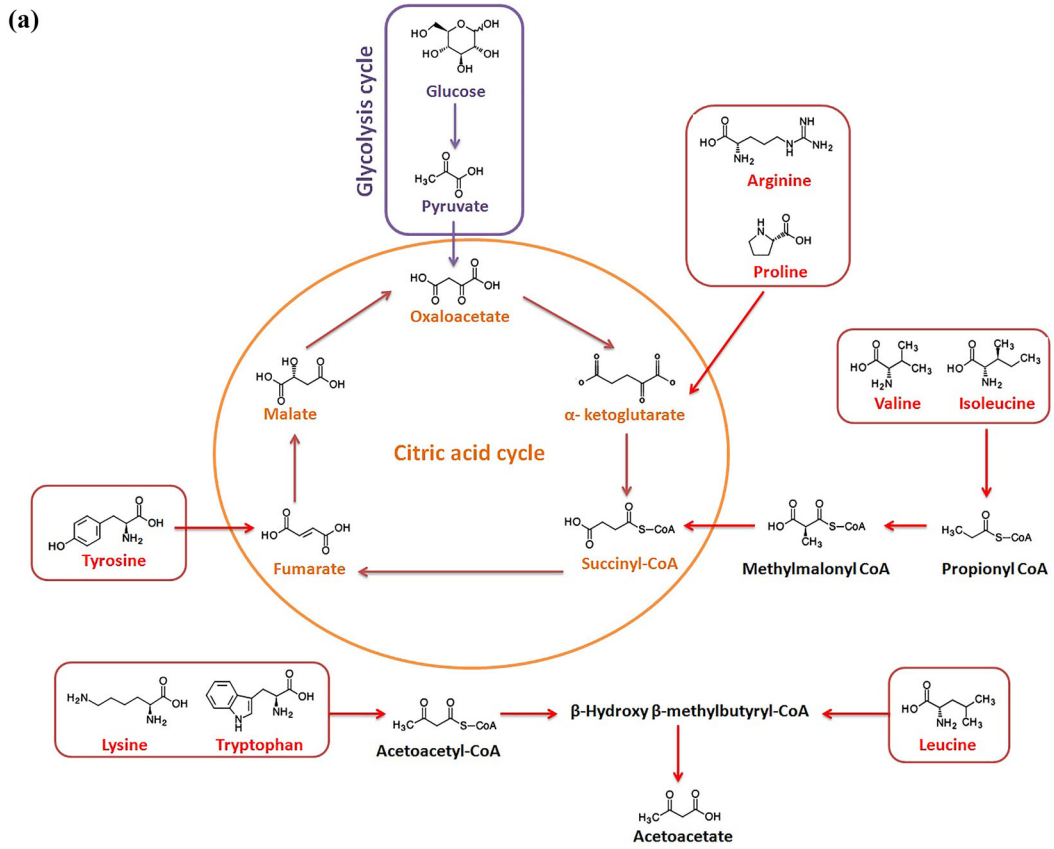
Reconciling of mutualistic metabolic profile coupled consistency between host and gut microbiome

The *in-silico* analysis performed in the present review elucidates the interlinked hub genes between the human host and gut microbiome, which entirely controls the gene clusters of A.A. degradation pathways. The A.A.s are the most critical metabolic substrate for intermediary metabolism and energy for growth in humans. The genes involved in A.A. degradation metabolic pathway were retrieved from the KEGG database and a schematic representation of A.A. degradation pathway is illustrated in Figure 4a. Here, we considered 28 experimentally characterized essential genes involved in the A.A. degradation pathway for network construction. From the analysis, four genes (*PdhA1*, *Dbt*, *GcsH,* and *DlsT*) appear to be highly interconnected with each other. Based on Gene Ontology (G.O.) terms, E-value, and network topological parameter, the interacting genes could be classified according to its biological functions, which are represented in the Supplementary Table.

In addition, 14 genes are found to be common across humans and the gut flora. Such genes have been attributed to Firmicutes (11 genes), Bacteroidetes (8), Actinobacteria (10), and Proteobacteria (13), as shown in Figure 4b. Interestingly, 2-oxoglutarate dehydrogenase (*ogdH*), Pyruvate dehydrogenase (*pdhAB*), Serine dehydratase (*sdaA*), 2-oxoisovalerate dehydrogenase (*bckdhA*), Glycine cleavage system H protein (*gcvH*), Isocitrate dehydrogenase (*idh2*), and Cystathionine gamma-lyase (*cth*) act as a functional intermediate during the metabolic cross-talk between human host and the gut microbes in A.A. degradation metabolism, as represented in Figure 4c, Supplementary Figures S1–5. The beta subunit of pyruvate dehydrogenase E1 component (pdhB) is a unique gene in δ-proteobacteria. These interactive essential genes may act as mediators during the metabolic-cross talk and interact with host immunity, which may be used to inspect dysbiosis of gut flora.

Vitamins

Vitamins can be classified as micronutrients having various impacts on the host physiology and immunity (Yoshii et al. 2019). The gut microbiome can utilize the dietary vitamins



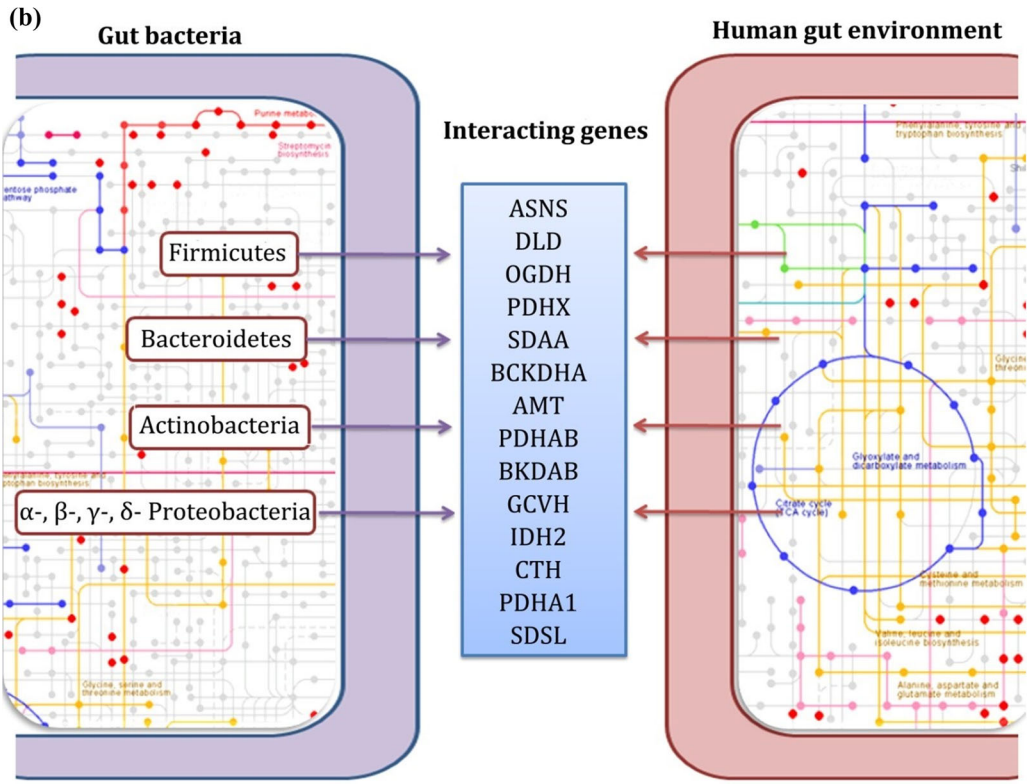


Figure 4. Interlinked hub genes for amino acid metabolism between host and gut microbiome (a) a schematic representation of amino acid degradation pathway, (b) Comparative metabolic-mutualistic genes identified from the amino acid degradation pathway across human gut microbiome, and (c) Functional description of common and unique genes found across human gut microbiome.

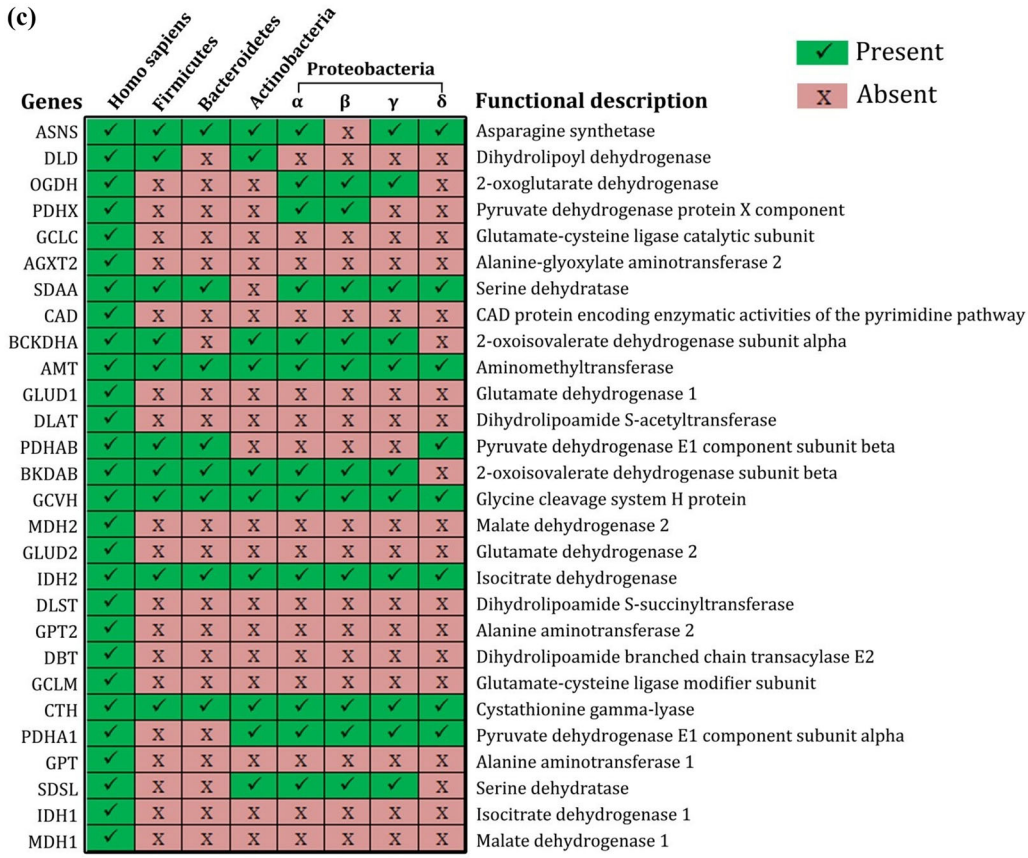


Figure 4. Continued.

and also produce vitamin B complex (generally produced and absorbed in the colon) and fat-soluble vitamin K (Magnúsdóttir et al. 2015; Said and Mohammed 2006). *De novo* synthesis of vitamins can be attributed to lactic acid bacteria (LAB) and *Bifidobacterium* spp. (LeBlanc et al. 2013). The intestinal bacteria which produce vitamin B1 include *Bacteroides fragilis, Fusobacterium varium, Clostridium difficile, Lactobacillus sp., Prevotella copri*, *Bifidobacterium* sp. and *Ruminococcus lactaris* (Magnúsdóttir et al. 2015; Costliow and Degnan 2017). In addition, these bacteria, along with *L. plantarum* and *L. fermentum*, also produce vitamin B2 in the large intestine (Yoshii et al. 2019; Costliow and Degnan 2017).

Fat-Soluble Vitamins (FSV) modulate the gut microbial composition by interfering in the metabolic mechanisms. The gut microbiome serves an essential role in the production, metabolism, and transport of FSV in the host. The absorption, metabolism, and immune function of vitamin A is modulated by the gut microbes (Stacchiotti et al. 2020). Vitamin D is regulated by gut microbes via Fibroblast Growth Factor 23, although it is naturally produced in the host skin due to sunlight exposure and dietary intake. The metabolism of vitamin D is also regulated by the gut microbes via Fibroblast Growth Factor 23 (Bora et al. 2018). The gut microbiome also plays vital roles in the activation of vitamin D, as few microbes (*Streptomyces griseolus* and *Sebekia benihana*) possess enzyme (CYP105A1, CYP-sb3a) responsible for the hydroxylation of steroids (Szaleniec et al. 2018, Stacchiotti et al. 2020), which is important for the metabolic activation of vitamin D. Vitamin E serves as an anti-oxidant for the cellular membranes and circulating lipoproteins and also has a crucial role in the prevention and treatment of degenerative diseases (Wallert et al. 2014; Stacchiotti et al. 2020). The CYP450- dependent metabolism of vitamin E is initiated by the gut microbiome in the intestinal lumen (Stacchiotti et al. 2020). Furthermore, gut microbes are capable of synthesizing vitamin K2 (Fusaro, et al. 2017), which is used to maintain homeostatic processes of the bone and vascular systems (Fusaro, et al. 2011; Stacchiotti et al. 2020).

Lipids

Lipids are also an important nutritional component of the diet since they act as reservoirs of energy. The intestinal microbiome can digest and absorb lipid components. Microbial methyl metabolism is associated with the host lipid metabolism and the metabolites generated from this pathway have a critical role in regulating the synthesis of phosphatidylcholine in host (Lin and Wang 2017). Supplementation of metabolites from *Clostridium bifermentans* grown in conditioned media to mice receiving a low-fat diet enhanced the expression of a key enzyme, diacylglycerol O-acyltransferases 2, which take part in the esterification of lipids before its transport (Martinez-Guryn, et al. 2018). This indicates either extracellular protein or microbial metabolites can influence the uptake of lipids by the host, which needs further investigation. Lipids derived from gut

commensals are also reported to be essential for sustaining intestinal homeostasis. Patients diagnosed with IBS have been found to have low levels of *Bacteriodes* derived sphingolipids and their deficiency has been positively correlated with pro-inflammatory responses in the intestine (Brown, et al. 2019). Glycosphingolipid GSL-Bf717, derived from the gut bacteria *B. fragilis*, can prevent oxazolone-induced colitis due to their anti-proliferative properties against iNKT cells (An et al. 2014). Hence, gut microbiota-derived lipids can be a possible therapeutic tool for the treatment of several metabolic and autoimmune disorders.

Polyphenols and minerals

Dietary polyphenols are mainly present in fruits, vegetables, seeds, cocoa-based products, tea, wine, etc. and are known for their anti-oxidant properties and mainly include flavones, proanthocyanidins, catechins, anthocyanidins, flavonols, and phenolic acids, etc. (Pérez-Jiménez et al. 2010; Singh, et al. 2017). After the conversion of polyphenols to their aglycone, they undergo breakdown by the microbes in the colon via dehydroxylation, decarboxylation, and ring breakage, finally producing simpler phenolic compounds, for example, hydroxyphenyl-acetic acids and hydroxyphenylpropionic acids (Rowland, et al. 2018). The primary deglycosylation of secoisolariciresinol diglucoside involves the activity of *Bacteroides ovatus*, *Bacteroides distasonis, Clostridium cocleatum*, *B. fragilis,* and *Clostridium saccharogumia*. Bacteria like *Eubacterium callanderi, Peptostreptococcus productus, Butyribacterium methylotrophicum, Blautia producta,* and *Eubacterium limosum* are involved in the demethylation of lignan aglycone. Dehydroxylation of secoisolariciresinol is mediated by *Clostridium scindens* and *Eggerthella lenta* and the final phase of dehydrogenation of enterodiol to enterolactone, and closure of the lactone ring is catalyzed by Clostridiales, mainly *Lactonifactor longoviformis* (Rowland, et al. 2018; Clavel et al. 2006; Clavel et al. 2007; Quartieri et al. 2016).

Phytoestrogens (P.E.) are a category of polyphenols that is similar to human estrogens. It is present in plants or plant derivatives like soya, chocolate, vegetables, flaxseed and other seeds, fruits, cereals, tea, etc. Stilbenes, ellagitannins, coumestans, isoflavones, and lignans are major classes of phytoestrogens (P.E.), structurally analogous to endogenous estrogens (Landete et al. 2016), providing many health benefits, including anti-oxidant, anti-neoplastic, anti-inflammatory and apoptotic activities (Peirotén, Bravo, and Landete 2020). Isoflavones, ellagitanins, and lignans are converted by the gut microbiome into equol, urolithins, and enterolignans, respectively (Landete et al. 2016). The transformed metabolites render protection against certain chronic diseases such as cardiovascular disease, menopausal symptoms, cancer, and osteoporosis (Landete et al. 2016; Hooper and Cassidy 2006). Equol and enterolactone derived from microbial degradation of lignin could cross the blood-brain barrier and exert anti-inflammatory properties in murine microglia against lipopolysaccharide-induced inflammation (Johnson et al. 2019). The microbial metabolites obtained after fermentation of polyphenols were also reported to have antidiabetic and anti-oxidant properties (Gowd, et al. 2018).

Marine multi-mineral blend (MMB) can act as a gut-health improving functional food component. Seaweed and seawater-derived functional food component abundant in bioactive calcium and magnesium along with 70 other trace elements increased the diversity of the gut microbiome in adult male rats (Crowley, et al. 2018). A study conducted to understand the effects of the microbiome and its biochemical activity upon supplementation of inulin and calcium-rich milk mineral into pork sausage revealed that an enriched diet enhanced SCFA formation and the milk mineral reduced the formation of nitroso compounds in the intestine (Thøgersen, et al. 2020).

Influence of gut microbiome in gut metabolic functions

Short chain fatty acids: The beneficial microbial metabolites

The most dominant SCFAs produced by the gut microbes include simple 2-carbon to 5-carbon aliphatic-chain fatty acids such as acetate (60%), propionate (25%), butyrate (15%), and valerate (Kumar, Rani, and Datt 2020; Topping and Clifton 2001; Tazoe et al. 2008; Tang, Li, and Hazen 2019). The most predominantly available SCFA is acetate, which is utilized by the gut microbes to synthesize other SCFAs like butyrate, propionate, etc., in a growth-enhancing cross-feeding manner (Kumar, Rani, and Datt 2020). Butyrate is the most important source of energy for the colonocytes and also improves the epithelial integrity and barrier function, thereby preventing inflammation (Hamer et al. 2008; Leonel and Alvarez-Leite 2012; Jena et al. 2018). Mainly utilized as a source of energy, acetate is also known to reduce appetite (Frost, et al. 2014). Propionate reduces intrahepatocellular lipid content, serum cholesterol, reduces weight gain, and also regulates appetite (Chambers, et al. 2015). The SCFAs also help in the dilation of blood vessels and reduces blood pressure (Onyszkiewicz, Jaworska, and Ufnal 2020). The SCFAs are biologically significant with respect to quantity and proportion (Chen et al. 2017) and are transported into circulation via the AMPK pathway, GPCR signaling, and/or HDAC inhibition pathway (Figure 5).

Mechanisms of SCFA transportation

The transportation of SCFAs occur via the apical and basolateral membranes of colon cells (Den Besten, et al. 2013). The transportation of SCFAs can take place via three different modes. One of the mechanisms is via the anti-port transport, where the transport of SCFA out of the intestinal lumen is coupled with the transport of HCO_3^- into the intestinal lumen (Mascolo, Rajendran, and Binder 1991). Another mechanism is via the monocarboxylate transporter 1 (MCT-1) (SLC16A1), where a co-transport of $SCFA^-$ occurs with H^+ (Teramae, et al. 2010; Den Besten, et al. 2013). The third type of transport is the co-transport of

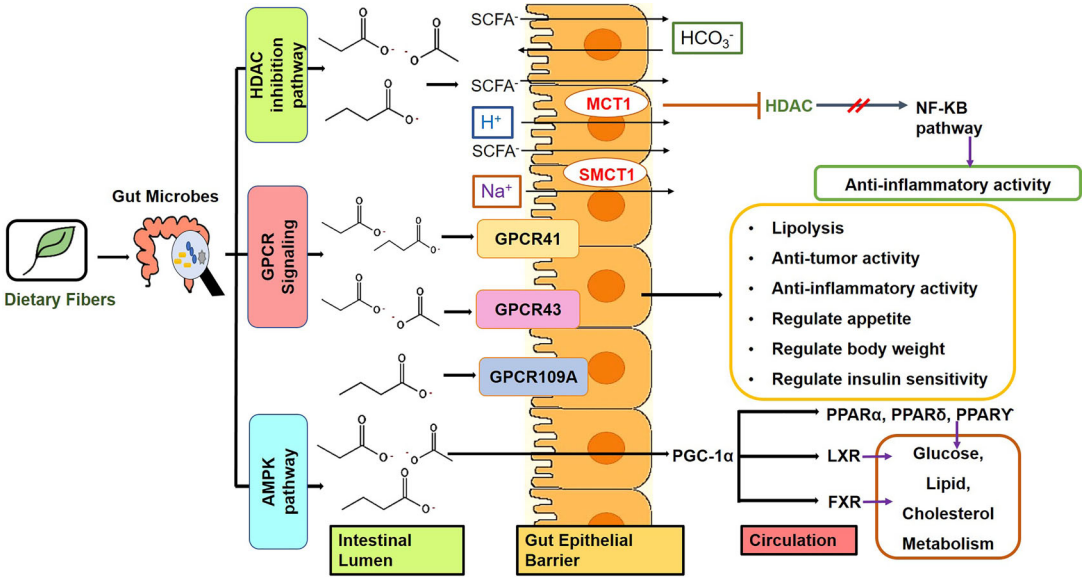


Figure 5. Transportation of microbial SCFAs. The gut microbes degrade dietary fibers and produce SCFAs that are transported into the circulation via AMPK pathway, GPCR signaling, and/or HDAC inhibition pathway.

$SCFA^-$ with Na^+ via the sodium-coupled monocarboxylate transporter 1 (SMCT1) (Takebe, et al. 2005; Den Besten, et al. 2013). Among these mechanisms, the SCFAs are mainly transported by active transport using mainly two receptors, MCT-1 and SMCT-1. The SCFAs transported by these mechanisms modulate the host physiology through the direct inhibition of histone deacetylases (HDACs) (Kumar, Rani, and Datt 2020) (enzymes that remove acetyl groups from lysine residues on histone N-terminal) (Kim and Bae 2011), which leads to the enhanced transcription of genes, causing altered gene expression due to enhanced histone acetylation (Kumar, Rani, and Datt 2020). The inhibition of HDAC via SCFAs leads to alteration of Nuclear Factor Kappa-light-chain-enhancer of activated B cells (NF-kB) signaling pathway (Usami, et al. 2008), which lowers the production of inflammatory cytokines Interleukin (IL)-8, IL-6, and Tumor necrosis factor (TNF) α thereby providing anti-inflammatory benefits (Kumar, Rani, and Datt 2020).

The SCFAs also modulate the host physiology via certain G protein-coupled receptors (GPCRs). GPCR-43 and GPCR-41 are mainly known to be the receptors for SCFs (Brown, et al. 2003; Le Poul, et al. 2003) and are also regarded as Free Fatty Acid Receptor 2 (FFAR2) and FFAR3, respectively (Kumar, Rani, and Datt 2020). The GPCR43 is mainly expressed in immune cells while the GPCR41 is expressed in the adipose, endothelial, and immune cells (Brown, et al. 2003). Butyrate and isobutyrate are known to activate GPCR41, whereas propionate activates both GPCR41 and GPCR43 more actively than butyrate and acetate. Acetate, on the other hand, is quite specific to GPCR43 (Le Poul, et al. 2003). Both the receptors were coupled to the formation of inositol 1,4,5-trisphosphate, activation of extracellular signal-regulated kinases (ERK) 1/2, Cyclic adenosine monophosphate (cAMP) accumulation inhibition, and the release of intracellular Ca^{2+} (Le Poul, et al. 2003). The GPCR43 is mainly expressed in L cells of the intestine (Tolhurst, et al. 2012). SCFAs mediated activation of GPCR43 causes the improved release of peptide YY (PYY) hormone and glucagon-like peptide 1 (GLP-1), which are known to modulate appetite in the host (Tolhurst, et al. 2012). Propionate stimulates the production of PYY and GLP-1 from human colonic cells (Chambers, et al. 2015). GPCR43 is known to aid in regulating obesity and maintaining the body's energy reserve (Kimura et al. 2014). The SCFAs also regulate the inflammasome pathway via activation of GPCR43, which is a significant pathway enhancing the integrity of gut epithelial tissues (Macia, et al. 2015). Circulating SCFA is related to circulating GLP-1 concentrations, lipolysis in the entire body, and peripheral insulin sensitivity in the host (Müller, et al. 2019). GPCR41 and GPCR43 are activated by the SCFAs in the enteroendocrine cells, while GPCR41 alone is activated in enteric neurons and GPCR43 in enteric leukocytes (Nøhr, et al. 2013). Dietary administration of grape seed proanthocyanidin (GSP) in weaned pigs revealed that GSP positively altered the gut microbiome composition. The enhanced expression of GPR43 in adipose tissue indicated the improved propionate production by microbes, which in turn improved the lipid metabolism (Wu et al. 2019).

GPCR109A (hydroxycarboxylic acid receptor 2), a GPCR for nicotinate, can recognize butyrate with little affinity but cannot recognize acetate or propionate. GPCR109a is known to be expressed in various cells in the host body, such as gut epithelial cells, adipocytes, and immune cells (Thangaraju et al. 2009; Taggart et al. 2005; Tunaru et al. 2003; Liu et al. 2014; Li et al. 2020). GPCR109A also has a role in tumor-suppression activity on activation by butyrate in the colon and is also linked with the regulation of inflammatory cytokines (Thangaraju et al. 2009). Through GPCR43 and GPCR109A, the SCFAs produced via the breakdown of dietary fibers by the gut microbes can protect against diabetic nephropathy (Li et al. 2020).

Table 2. The influence of microbial metabolites in the prevention of certain health disorders.

Microbial metabolite	Metabolite synthesizing microbe(s)	Disorder	Protective action of the metabolite	Reference(s)
Acetate	*Bacteroides*	Type 1 diabetes	Lowered occurrence of diabetogenic T-cells in the pancreatic lymph nodes and spleen	Mariño et al. (2017)
Aryl hydrocarbon receptor ligands and indole3-acetic-acid	*Allobaculum* and *Lactobacillus reuteri*	Inflammatory Bowel Disease	Stimulation of IL-22 production	Zenewicz et al. (2008) Lamas, et al. (2016)
Hydrogen sulfide	*Desulfovibrio*	Type-2 diabetes	Modulation of thioredoxin binding protein-2 expression in islets	Okamoto, et al. (2013) Canfora et al. (2019)
Urolithin	*Gordonibacter urolithinfaciens* and *Gordonibacter pamelaeae*	Alcoholic liver disease	Decreased triglyceride levels, aspartate aminotransferase/ alanine aminotransferase level in liver induced by alcohol and IL-1β, TNF-α and IL-6 level.	Selma et al. (2014) Jala et al. (2020)
Butyrate	*F. prausnitzii* and *Roseburia sp.*	Colon cancer	Inhibition of proto-oncogene *c-Myc* expression and enhanced apoptosis rate	Zeng et al. (2020) Duncan et al. (2004)
Propionate	*P. succinatutens, Negativicutes and Bacteroidetes.*	Acute leukemia	cAMP level-dependent anti-proliferative effect and free fatty acid receptor-2 activation	Watanabe, Nagai, and Morotomi (2012) Ríos-Covián et al. (2016) Bindels et al. (2012)
5,10-methenyltetrahydrofolic acid polyglutamate	*Lactobacillus reuteri* strain ATCC PTA 6475	Acute colitis	Reduction in TNF expression in TLR-2 agonist activated human monocytoid cells	Thomas, et al. (2016)
Desaminotyrosine	*Clostridium orbiscindens*	Influenza	Lowered immunopathology of lungs and enhanced type I interferon signaling	Steed et al. (2017)

Apart from the GPCRs and HDAC inhibition pathways, the SCFAs also act through the AMP-activated protein kinase (AMPK) pathway, via which it regulates fatty acid oxidation and lipolysis in the liver and muscle (Den Besten et al. 2013). The stimulation of the AMPK pathway upregulates the expression of peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1α, which in turn controls the transcriptional activity of various transcription factors, peroxisome proliferator-activated receptor (PPAR) α, PPAR δ, PPAR Υ, liver X receptor (LXR), and farnesoid X receptor (FXR), that plays crucial roles in the regulation of glucose, lipid, and cholesterol metabolism (Den Besten et al. 2013; Jäger et al. 2007; Lin, Handschin, and Spiegelman 2005). Acetate and butyrate can enhance the fat oxidation in muscles in an AMPK-dependent manner or alter the oxidative state of muscle fibers, hence enhancing metabolic flexibility. In the liver, SCFAs such as acetate and butyrate could directly be utilized as a substrate for lipogenesis, while propionate is mostly utilized for gluconeogenesis. Therefore, it indicates that SCFAs positively modulate hepatic and peripheral insulin sensitivity along with the regulation of glucose homeostasis (Canfora, Jocken, and Blaak 2015). The AMPK-dependent action of SCFAs enhances intestinal integrity and homeostasis (Li et al. 2019). The SCFAs play vital roles in the gut-brain axis signaling; hence any variation in the amount of SCFAs can impair the gut-brain axis signaling leading to disturbances in CNS, ultimately causing neurodevelopmental and/or neurodegenerative disorders (Silva, Bernardi, and Frozza 2020). Precision dietary intake based on individual gut microbiome regulates diversity and confers health benefits (Wan and Jena 2019). Dysregulated microbial fermentation of dietary fibers also negatively impacted host health and cause cholestatic liver disease (Singh, et al. 2018).

Bile acids and cholesterol

Bile acids (BAs) are produced from cholesterol in the liver by the rate-limiting enzyme cholesterol 7α-hydroxylase (Chiang and Ferrell 2020). In the liver, the primary BAs are biosynthesized and metabolized by the gut microbes and converted into secondary bile acids (Sayin, et al. 2013). Hence the biotransformation of bile acids is possible due to the combined activity of the host and its gut microbiome. The secondary bile acids hence derived, influence the gut microbial composition and function, and the host physiology (Winston and Theriot 2020). The microbial transformation of primary bile acids such as cholic and chenodeoxycholic acid maintains a healthy bile acid pool, and this is executed through deconjugation, oxidation/epimerization, 7-dehydroxylation, esterification, and desulfation (Midtvedt 1974; Gérard 2014). *Lactobacillus* spp. deconjugates bile acids to unconjugated bile acid and glycine/taurine (Gilliland and Speck 1977). Secondary bile acids, deoxycholic acid (DCA), lithocholic acid (LCA) has a potential effect on host physiology (Kuno et al. 2018).

BAs have various effects on host metabolism, and dysregulated BAs pool could lead to various disease conditions (Chen, Thomsen, and Vitetta 2019; Sheng, Jena, Hu, et al. 2017; Sheng, Jena, Hu, et al. 2017; Jena et al. 2017). The regulation of bile acid synthesis is mediated via activation of FXR, which is a negative feedback regulation in the ileum

and liver (Tang, Li, and Hazen 2019; Sayin, et al. 2013). The gut microbiome-bile acid interaction also occurs via the Takeda G-protein-coupled bile acid protein 5 (TGR5) (Sayin, et al. 2013; Hylemon et al. 2009). The TGR5 also aids in energy homeostasis by improving intracellular thyroid hormone action, enhancing thermogenesis in brown adipose tissue (Watanabe, et al. 2006). Various active transporters present on the cells of the ileum apical sodium-dependent bile acid transporter (ASBT) and organic solute transporter α-β (OSTα/β), and liver Na^+ -taurocholate cotransporting polypeptide (NTCP) and organic anion transporting polypeptide (OATP) aid in the transportation of bile acids through the enterohepatic circulation to the liver (Chiang and Ferrell 2020; Alrefai and Gill, 2007) After reaching the liver, the expression of the Cyp7a1 gene is inhibited due to the upregulated expression of a small heterodimer partner (SHP), which binds to liver receptor homolog-1 (LRH-1) due to the activation of FXR by bile acids (Goodwin, et al. 2000). Apart from the liver, BA can also activate FXR in the distal ileum, which leads to the expression of Fibroblast Growth Factor 19 (FGF19). On reaching the liver via enterohepatic-circulation, FGF19 binds to the FGF receptor 4 (FGFR4)/β-klotho heterodimer complex and stimulates a c-Jun N-terminal kinase (JNK) 1/2 and ERK1/2 signaling cascade that also inhibits the expression of Cyp7a1 (Potthoff, Kliewer, and Mangelsdorf 2012; Yu et al. 2005; Chen et al., 2019; Kong et al., 2012). The FXR is also known to control the synthesis of GLP-1 (Trabelsi et al. 2015). Secondary BAs, Ursodeoxycholic acid (UDCA) safeguard the colon cells from apoptosis and oxidative damage (Barrasa et al. 2013). In the case of colonic inflammation, UDCA and lithocholic acid (LCA) showed anti-inflammatory activities (Ward, et al. 2017). Harmful alteration in gut microbiome-mediated bile acid signaling could also make the host susceptible to obesity (Wei et al. 2020). High amounts of DCA and LCA could result in pathological conditions, such as oxidative stress, membrane damage, and also gastrointestinal carcinogenesis in the colon (Barrasa et al. 2013; Jena et al. 2017).

Cholesterol is synthesized in the host and is also acquired by the host to synthesize other metabolic components such as BAs, steroid hormones, etc. (Midtvedt and Midtvedt 1993). Cholesterol on reaching the large intestine is metabolized by the gut microbiome, majorly to coprostanol with little amounts of coprostanone (Gérard 2014). Depending on the cholesterol metabolizing bacterial load in the gut, the rate of cholesterol transformation into coprostanol varies among the human population (Veiga et al. 2005). Cholesterol-reducing bacteria is isolated from rats (Eyssen et al. 1973) and baboons (Gérard 2014) belonged to the genera *Eubacterium* (Eyssen et al. 1973), whereas in humans, it was found to be *Bacteroides* spp. strain D8 (Gérard et al. 2007). Whether a reduction in the population of this strain in the gut has a significant impact on the systemic health of the host needs additional investigations. A recent study has found that the microbial cholesterol dehydrogenase enzyme that converts cholesterol to coprostanol is encoded by *ismA* genes of Cluster IV *Clostridium* present in the human gut (Kenny, et al. 2020). The microbial transformation of cholesterol to BAs was proven to have a significant role in the overall cholesterol cycle, and hence microbiome-based interventions can be used as a therapeutic measure to control cholesterol levels in humans (Bourgin, et al. 2020).

Trimethylamine

Trimethylamine (TMA), a tertiary aliphatic amine, is synthesized in the colon by gut microbes such as *Lactobacillus*, *Clostridium*, *Proteus*, *Desulfovibrio*, and *Collinsella* from choline, phosphatidylcholine, L-carnitine, present in the diet (Onyszkiewicz, Jaworska, and Ufnal 2020). TMA enters into the portal circulation and is oxidized by hepatic enzymes called flavin-containing monooxygenases (FMOs; primarily the FMO3 isoform) to produce Trimethylamine N-oxide (TMAO) (Tang, Li, and Hazen 2019). The primary microbial catabolic enzyme system for the conversion of choline into TMA in the human gut microbiome is the choline-utilization gene cluster which encodes the catalytic and regulatory polypeptides, choline TMA-lyase (CutC), and choline TMA-lyase activating enzyme (CutD) (Craciun and Balskus 2012). Other microbial enzyme systems that are involved in TMA generation comprise carnitine monooxygenase for the conversion of carnitine into TMA (Zhu et al. 2014), and blocking TMA formation reduced the circulating TMAO level (Roberts, et al. 2018). Thus, the TMAO circulation is determined by the gut microbiome and numerous other factors such as choline-rich diet, the activity of liver FMO, the function of the kidneys, etc. (Simó and García-Cañas 2020).

Dietary influence on metabolic functioning of the gut microbiome and its impact on host health

Metabolic activities of the gut microbiome rely to some extent on the dietary intake of nutrients, and the change in the metabolic functioning of the microbiome can have profound effects on the host. A diet comprising of high protein content altered the microbial consortia of the colon by reduction of butyrate producers such as *R. bromii* and *F. prausnitzii* and promoted the populations of *E. coli*, *Enterococcus* spp., and *Streptococcus* spp., enhancing cadaverine levels (Mu et al. 2016). This fluctuation of microbial metabolism in humans is unhealthy because excess amounts of cadaverine damage the DNA (Holmes et al. 2011) and stimulate oxidative stress, while the shortage of butyrate weakens immunity (Mu et al. 2016). Protein deficient diets can even influence the utilization of non-protein-derived metabolites by the gut microbiome. An example of this is the excess excretion of trimethylamine, trimethylamine-N-oxide, and dimethylamine due to microbial degradation of dietary choline in mice fed with a protein-deficient diet (Mayneris-Perxachs, et al. 2016).

Microbiota-Accessible Carbohydrates (MACs) are carbohydrates accessible to the microbes for performing metabolic activities, and they are acquired either from the diet or produced by the host or synthesized by the microbes themselves. A western diet comprising of low-MAC has been

proven to deplete the production of SCFA derived from the host microbiome (Sonnenburg and Sonnenburg 2014). This confirms that certain carbohydrates are crucial for the gut microbiome to carry out the metabolic process that yields beneficial molecules to the host. Moreover, the absence of MAC in diet shifts the microbial consortia to feed upon host mucus glycans (Sonnenburg, et al. 2005), and persistence of this condition might even culminate in inflammatory responses. High-fat diet consumption in mice was found to enhance the microbial enzymes of carbohydrate metabolism for energy production (Daniel, et al. 2014). Diet can even modify the host's therapeutical response by altering the metabolism of gut commensals without interacting with the drug (Ke et al. 2020). Moreover, dietary changes with respect to age can also influence the metabolism of the host. For example, the bacterial bile acid metabolism and development of host bile acid production was improved when taurocholic acid or β-tauro-murocholic acid were orally administered to mice of the post-natal stage (van Best et al. 2020). Thus, it can be perceived that diet not only changes the microbial population and diversity in the gut but also alters the functioning of the microbiome. A balanced diet is not just about providing an adequate amount of essential nutrients to host by diet but also extends to the maintenance of a functional microbial ecosystem. Dietary regimes rewarding both these qualities can improve host health remarkably.

Improving the microbiome function through microbiome-based interventions

A vast majority of scientific studies have been conducted to implement fecal microbiota transplantation (FMT), administration of probiotics and prebiotics aimed at countering infectious and noninfectious diseases. According to WHO/FAO 2002, probiotics are 'live microorganisms which when administered in adequate amounts confer a health benefit on the host' (). In contrast, prebiotics is redefined as 'a substrate that is selectively utilized by host microorganisms conferring a health benefit' by Gibson, et al. (2017). Probiotics formulated using strains of *Saccharomyces*, *Bifidobacterium* and *Lactobacillus* are effective and are widely used, and strains such as *Propionibacterium* spp., *Roseburia* spp., *Faecalibacterium* spp. and *Akkermansia* spp. are some of the promising candidates for probiotics in the future. Besides the well-studied fructans and glycans, polyphenols and oligomers of human milk, mannose, pectins, and starch are some of the effective prebiotic components examined in the latest (Sanders et al. 2019). Probiotics benefit host health by various mechanisms, including the production of antibacterial molecules, enhance mucosal barrier, and stimulate adaptive immune responses, etc. (Sherman, Ossa, and Johnson-Henry 2009). Prebiotics activates the immune system and increases the bioavailability of minerals (Charalampopoulos and Rastall 2012). Probiotics and prebiotics can be incorporated to design functional foods to combat many metabolic disorders subjected to evidence-based clinical studies.

Recent studies have confirmed that metabolic products of microbes can improve the physiological functions of the host, which leads to the introduction of a new concept called 'post-biotics' in the literature (Aguilar-Toalá et al. 2018).

SCFAs, which are important by-products of microbial metabolism, can modulate energy metabolism, insulin production, and feeding behavior of the host (Kimura, et al. 2013; Canfora, Jocken, and Blaak 2015; Perry, et al. 2016). Research in post-biotic therapy is still in its infancy, and more information regarding their meritorious role in human health can be expected to be revealed in forthcoming studies. The role of some microbially derived metabolites and their mechanistic action in the prevention of certain diseases are listed in Table 2.

FMT involves the administration of fecal matter from a healthy donor to a recipient's intestinal tract to restore the dysbiotic gut microbiome (Borody and Khoruts 2012). FMT is one of the effective therapies employed in the treatment of *C. difficile* infection (CDI) (Bakken, et al. 2011). The levels of SCFA, such as propionate, acetate, and butyrate, and bile acids like deoxycholate and lithocholate were enhanced following FMT treatment in CDI patients (Seekatz et al. 2018). FMT was also found to re-instate the biosynthesis of secondary bile due to rebiosis and thereby reduced aging in progeroid mice (Bárcena, et al. 2019). These studies imply that the success of FMT relies on the ability to restore the microbiome in the intestine and, upon colonization confers health benefits.

Conclusion and future prospects

The gut microbiome is closely associated with human life activities and interacts closely with the host metabolism, gene expression, organism immunity, and disease development. The functional microbiome assists the host not only in the degradation of recalcitrant components of the diet but also provides beneficial compounds such as SCFA, essential vitamins, and amino acids. The metabolites derived from gut commensals are invaluable endowments to the host since they have protective action against several diseases. Understanding the role of such bio-transformed metabolites by the gut microbiome and their characterization in host health will open new ventures in the development of noninvasive diagnostic tools to treat several metabolic, neurological, and immune-related disorders. Identification and characterization of these metabolites will help to monitor the disease progression and accelerate the discovery of new post- and prebiotics. Changes in the functioning of the host at the molecular level due to the alteration of microbial metabolome will provide new insights to improve the quality of treatment. The construction of a repository of microbiota-derived metabolites will be highly advantageous to the field of microbiome research.

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Authors' contributions

R.R., PSS, and P.R., performed the analysis and preparation of draft; GSK and PKJ guided preparation of the manuscript; and J.S. guided literature review and analysis.

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