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REVIEW
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Recent Trends of Microbiota-Based Microbial Metabolites Metabolism in Liver Disease

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The gut microbiome and microbial metabolomic influences on liver diseases and their diagnosis, prognosis, and treatment are still controversial. Research studies have provocatively claimed that the gut microbiome, metabolomics understanding, and microbial metabolite screening are key approaches to understanding liver cancer and liver diseases. An advance of logical innovations in metabolomics profiling, the metabolome inclusion, challenges, and the reproducibility of the investigations at every stage are devoted to this domain to link the common molecules across multiple liver diseases, such as fatty liver, hepatitis, and cirrhosis. These molecules are not immediately recognizable because of the huge underlying and synthetic variety present inside the liver cellular metabolome. This review focuses on microenvironmental metabolic stimuli in the gut-liver axis. Microbial small-molecule profiling (i.e., semiquantitative monitoring, metabolic discrimination, target profiling, and untargeted profiling) in biological fluids has been incompletely addressed. Here, we have reviewed the differential expression of the metabolome of short-chain fatty acids (SCFAs), tryptophan, one-carbon metabolism and bile acid, and the gut microbiota effects are summarized and discussed. We further present proof-of-evidence for gut microbiota-based metabolomics that manipulates the host's gut or liver microbes, mechanosensitive metabolite reactions and potential metabolic pathways. We conclude with a forward-looking perspective on future attention to the "dark matter" of the gut microbiota and microbial metabolomics.

Keywords: microbial metabolomics, short-chain fatty acids, tryptophan metabolism, metabolic discrimination, liver therapies, metabolites alteration, liver diseases

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INTRODUCTION

The gut microbiome is a microbial ecosystem that has diverse effects on physiological metabolism, particularly microbial metabolic activity. The human gut microbiome is always changing. Many gastrointestinal metabolites are derived from dietary and environmental sources. Since a decade, the number of scientific publications on the gut microbiota has steadily increased. Gut microbiota-based metabolomics or metabolomics profiling examination has been proven to have the ability to screen and validate the metabolites' role in host and drug metabolism (1, 2). Clinical metabolomics profiling and chemical profiling from numerous host cells are used to evaluate a range of biological contexts at the level of metabolites or small molecules (low molecular weight, < 1500 Da) (3–7).

Clinical metabolomics has been advanced and placed as a division of systems biology. Gut microbiome-associated metabolites are directly connected with the liver via the portal vein. The gut

microbiota directly yields the metabolome (full set of metabolites) and organic compounds (i.e., ethanol, acetaldehyde, ammonia, etc.). Metabolic compounds and bacterial products (pathogen-associated microbial metabolites) are frequently metabolized in liver cells (2, 8, 9).

The gut-liver pivot alludes to the multiple interactions between the intestinal microbiome and the liver, which can produce microbial metabolites. Microbial metabolic profiling acts as a therapeutic agent for specific liver diseases. These microbial profiling techniques play a significant role in heterogeneous liver diseases (10–12). At the point of planning an investigation and looking at proof, understanding the utility and impediments of both designated and untargeted metabolomics approaches are fundamental. Microbial metabolite evolution (additionally referred to as "clinical fluxomics") can quantify and follow analytes through metabolic pathways (13, 14).

The metabolomics profiling in gut-microbiome and liver diseases have been rapidly growing since past decade. These data explain the importance of metabolomics research. The metabolome is inherently huge and complex. The non-targeted metabolome is more connected with the 16S rRNA microbiome composition than targeted metabolomics. This non-targeted metabolomics has identified novel metabolites in colorectal cancer (CRC) patients. High-throughput microbial community sequences have been studied (15, 16). Metabolites represent a functional change associated with genomic variation and differences in complex microbial communities. The microbial metabolites of SCFAs, such as butyrate, can influence gene expression, cell proliferation, and ultimately adenoma formation (17).

More interestingly, the microbial metabolic pathway-based human gut microbiome of monozygotic twins has been explained (18). Microbes such as *Escherichia coli* and *Saccharomyces cerevisiae* have 3,700 and 16,000 metabolites, respectively (19, 20).

Fundamental studies of various gut-organ axes are necessary in this domain. The metabotype (or metabolome) is basically different than the genotype. This metabotype designates what is happening in the cellular microenvironment. The genomics, transcriptomics, proteomics, metabolomics, and phenotype are now used in various areas in life science (21, 22). Untargeted and targeted metabolomics will transform what we source as medicine for every disease. Understanding of the microbiome and metabolome can be projected over the two decades.

GUT MICROBIOTA AND SHORT CHAIN FATTY ACIDS

Gut microbiota-derived SCFAs (i.e., acetate, propionate, and butyrate) were found in the human large intestine and are involved in microbial fermentation (23–25). **Table 1** shows that gut bacterial genera are involved in the fermentation process of SCFAs, amino acids, organic acids, polar metabolites, and dietary polyphenols. SCFAs play an important role in nutrients and energy from the intestinal epithelium. SCFAs are used for the maintenance of intestinal homeostasis. Various studies have confirmed that SCFAs participate in the regulation of NAFLD by activating G-protein-coupled receptor (GPR) 41 or 43, which are expressed in various areas, such as adipose, liver, tissues, peripheral blood, and intestinal cells (47, 48). As per previous publications, intestinal gluconeogenesis (IGN) functions as a regulator of NAFLD via upregulation of hepatic insulin sensitivity and downregulation of hepatic glucose production (HGP) through the gut-brain-liver neural circuit (49, 50).

As shown in **Table 1**, the SCFAs acetate, propionate, hexanoate, pyruvate, lactate, succinate, and butyrate are significantly targeted IGNs, where glucose was *de novo* synthesized from the gut epithelium. Bacteria that belong to *Clostridium, Eubacterium, Faecalibacterium, Roseburia,* and *Butyrivibriocrossotus* has been producing butyrate through the reduction of two molecules of acetyl-CoA with synthesis of one molecule of ATP. These are most prominent butyrogenic bacteria groups. Studies reported the depletion of those bacteria in atherosclerosis. Butyrate is normally involved with preservation of the intestinal barrier function, tight junction proteins regulation and mucus layer maintenance. Here, glucose signaling to the brain via a GPR42-mediated neural circuit mechanism was widely initiated; therefore, glucose tolerance and insulin sensitivity were upregulated (51, 52). SCFAs are a product of bacterial fermentation of dietary fiber. According to protein sources, SCFAs can be formed by the gut microbiome (53). **Figure 1** shows that the gut-liver axis is involved in SCFA alterations and their functional metabolism.

Additionally, GPR is initiated, and SCFAs mostly pass to the liver via the portal vein, where they can improve hepatic glycolipid homeostasis. This metabolic process initiation occurred via AMPK in a peroxisome proliferator-activated receptor (PPAR) γ-dependent manner (54). SCFAs travel across the blood–brain barrier (BBB) into the central nervous system (CNS) and can disturb neural development (neurogenesis, BBB permeability, microglia). The physiological process of gluconeogenesis, AMPK activity, and insulin sensitivity in the liver are significantly affected (52, 55). Finally, SCFAs are a significant signaling metabolome and are used for communication between host tissues and microbiota through the gut-brain-liver axis (56, 57).

GUT MICROBIOTA AND TRYPTOPHAN CATABOLITES

The amino acid tryptophan exists in common foods (i.e., bananas, chocolate, cheese, fish, milk, oats, wine, etc.). Tryptophan is a chemically complex amino acid that can undergo an extensive variety of transformations within its structure (58, 59). Tryptophan acts as an ideal molecule in bacterial catabolic activity. To support this concept, various signaling pathways in human cells result from tryptophan, including tryptamine and serotonin. Dietary tryptophan is involved in numerous intermediates within hosts. The kynurenine and serotonin pathways are directly transformed from tryptophan. Protein synthesis occurs through the conversion of gut microbes into indole derivative metabolites such as indole acetic acid (IAA), indole-3-propionic acid (IPA), and indole-3-aldehyde (IA) (58, 60).

TABLE 1 | Host and microbial metabolic effects of SCFAs and other metabolite properties reported in recent literatures.

Microbial source	Metabolites	Molecular Mass (Da)	Chemical formula	Physiological role	Ref
EHEC O157:H7 *Enterobacter sp.* *Bifidobacterium sp.*	Acetate (Acetic acid)	60.052	$C_2H_4O_2$	Recovers gut barrier function	(26, 27)
C. jejuni *S. aureus*	Butyrate (Butyric acid)	88.11	$C_4H_8O_2$	Recovers gut barrier function Decreases internalization; Rises the antimicrobial peptides	(25, 28) (29)
Clostridium, Eubacterium, Faecalibacterium, Roseburia, and Butyrivibriocrossotus				Pro-inflammatory studies -Anti-inflammatory expressions	(30)
Coprococcus spp.Roseburia spp.				Butyrate and acetate producers closely related to Ruminococcus.	(31)
Anaerostipes caccae & *Anaerostipes hadrus*				Butyrate producers, lactate and acetate utilizers.	(32, 33)
S. aureus *C. rodentium* *S. Typhimurium*	Propionate (Propionic acid)	74.08	$C_3H_6O_2$	Decreases internalization; Increases antimicrobial peptides Enhances colonization	(34) (35)
				Intracellular pH stress	(36)
S. aureus	Hexanoate (Hexanoic acid or Caproic acid)	116.1583	$C_6H_{12}O_2$	Decreases internalization; Increases antimicrobial peptides	(34)
S. Typhimurium	Butyrate	88.11	$C_4H_8O_2$	Targets Salmonella pathogenicity island 1	(37, 38)
	(Butyric acid)			Acylation of transcriptional regulator attenuates virulence	(39)
				Targets Salmonella pathogenicity island 1	(38, 39)
				Inhibits oxygen availability	(40, 41)
				Inhibits translocation by inducing antimicrobial macrophage function	(42)
S. Typhimurium *Lactobacillus delbruekii* *Lactobacillus Jensenii*	Lactate (D-Lactic acid)	90.08	$C_3H_6O_3$	Increases immune surveillance of mononuclear cells	(43)
S. Typhimurium	Pyruvate	88.06	$C_3H_3O_3$	Increases immune surveillance of mononuclear cells	(43)
C. jejuni *Lactobacillus delbruekii* *Lactobacillus Jensenii*	Lactate (D-Lactic acid)	90.08	$C_3H_6O_3$	Reduces virulence gene expression	(44)
C. difficile	Succinate	118.09	$C_4H_6O_4$	Exacerbates infection	(45)
EHEC O157:H7				Enhances virulence gene expression	(46)

C. jejuni, Campylobacter jejuni; S. aureus, Staphylococcus aureus; C. rodentium, Citrobacter rodentium; S. Typhimurium, Salmonella typhimurium; C. difficile, Clostridioides difficile; EHEC O157:H7, Escherichia coli O157:H7; Ref, References.

The kynurenine pathway contains many metabolic intermediates, collectively termed "kynurenines" and the final product, nicotinamide adenine dinucleotide (NAD+) (61, 62). The metabolic reaction of tryptophan to kynurenine is chemically converted to either indoleamine 2,3-dioxygenase 1 (IDO1, involved in immune and gut epithelial cells) or tryptophan 2,3-dioxygenase (TDO, hepatocytes) (62). The gut microbiota is a known driver of IDO1 expression (63, 64) and IDO1 regulation has been shown to regulate microbial community composition (65). These enzymes are highly increased in many cancer cells. Kynurenine derivatives are produced with aryl hydrocarbion receptor (AhR) ligands that help to promote cellular migration and immune tolerance, thus driving cancer progression (62). The host synthesizes kynurenines with the help of gut microbiota that have a genomic capacity to yield many intermediate small molecules in metabolic pathways, such as *Lactobacillus spp.,* and the pathogens *Pseudomonas aeruginosa* and *Pseudomonas fluorescens,* which produce these intermediates (66). We have listed in **Table 2**, **Figure 2** the tryptophan metabolite-based microbiome and biological effects in human gut environments. Finally, kynurenine pathway intermediates significantly inhibited insulin synthesis, excretion, and signaling in rats. Increased levels of kynurenic acid and xanthurenic acid are found in type 2 diabetes mellitus (T2DM) patients (61).

Tryptamine and tryptophan catabolic chemical reactions are processed by gut microbial bacteria such as *C. sporogenes* and *Ruminococcus gnavus* (78, 79). Tryptamine acts as a

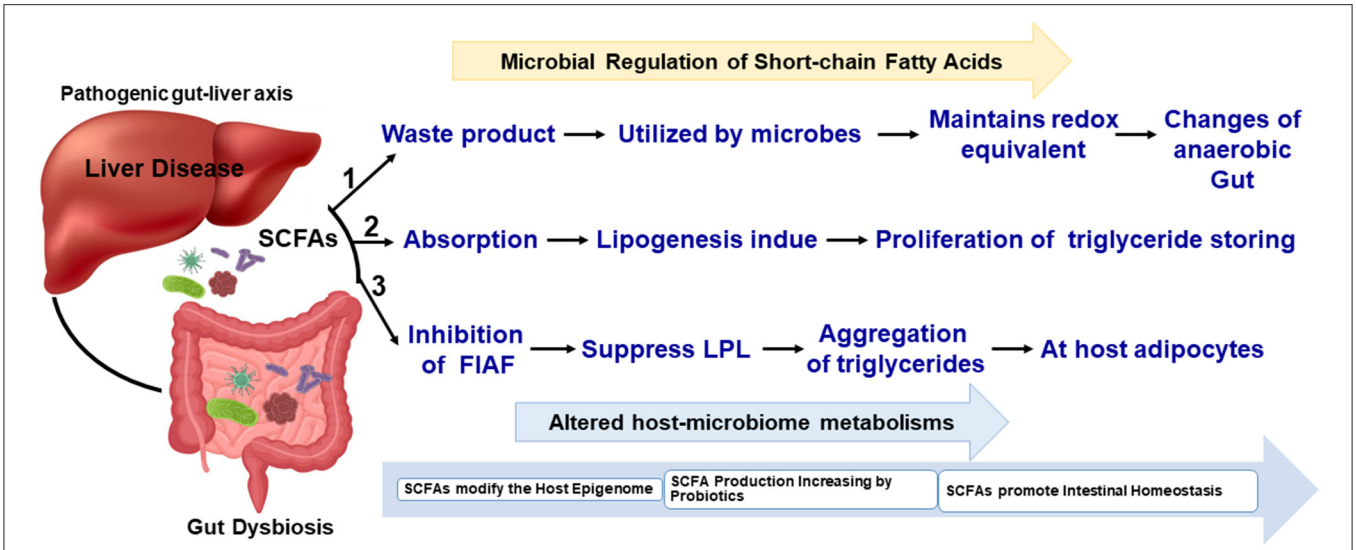

FIGURE 1 | Simplified schematic view of SCFAs in the gut microbiome and liver metabolisms. The biochemical process and metabolites metabolisms have been connected with gut-liver microbiome interactions.

TABLE 2 | Examples of metabolic effects in host-microbial chemical transformation tryptophane family metabolites on pathogens.

Microbial source	Metabolites	Molecular Mass (Da)	Chemical formula	Physiological role	Ref
P. aeruginosa	Indole	117.15	C_8H_7N	Increases biofilms; Decreases antimicrobials and virulence factors	(67)
S. Typhimurium				Increases multidrug resistance; Decreases motility and invasion genes	(68, 69)
C. albicans				Inhibits filamentation and biofilms	(70)
S. aureus				Decreases regulatory and toxin gene expression	(71)
V. cholerae				Increases biofilms; Upregulates polysaccharide production	(72)
EHEC O157:H7				Upregulates type III secretion system effectors	(73)
EHEC O157:H7	Indole-3- Aldehyde	145.156	C_9H_7NO	Inhibits filamentation and biofilms	(74)
P. aeruginosa	(Indole-3-carboxaldehyde)			Inhibits filamentation and biofilms	(74)
C. albicans				Upregulates IL-22 production by innate lymphoid cells	(65)
EHEC O157:H7	Indole-3 acetate	175.184	$C_{10}H_9NO_2$	Inhibits biofilms, motility, and formation of lesions	(75)
EHEC O157:H7	7-hydroxyindole	133.15	C_8H_7NO	Inhibits biofilms	(76)
EHEC O157:H7	Skatole (3-methylindole)	131.172	C_9H_9N	Inhibits biofilms	(77)

P. aeruginosa, Pseudomonas aeruginosa; S. Typhimurium, Salmonella typhimurium; C. albicans, Candida albicans; S. aureus, Staphylococcus aureus; V. cholerae, Vibrio cholerae; EHEC O157:H7, Escherichia coli O157:H7; Ref, References.

β-arylamine neurotransmitter that can stimulate gut strength. In the gut microbial environment, tryptamine is known to induce the release of the neurotransmitter 5-hydroxytryptamine (5-HT) or serotonin via enterochromaffin cells, and it is involved in mucosal secretion and gut motility. 5-HT promotes gastrointestinal motility by acting on enteric nervous systems. However, the signaling molecule tryptamine affects the intestinal gut microbial composition, diversity, and metabolism in humans (80, 81). Here, ∼90% of 5-HT or serotonin in the body is produced by enterochromaffin cells, which cannot cross the blood–brain barrier. The binding of 5-HT with specific 5-HT receptors produces various biological responses. In the central nervous system, 5-HT plays a central role in sleep, mood, appetite, behavior, and the maintenance of neurons and interstitial cells of Cajal within the gut myenteric plexus (80). In mice, *Ruminococcus flavefaciens* and *Adlercreutzia equolifaciens* reduced the beneficial properties of duloxetine. 5-HT is affected by the gut microbial composition, which acts as a gut microbial inhibitor (82, 83).

GUT MICROBIOTA AND ONE CARBON METABOLISMS

The membrane metabolite of choline acts as a water-soluble compound. This is an essential nutrient for human and

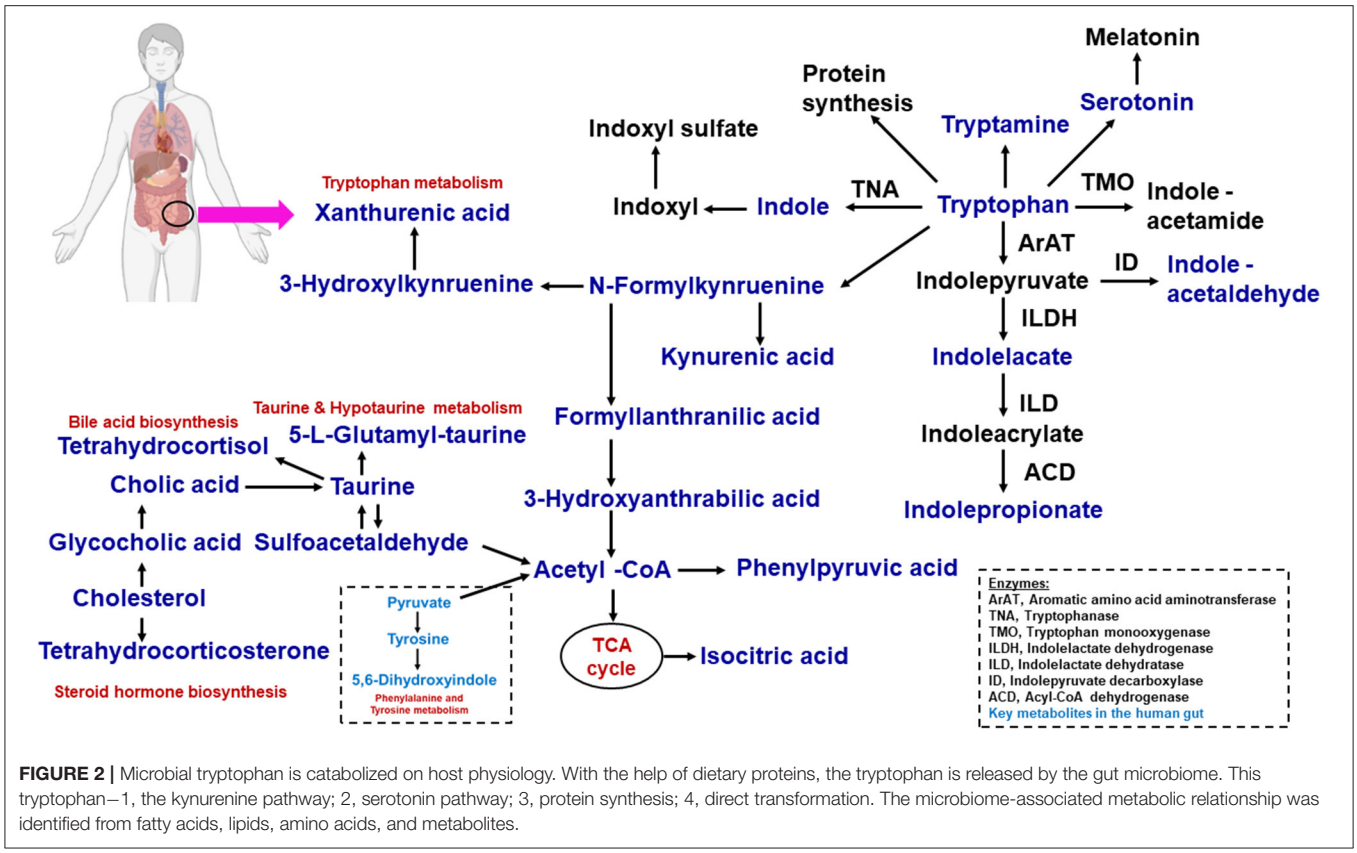

FIGURE 2 | Microbial tryptophan is catabolized on host physiology. With the help of dietary proteins, the tryptophan is released by the gut microbiome. This tryptophan−1, the kynurenine pathway; 2, serotonin pathway; 3, protein synthesis; 4, direct transformation. The microbiome-associated metabolic relationship was identified from fatty acids, lipids, amino acids, and metabolites.

animal cellular metabolism. Choline can contribute to cellular outer membrane functions, neurotransmission roles, and methyl donors for various biosynthetic metabolic reactions (84). Endogenously, choline is formed. Choline is widely used by anaerobic gut microorganisms to generate trimethylamine (TMA) and acetaldehyde (85). The gut microbiota plays an ameliorative role in liver diseases. Liver diseases such as fatty liver, hepatitis, and cirrhosis are related to bile acid secretion disorder and metabolic syndrome (56, 86, 87). **Table 3** lists the more important metabolites in the human gut microbiome.

TMA is present across the host gut and can be processed to trimethylamine-N-oxide (TMAO) in the liver cellular microenvironment through flavin-containing monooxygenases 1 and 3 (FMO1 and FMO3). In the past few decades, gut-microbial-host cometabolites have been identified via metabolomics analysis in serum to predict the risk of cardiovascular diseases (99–101). TMAO enhances atherosclerosis by inducing multiple macrophage receptors, acting as a hallmark of thrombosis, and enhancing platelet reactivity (99, 100). Here, the gut microbiota facilitates the regulation of hepatic inflammation by the TMA, TMAO and FMO pathways.

Isotopic labeling studies have revealed that alterations of nutritional L-carnitine, a rich amino acid derived from red meat, increases TMA through microbiota-dependent conversion and leads to > 20-fold growth in atherogenic TMAO in omnivores vs. vegans and lactovegetarians (102). Recently, trimethyllysine (TML) was identified as a precursor to TMAO and could be used as a predictor of major adverse cardiac events. TML has improved risk stratification in acute coronary syndrome. TML is used to predict the risk of major adverse cardiac incidents and acts as a clinical biomarker for myocardial infarction (103, 104).

The B vitamins pyridoxine (vitamin B6), folic acid (vitamin B9) and cobalamin (vitamin B12) play essential roles in one-carbon metabolism. These vitamins act as cofactors in folate metabolism and one-carbon metabolic pathways. Moreover, B vitamins are not adequate in host synthesis to optimize metabolic conditions. B vitamins are also obtained from nutritional sources and *de nova* produced via the gut microbiota (105, 106). With the help of folate metabolism, the production of B vitamins by the colonic microbiota actually exceeds the dietary intake (107). Eight B vitamins (B1, B2, B3, B5, B6, B7, B9, and B12) have been discovered, and 40–65% of human gut bacteria have the genomic possibility to produce these vitamins. As per a prior database, 88% of vitamins in the gut microbiome were validated (106).

Folate metabolism (methotrexate and sulfasalazine) and genetic disorders very commonly occur due to B vitamin shortages and poor nutritional consumption. Pellagra (vitamin B3), anemias (vitamins B9 and B12), cerebellar ataxia (vitamin B12), and cognitive impairment (vitamins B9 and B12) have been linked with dietary deficiency that can be treated with vitamin supplementation. Here, there are age-dependent alterations in gut microbial metabolism of B vitamins (79, 108). An infant gut microbiome revealed that enriched genes could confuse the *de novo* biosynthesis of folate. The adult microbiome is enriched for

TABLE 3 | Recent summary of host interaction and gut microbiome effects of significant amino acid metabolites on pathogens.

Microbial source	Metabolites	Molecular Mass (Da)	Chemical formula	Physiological role	Ref
C. difficile	Deoxycholate (Cholanoic acid)	392.572	$C_{24}H_{40}O_4$	Prevents growth	(88–90)
C. difficile	Lithocholate (Lithocholic acid)	376.5726	$C_{24}H_{40}O_3$	Prevents growth	(88–90)
Influenza	Desaminotyrosine (3-(4-Hydroxyphenyl)propionic acid)	166.17	$C_9H_{10}O_3$	Upregulates type I interferons	(91)
S. Typhimurium	Vitamin B6 (Pyridoxine)	169.18	$C_8H_{11}NO_3$	Encourages bacterial clearance	(92)
S. aureus	Vitamin B2 (Riboflavin)	376.36	$C_{17}H_{20}N_4O_6$	Shields against septic shock	(93)
L. monocytogenes				Upregulates antimicrobial agent	(94)
S. aureus	D-proline	115.13	$C_5H_9NO_2$	Inhibits biofilms	(95)
S. aureus	D-tyrosine	181.19	$C_9H_{11}NO_3$	Inhibits biofilms	(95)
S. aureus	D-phenylalanine	165.19	$C_9H_{11}NO_2$	Inhibits biofilms	(95)
EHEC O157:H7	D-serine	105.09	$C_3H_7NO_3$	Inhibits type III secretion system	(96)
V. cholerae	Trimethylamine	59.11	C_3H_9N	Overwhelms infection	(97)
V. cholerae	Cholic acid	408.57	$C_{24}H_{40}O_5$	Overwhelms infection	(97)
V. cholerae	SCFAs			Overwhelms infection	(97)
V. cholerae	Several free D-amino acids			Increases antimicrobial H_2O_2	(98)

C. difficile, Clostridioides difficile; S. Typhimurium, Salmonella typhimurium; S. aureus, Staphylococcus aureus; L. monocytogenes, Listeria monocytogenes; EHEC O157:H7, Escherichia coli O157:H7; V. cholerae, Vibrio cholerae; Ref, References.

those involved in the metabolism of folate and it is condensed from tetrahydrofolate (109, 110). Therefore, the gut microbiota is a fundamentally significant source for vitamin manufacture, which may be important for vitamin deficiencies. Finally, as shown in **Table 4**, metabolites and pathways associated with the gut microbiome in various liver diseases are summarized.

GUT MICROBIOME AND LIVER AMMONIA METABOLISM

Human liver is continually involved in ammonia detoxification. Ammonia fixation in the liver by glutamine and urea synthesis play main role in hepatic ammonia detoxification, and pH regulation under pathogenic condition. The liver and gut microbiota play a central role in nitrogen metabolism (127). Bacteria have involved in protein utilization and amino acid degradation. The understanding of bacteria process that carry out proteolysis and their following metabolic reactions is extremely relevant to human gut health. In large intestine, due to the protein catabolism, the toxic products of ammonia, indoles, and phenols were produced (128, 129). Amino acid fermentation has been primarily produced that the acetic, propionic, butyric, isobutyric, and isovaleric acid. From amino acid catabolism, the ammonia is constantly produced as a metabolic waste. The free ammonia is very toxic which rapidly converted to non-toxic urea via urea cycle in the liver and frequently excluded in urine (130). The liver can generate many enzymes which could change ammonia into urea (128). While ammonia level in blood becomes high, it may convert to toxic to brain. This condition is called as hyperammonemia (131). Hyper-ammonia producing ruminal bacteria (HAB) such as *Peptostreptococcus anaerobius, Clostridium sticklandii,* and *Clostridium aminophilum* has been involved to generate ammonia at high level (132). In this condition, the oxidation of ammonium to nitrite (NO_2^-) with help of *Betaproteobacteria* and *Gammaproetobacteria* can happen by ammonia oxidizing bacteria (AOB). Liver failure and hepatocellular metabolic dysfunction can happen due to disturbed body nitrogen homeostasis. Due to the ammonia imbalance, hepatic encephalopathy is formed, which occurs when liver is high risk condition (133). Finally, chronic liver insufficiency is frequently associated with metabolic acidosis.

INTESTINAL MICROBIOTA AND BILE ACID METABOLISM

Bile acids (BAs) are important for cholesterol synthesis metabolism and fat breakdown and are synthesized from the liver and deposited in the gallbladder (134). In the small intestine, these BAs are secreted during digestion. BAs are reabsorbed in the terminal ileum by over 95% and returned to the liver by the portal vein. The absorption of directory fats, fat-soluble vitamins, and cholesterol is promoted by BAs (135). In addition, BAs act as signaling molecules that regulate glucose and lipid metabolism via farnesoid X receptor (FXR) activation and binding of G-protein coupled BA receptor 1 (136–138).

BAs are amphipathic molecules that influence intestinal mucosal integrity. The liver synthesizes BAs that are then involved in synthesizing antibacterial peptides, cholic acid, and chenodeoxycholic acid (139). Antimicrobial peptides (angiogenin 1) are formed when BAs bind to FXR. Activated

TABLE 4 | Some examples of the most recently reported summary of gut microbiota-host interactions in various liver diseases-based metabolomics composition, and synthetic method.

Metabolites	Metabolic pathways	Genera or species	Ref
Phenylacetylglutamine (PAGln) and phenylacetylglycine (PAGly)	Synthesized during host hepatic phase II metabolism via conjugation of either glutamine or glycine to phenylacetic acid, an intermediate in microbial fermentation of phenylalanine	Conjugation of phenylacetic acid to glutamine or glycine occurs in the host liver; see *p-cresol* (above) for information about its precursor, phenylacetic acid	(3, 4)
Acetate (Acetic acid)	Pyruvate decarboxylation to acetyl-CoA	*Akkermansia muciniphila, Bacteroides spp., Bifidobacterium spp., Prevotella spp., Ruminococcus spp.*	(111–114)
	Wood–Ljungdahl pathway	*Blautia hydrogenotropphica*, *Clostridium* spp., *Streptococcus spp.*	(111–114)
Propionate (Propanoic acid)	Acrylate pathway	*Coprococcus catus, Eubacterium hallii, Megasphaera elsdenii, Veillonella spp.*	(111–114)
	Succinate pathway	*Bacteroides spp., Dialister spp., Phascolarctobacterium succinatutens, Veillonella spp.*	(111–114)
	Propanediol pathway	*Roseburia inulinivorans, Ruminococcus obeum, Salmonella enterica.*	(111–114)
Butyrate (Butanoic acid)	Classical pathway via butyrate kinase	*Coprococcus comes*, *Coprococcus eutactus*	(111–114)
	Alternate pathway using exogenous acetate	*Anaerostipes spp., C. catus, E. hallii, Eubacterium rectale, Faecalibacteerium prausnitzii, Roseburia spp.*	(111–114)
SCFAs and branched-chain fatty acids	Amino acid fermentation through various dissimilatory proteolytic reactions	*Acidaminococcus spp., Acidaminobacter spp., Campylobacter spp., Clostridia spp., Eubacterium spp., Fusobacterium spp., Peptostreptococcus spp.*	(112–115)
'Kynurenines' (Kynurenine and its byproducts)	Many bacterial enzymes homologous to mammalian enzymes of the kynurenine pathway	*Lactobacillus spp., Pseudomonas aeruginosa, Putative: Pseudomonas spp., Xanthomonas spp., Burkholderia spp., Stenotrophomonas spp., Shewanella spp., Bacillus spp., members ofRhodobacteraceae, Micrococcaceae and Halomonadaceae families*	(66, 116)
Indole (Tryptophan metabolites)	Hydrolytic β-elimination of tryptophan to indole (tryptophanase)	*Achromobacter liquefaciens, Bacteroides ovatus, Bacteroides, thetaiotamicron, Escherichia coli, Paracolobactrum coliforme, Proteus vulgaris*	(116, 117).
Indole derivatives	Multiple	*Bacteroides spp., Clostridium spp. (Clostridium sporogenes, Clostridium cadaveris, Clostridium bartlettii), E. coli, Lactobacillus spp., E. halli, Parabacteroides distasonis, Peptostreptococcus spp. (Peptostreptococcus anaerobius)*	(4, 78, 116–119)
Tryptamine	Decarboxylation of tryptophan	*C. sporogenes, Ruminococcus gnavus*	(78)
Serotonin	Induction of host synthesis	*Indigenous spore-forming bacteria, dominated by Clostridium spp. and Turicibacter spp.*	(120, 121)
Histamine (Amino acid)	Decarboxylation of histidine (histidine decarboxylase: HDC)	*E. coli, Morganella morganii, Lactobacillus vaginalis Putative: Fusobacterium spp.*	(122, 123)
Imidazole propionate (ImP)	Non-oxidative deamination of histidine to urocanate followed by reduction of urocanate to ImP by urocanate reductase (UrdA)	*Aerococcus urinae, Adlercreutziae equolifaciens, Anaerococcus prevotii, Brevibacillus laterosporus, Eggerthella lenta, Lactobacillus paraplantarum, Shewanella oneidensis, Streptococcus mutans*	(124)
Dopamine	Decarboxylation of levodopa (l-DOPA) via tyrosine decarboxylase (TyrDC)	*Enterococcus spp. (Enterococcus faecalis, Enterococcus faecium, 77 human isolates of Enterococcus spp.), Lactobacillus brevis, Helicobacter pylori*	(125, 126)
p-Cresol	From tyrosine or phenylalanine via two pathways: direct cleavage of the Cα-Cβ bond in tyrosine to yield p-cresol by tyrosine lyase; and a series of reactions involving transamination, deamination and decarboxylation of tyrosine or phenylalanine via formation of the cresol precursor phenylacetic acid	*Assay proven: Blautia hydrogenotrophica, Clostridioides difficile, Olsenella uli, Romboutsia lituseburensis* *Predicted: Acidaminococcus fermentans, Anaerococcus vaginalis, Anaerostipes spp., Bacteroides spp., Bifidobacterium infantis, Blautia spp., Citrobacter koseri, Clostridium spp., Eubacterium siraeum, Fusobacterium spp., Klebsiella pneumoniae, Lactobacillus spp., M.elsdenii, Roseburia spp., Ruminococcus spp., Veillonella parvula*	(118)

The microbial fermentation process depending on SCFAs, amino acids, organic acids, polar metabolites, and dietary polyphenols several liver diseases. HDC, Histidine decarboxylase; TyrDC, Tyrosine decarboxylase; Ref, References.

FXR is involved in reducing the activity of the CYP7A1 gene through the nuclear receptor FXR. These peptides may inhibit intestinal mucosa overgrowth via the intestinal epithelial cell potential to block bacterial uptake, improving the gut barrier role (139). Most intestinal BAs are reabsorbed by the intestine, with 90–95% of BAs involved in enterohepatic circulation. The remaining BAs enter the colon, where the gut microbiome converts them into secondary and tertiary BAs (140, 141). Alterations in circulating BAs act as signaling molecules that disturb glucose and lipid metabolism and predispose individuals to NAFLD. The dysbiosis and disparity of BAs has been shown to play a significant role in liver disease control (141).

BAs are key signaling microbial metabolites involved in lesser-known axes. BAs are steroid acids, the conclusive end products of the liver cholesterol digestion system. There are four types of BAs: essential BAs, bile salts (or conjugated BAs), auxiliary BAs, and tertiary BAs. Essential BAs are liver-derived compounds and comprise a hydroxylated steroid center (142, 143). Cholic scarring and chenodeoxycholic corrosion could be caused by dysfunction of BAs. Bile salts are essential BAs that are conjugated with glycine or taurine (in people, higher primates, and rats) or taurine (in most other warm-blooded creatures) within liver metabolism (144).

These amino acid adjustments permit the bile salts to remain within the gently acidic pH of the upper portion of the little digestive tract. Auxiliary BAs are shaped by means of the activity of colonic microbes on bile salts, which remove the amino conjugates and assist in dihydroxylation of the parent compounds. This leads to the generation of compounds such as deoxycholic corrosive and lithocholic corrosive compounds (145–147). The more hydrophobic and hepatotoxic auxiliary BAs (such as lithocholate) may be altered by glucuronidation, hydroxylation, or sulfation to assist in their production. Tertiary BAs are shaped by the liver when bacterially created auxiliary keto-bile acids return to the liver and are degraded. For example, chenodeoxycholic corrosive (an essential bile salt) is converted to 7-ketolithocholic corrosive (an auxiliary bile corrosive) and then back to ursodeoxycholic corrosive (a tertiary bile corrosive) (148–150). **Figure 3** summarizes the basic function of the liver and gut microbiome.

For metabolomic analysis, BA examination is a perfect reference metabolite (151). Naturally, there are more than 100 known BAs (i.e., essential BAs, auxiliary BAs, and tertiary BAs). Sensitive and multifold BA examinations imply quickly surveying a large number of BAs. This often results in a distinctly better understanding of the BA connections to one another and their individual physiological parts (152, 153). Whereas, metabolomic research on bile acids is providing new knowledge about human physiology and human pathologies, a few cautionary considerations must be kept in mind when studying BAs in non-human models. For example, rodents can hydroxylate bile acids at the 6-beta position (muricholates), whereas pigs can hydroxylate BAs at the 6-alpha position. As a result, discoveries with respect to the BA digestion system in animal models may not match those in people. The biological signaling of metabolites in the liver cellular microenvironment has a pleiotropic effect. These metabolites and the small-molecule metabolome are widely synthesized by the gut microbiota, as described in **Tables 1**–**4**.

In this review, we provided a fundamental overview of the gut microbiota and clinical metabolomics, including their history and recent developments, and future biomarker candidate metabolites. Currently, gut microbiota-associated metabolomics is in an early phase and needs to be more extensively researched. Identifying therapeutic biomarkers for various gut microbiome- and metabolome-based liver diseases are mandatory.

CONCLUSIONS AND FUTURE PERSPECTIVES

In this review, we highlighted the SCFA, tryptophan, one-carbon metabolism, and bile acid metabolism in the gut microbiome from recent developments with the most promising microbial metabolites. The metabolites in the liver disease microenvironment provide deep knowledge of the metabolic pathways and microphysiological metabolism. The innovative approach of untargeted metabolomics is a quantitative method that is a unique, powerful new technology that can be combined with computational technologies. Improvements in the gut-liver metabolomics community, along with the continued effects of rapidly growing liver biology, have proven reasonably effective in understanding the gut-liver metabolic pathways and chemical reactions. Based on recent publications, the microbial metabolites of TMA, TMAO, tryptophan, SCFAs, vitamins, and the indole family have been found to come from the gut microbiota.

On the technology innovation front, we surveyed how gut microbiota and microbial metabolomics affect liver function and how to design and develop a clinical biomarker metabolite to protect the liver at the cellular microenvironmental level. The liver mechanisms and metabolic degradation analysis of the potential gut microbiome-associated liver metabolism are discussed. The key pitfall is still perhaps in the identification of microbial structural explanations of gut-liver metabolomics due to the lack of universal metabolite-specific libraries.

For the future perspective of gut-liver metabolomics in clinical biomarker development, we have realized a few thoughts:

1. The thickness and weight of liver tissue biopsy should be considered in the experimental design. To achieve a highly effective microbial metabolite, low-cost and facile modification methods should be used as much as possible. It is necessary to apply gut-liver metabolomics chemistry to expand their biological properties.
2. The solid liver tissue metabolome has a rich phenotypic response. This kind of metabolite production should be investigated further, including its processing and interfaces within the gut microbial environments.
3. Gut microbial metabolomics and metabolite chemical reactions at the microlevel need more attention in all gut-liver diseases. Defining how to address biochemical boundary communication in the liver tissue metabolome will help to better understand and optimize metabolomics functions at the gut-liver microcellular level.

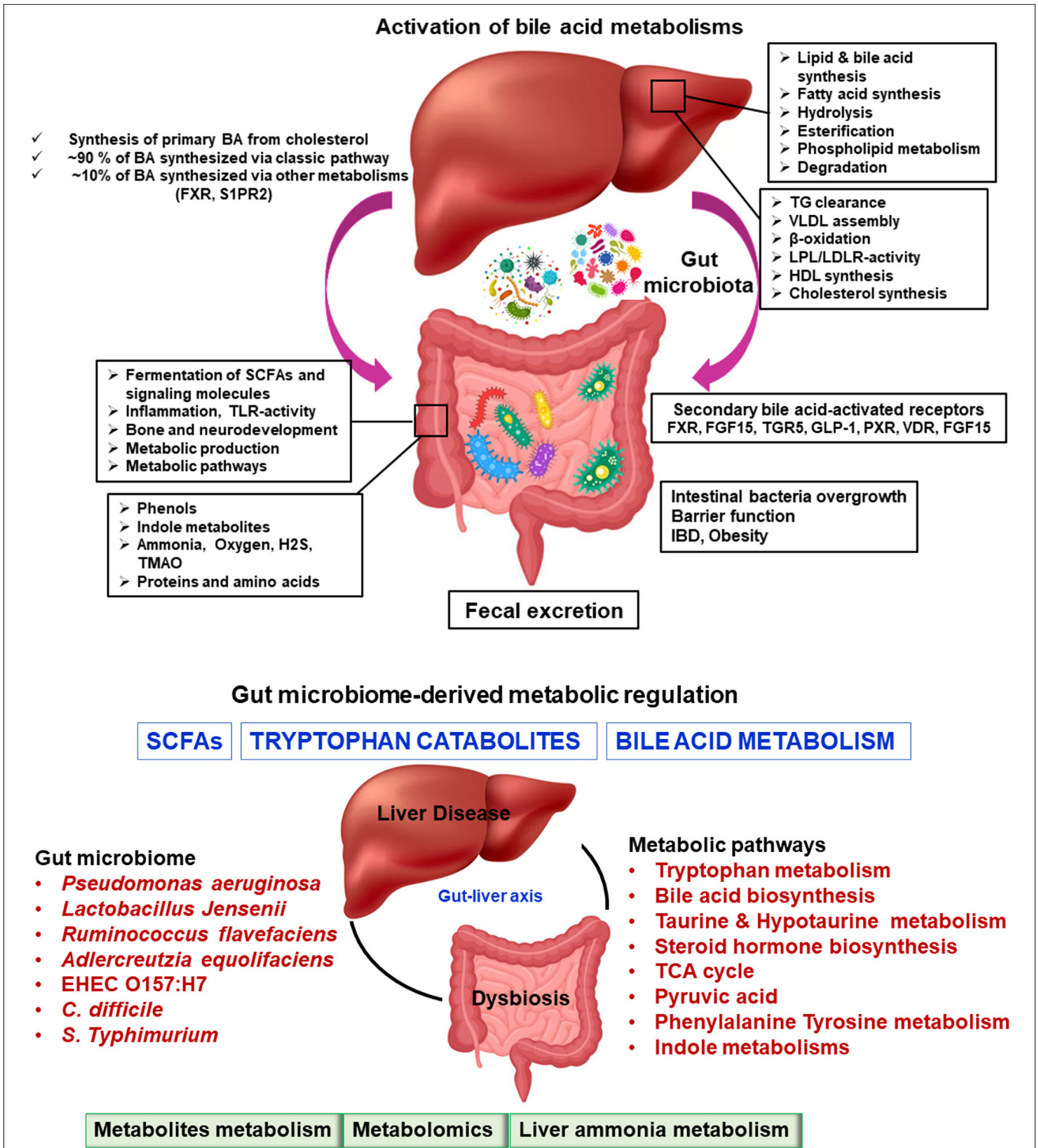

FIGURE 3 | Microbiome-modulated metabolites and disease. Metabolite-based effects on liver disease process may be localized to the gastrointestinal tract which can influence to liver, heart, brain, etc. The summary of altered metabolic environments in gut-liver metabolic process.

4. The changes in molecular numbers should not be selectively mistreated for organic/inorganic metabolites in the gut microenvironment. High levels of change are a challenge when carrying out gut microbial metabolite-metabolite chemical reactions. Biological chemists are anticipated to develop novel microbial biomarkers/metabolites,

tools, and materials for liver diseases with effective clinical applications.

5. Metagenomics, metabolomics, microbial metabolite profiling, and microbial small molecule screening are urgently needed to evaluate gut-liver disease properties. Moreover, more standard molecular, clinical and analytical measurement methods for gut-liver diseases are needed, which should be benchmarked.

AUTHOR CONTRIBUTIONS

RG wrote the manuscript draft, revised, and approved. J-JJ, DK, and KS participated in the revising the manuscript and approved. All authors contributed to the article and approved the submitted version.

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