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*Review Article*

# The Role of the Gut Microbiome and the Hepatic Axis in the Pathogenesis of Metabolic Syndrome and Therapeutics

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The increased global prevalence of viral and noninfectious liver illnesses has coincided with a surge in scientific interest in gut microbiota (GM), a multispecies community of bacteria, fungi, archaea, and protozoans. Dietary nutrients that make up the host's microbiome are responsible for maintaining intestinal homeostasis, whereas a disconnect between gut flora and nutrition might have serious consequences for digestive health. The risk of liver dysfunction was continuously elevated by changes in the commensal bacteria of the gut microbiome, which were carried to the liver via the portal vein. Insights into the role of gut microbiota in alcoholic liver disease, nonalcoholic liver disease, primary sclerosing cholangitis, and other liver disorders, as well as their link to liver cancer, continue to emerge. Systemic host defence against infections by the gut microbiota depends on the interplay between the microbiome, liver immunology, and liver disorders. Translocation of microbiota to the liver following injury and/or inflammation may mediate dysbiosis and the formation of gut microbial metabolite. This review discusses the role of the gut microbiota in connection to dysbiosis and how this knowledge might help us better understand the pathophysiology of various liver illnesses.

## 1. Introduction

Out of all the diverse commensal relationships that microbes have formed on and in the human body, their functioning in the gut has intrigued researchers since Tas et al. first discovered them in high throughput DNA sequencing, and comparative metagenomics have enhanced the research surrounding the microbiome universe [1]. The human gut is an intricate structure, and trillions of microbes such as bacteria, fungi, viruses, eukaryotes, and archaea that are living there are referred to as gut microbiome (GM) [2]. Lower gastrointestinal tract or the colon is inhabited primarily by the following five anaerobic bacteria: *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia*; the first 2 are responsible for more than 90% of the gut microbiota [3, 4]. Besides the bacteria, various fungal and viral populations have also been identified through genotyping which contribute benefits and pathogenesis to the symbiotic environment. Figure 1(a) represents the diverse microbiota inhabiting the human gut.

Firstly, at the top, composing >99% of the biota load is bacteria. Mainly five phyla dominate as follows: *Bacteroidota*, *Bacillota* (*Firmicutes*), *Actinomycetota*, *Pseudomonadota*, and

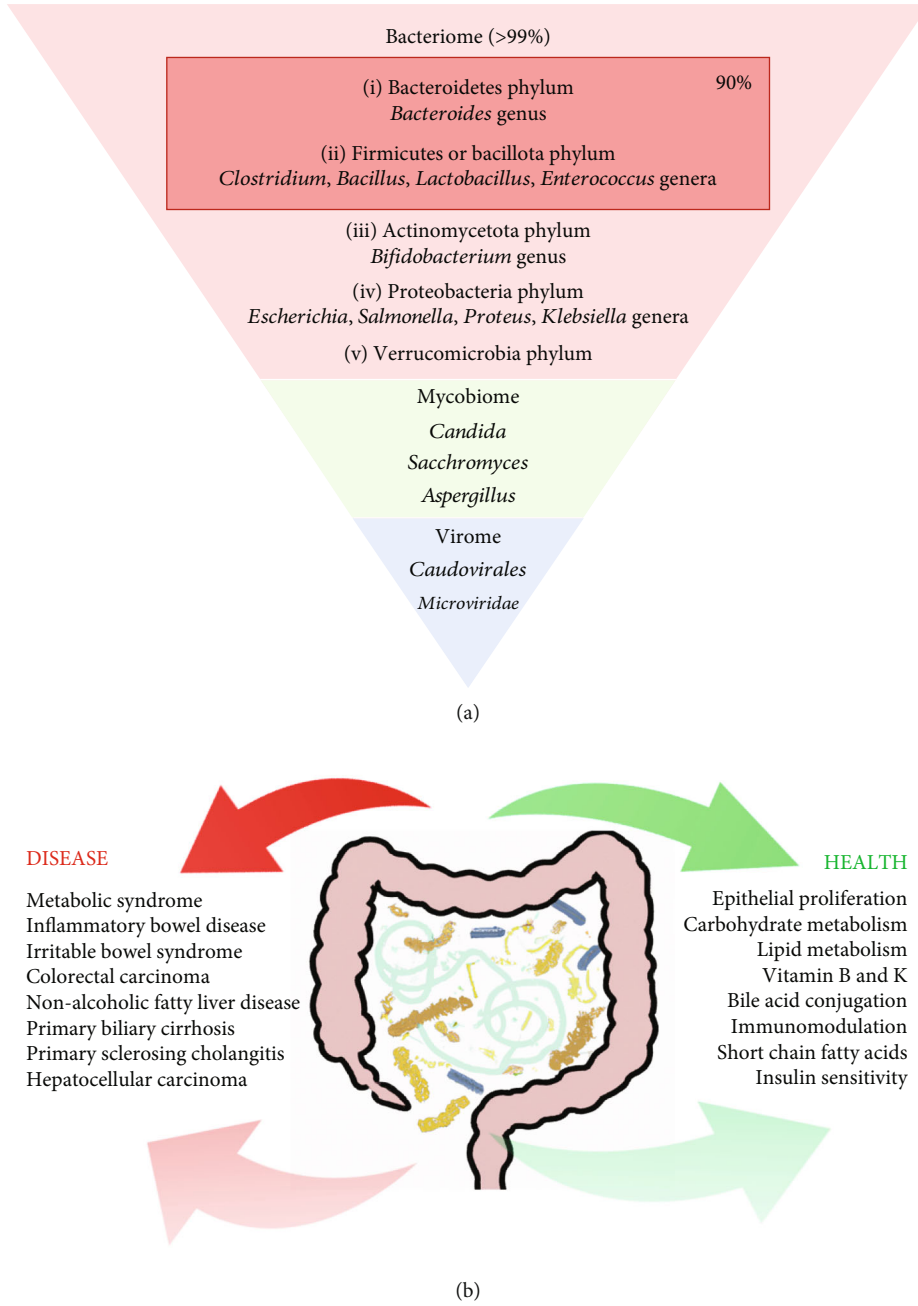


Figure 1: (a) The composition of gut microbiome. (b) Role of gut microbiome in health and disease.

*Verrucomicrobiota* [5]. Secondly, mycobiome is dominated by yeasts mainly *Candida*, *Sacchromyces*, and *Aspergillus* [6]. Virome constitutes about <0.1% of biome and is contributed mainly by bacteriophages like *Caudovirales* and *Microviridae* [7].

Important roles of GM include the roles it plays in the absorption of various nutrients and minerals, synthesis of enzymes, vitamins and amino acids, metabolism of bile acids (BA), and production of fermentation by-products such as short-chain fatty acids (SCFAs). SCFAs like acetate, propionate, and butyrate maintain the gut health by providing energy for epithelial cells, enhancing epithelial barrier integrity, and imparting immunomodulation and shield against pathogens [8]. Observing its metabolic diversity, it referred to GM as "the new virtual metabolic organ" [9]. Besides contributing to health, GM is also known to facilitate many disease pathogeneses like inflammatory bowel disease, irritable bowel syndrome, metabolic syndrome, and liver disorders like nonalcoholic fatty liver disease, alcoholic liver disease, and so on. Figure 1(b) compares the role of the microbiome in health vs disease. Interest in the gut microbiome, particularly its role in liver health and disease, has increased over the past several decades. Mouse disease models have been used extensively to decipher the cross talks of GM and liver. In this review, we dive into these cross talks and study the function of microbiota in various liver disorders.

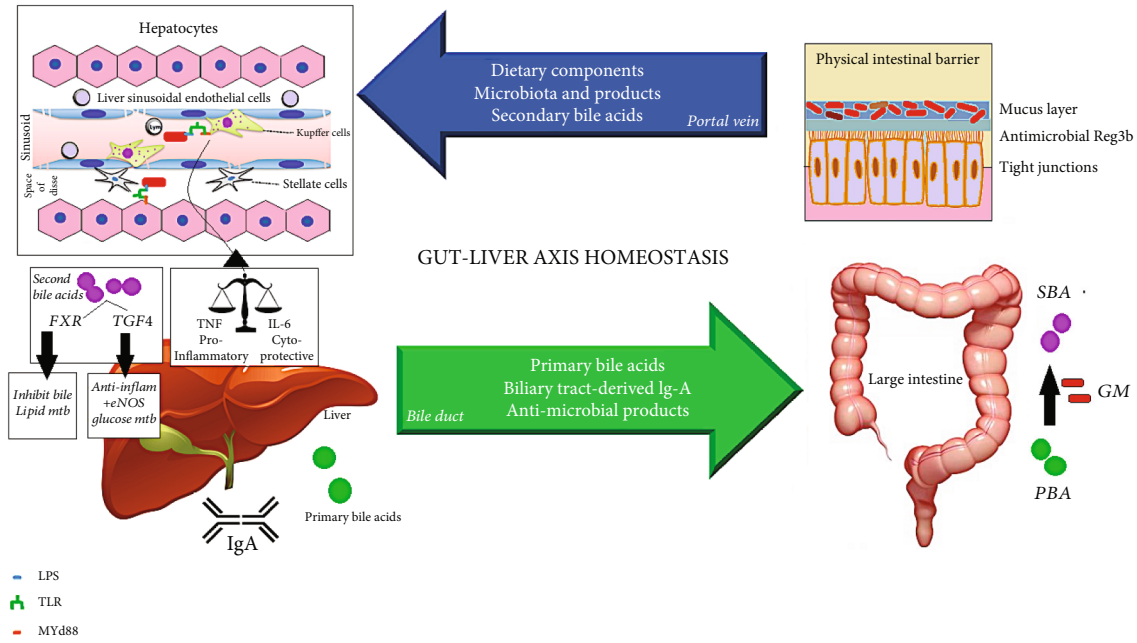


Figure 2: Gut liver axis and homeostasis.

## 2. Gut Liver Axis

With the objective to understand the role of GM in liver diseases, it is imperative to know about the gut-liver axis. Physiologically, an "axis" is a complex set of feedback interactions between two or more organs. The gut-liver axis is the bidirectional interaction due to signals generated by nutritional, genomic, and environmental aspects between the gut microflora and the liver [10]. This crosstalk is instituted by [1] portal vein that transports intestinal cargos to the liver, and [2] the bile duct system of the liver that pours bile and antibodies into the intestine. Based on the aforementioned two-way passage system between the two organs, it is no surprise that in a healthy human, it would be normal to find some footprints of the gut microbiota. Normally, minute quantities of bacterial mRNA and LPS, a component of the outermost bacterial membrane, are detectable in the liver [11, 12] and peripheral blood. Since the intestinal epithelium is the crucial point of entry of dietary and microbial paraphernalia, the existence of intestinal barrier as a physical and functional fence to regulate the materials entering the liver makes perfect sense. Furthermore, it is a curious case as to how the liver handles this microbiota that, in composition, is largely Gram negative, and also, how it guards itself and the systemic circulation from the detrimental effects of the toxins. Figure 2 represents gut-liver axis homeostasis.

Upper blue arrow depicts substances released through intestinal absorption in the portal vein—dietary absorbents, microbial products, and secondary bile acids which are produced as a result of conjugation by the intestinal flora. The section on the left depicts processes occurring at a cellular level in the liver. Microbial products (red capsules) are handled by the TLR (Toll-like receptors) on the Kupffer cells and hepatocytes, which leads to the production of proinflammatory TNF (tumor necrosis factor). In a homeostatic balance, these proinflammatory cytokines are downregulated by the Kupffer cells via the production of cytoprotective IL-6. Both the Kupffer and liver sinusoidal endothelial cells (LSEC) help in the clearance of LPS and maintain its concentration at physiological levels. The lower green arrow depicts the substances that are secreted by the liver into the intestine in the bile. These include primary bile acids secreted by hepatocytes, IgA, which is produced as a result of gut microbiota stimulation and anti-inflammatory responses through FXR (farsenoid X receptor) and TGF4 (tumor growth factor 4).

*2.1. Intestinal Barrier.* Intestinal barrier is constituted by the mucus layer, the tight junctions between absorptive epithelial cells and various antimicrobial molecules. Firstly, epithelial barrier can be disrupted by dietary factors like a high-fat diet [13] and a high saturated fat diet [14, 15] leading to endotoxemia, which might be because of endoplasmic reticulum stress induced by fatty acids in epithelial cells leading to their inability to make tight junctions or secrete mucus [16]. Elevated TNF levels, in addition to alcohol administration to mice and men, disrupt the tight junction and increased plasma LPS levels [17]. Mucosal inflammation as a result of DSS intake and IBD also leads to a disordered intestinal barrier and appearance of bacterial by-products in the liver. Secondly, for functional defence, the mucus layer is secreted by the goblet cells. Loss of Muc-1, a mucus component, in gene-targeted mice led to the development of spontaneous colitis due to a lack of mucosal barrier [18]. Lastly, the Paneth cells present in the small intestinal crypts secrete defensins, cathelicidin, lysozyme, and C-type lectins like Reg3b [19, 20]. These defence proteins attack bacteria by targeting peptidoglycan of Gram-positive bacteria and outer membrane of Gram-negative bacteria [21]. In a research, it was observed that a deficiency of Reg3b enhanced the microbiota load in the colon and liver [22].

*2.2. Vascular Barrier.* Moving on to the portal vein, which is a passage that carries the nutrients and additional unavoidable microbial luggage from the intestine to the liver, there has been evidence that the microbial metabolites in it like trimethylamine, SBA, and SCFA influence the gut microbiota composition. For example, a high-fat diet increased taurine-conjugated BAs and promoted the population of pathogenic bacteria in the gut [23]. LPS in the portal vein can easily enter the liver because of a larger number of bacteria present in the gut.

*2.3. Hepatic Barrier.* When bacteria or its products enter the liver environment, the LPS component is readily detected by Toll-like receptor and the TLR signaling adaptor on the Kupffer cells and hepatocytes called Myd-88, and this complex activates proinflammatory cytokines like TNF-$\alpha$ and IL-1$\beta$, which are potentially downregulated by LPS-stimulated Kupffer cells that secrete the anti-inflammatory cytokine IL-10. Liver parenchyma cells can get destroyed due to high levels of LPS present in the liver [24]. Another important defence molecule is IgA, whose secretion is dependent on GM as it is nearly absent in germ-free mice [25]. IgA provides protection at the mucosal-microbial interface and regulates microbial load. For instance, inability to IgA class-switch in mice led to increased anaerobic bacterial load [26], and IgA deficiency led to the injury of the susceptible intestine in mice [27], and in pIgR-deficient mice, caecal microbiota diversity was altered [28]. Additionally, a review by Zhang et al. [29] indicated that the barrier function of liver sinusoidal endothelial cells (LSECs) has vital importance in hepatic homeostasis. LSECs have many crucial roles including the reduction in nuclear localization of nuclear factor-kappa B (NF-$\kappa$B) under LPS stimulation resulting in tolerance to physiological concentration of LPS [30] and also have anti-inflammatory and antifibrogenic function as they deactivate the Kupffer cell and HSC [10, 31]. Around 75% and 25% of LPS in the liver get eliminated by LSEC and the Kupffer cells, respectively [32]. One of the beneficial roles of GM is that LPS-stimulated Kupffer cells produce IL-6 that has a very important role in liver regeneration [33].

## 3. Gut Microbial Metabolites

*3.1. SCFA.* Fermentation of dietary fibres and resistant starch by colonic bacteria produces SCFA acetate, propionate, and butyrate. Their role is in energy supply, T reg colony regulation, and lipid metabolism via downregulating PPAR. Butyrate regulates transepithelial fluid transport and intestinal motility, maintains intestinal barrier, and ameliorates mucosal inflammation [34–38].

*3.2. SBA.* GM breaks down the primary bile acids to secondary bile acids (SBA) that can activate immunologically important receptors like FXR and Gpbar-1 or TGF5, and slow-generation of adaptive immunity to microbial settlers through the liver's immune response. FXR and TGR5 inhibit the expression of proinflammatory cytokines in the liver. Bile acids (BAs) activate FXR in hepatocytes to inhibit cytokine expression and BA production. BAs also activate TGR5 in the Kupffer cells to inhibit cytokine expression and thus, in turn, inflammation [39].

*3.3. Role in Liver Diseases.* Altered gut microflora is associated with pathophysiology of various liver disorders such as alcohol-associated liver disease (ALD), nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), hepatocellular carcinoma (HCC), primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC), and liver cirrhosis. NAFLD and ALD progress on a spectrum of stages (Table 1). This spectral progression ranges from the benign steatosis and steatohepatitis (or NASH, i.e., nonalcoholic steatohepatitis) to the irreversible cirrhosis and then ultimately leads to hepatocellular carcinoma [40–43]. Table 1 summarizes the various liver diseases caused by dysbiosis in gut microbiota.

*3.4. Role in NAFLD.* Nonalcoholic fatty liver disease (NAFLD) is the hepatic expression of cardiometabolic syndrome that frequently includes obesity, high blood sugar levels, dyslipidaemia, and hypertension [45, 46]. It is quickly becoming the most prevalent liver disease around the globe. NAFLD can be characterized by an excessive build-up of lipids in the liver caused by a reason other than alcohol [47]. Multiple risk factors that have been found to be associated with it include obesity, metabolic syndrome, type 2 diabetes mellitus, and dyslipidaemia, in addition to dietary factors such as consumption of excessive energy-rich food like high-fat or high-carb diets [47, 48]. Although the aetiology and progression of NAFLD are still not clear, research studies indicate that in conjunction to insulin resistance and inflammation [49], gut microbiota and circadian rhythmicity of hepatic metabolic genes also play crucial roles in the pathogenesis of NAFLD [47, 48]. Germ-free mice colonized with microbiota from obese mice exhibit a greater percentage of body fat compared with germ-free mice colonized with microbiota from lean mice, linking the microbiota causatively to obesity development [52].

*3.4.1. Dysbiosis.* Intestinal dysbiosis is defined as disruption of symbiosis due to imbalance of various microbial entities inhabiting the intestine [53]. This dysbiosis results in a sequel of events resulting in various liver diseases as shown in Figure 3. Obesity, a key risk factor of NAFLD, is linked with gut dysbiosis. A study by Ghoshal et al. revealed an increased population of *Lactobacillus* and *Firmicutes* along with a decreased population of *Ruminococcaceae* and *Oscillibacter* in NAFLD patients as compared to healthy controls [54]. In another cohort of NAFLD patients, faecal samples of patients having advanced fibrosis showed increased *Proteobacteria* and *Escherichia coli* bacteria whereas *Firmicutes* were reduced [55].

*3.5. Impairment of Intestinal Barrier.* Obesity, independent of diet, induces dysbiosis by disrupting the intestinal barrier's TJs and mucus layers and leading to leaky gut and endotoxemia. The leaked bacterial substances can alter host gut immunity to cause low-grade inflammation [56].

Table 1: Gut microbiota-associated liver disease.

| S. no. | Disease | Dysbiotic features | Reference |
|---|---|---|---|
| 1 | NAFLD | Increase in *Proteobacteria*, *Enterobacteriaceae*, *Lachnospiraceae*, and *Escherichia*<br>Reduction or no change in *Bacteroidetes*<br>Decrease in *Prevotella* and *Firmicutes* | [44, 45] |
| 2 | CIRRHOSIS | Increase in *Enterobacteriaceae*, *Enterococcaceae*, and *Streptococcaceae*<br>Reduce *Lachnospiraceae* and *Ruminococcaceae* | [46] |
| 3 | NASH | Increased Firmicutes/Bacteroidetes ratio | [47] |
| 4 | ALD | Elevated proinflammatory *Enterobacteriaceae* levels, decreased levels of butyrate-producing *Clostridiales* species. | [48] |
| 5 | PSC | Increase in *Veillonella* and *Enterococcus*, *Fusobacterium*, and *Lactobacillus* | [49] |
| 6 | HCC | Decrease in *Ruminococcus*, *Oscillibacter*, *Faecalibacterium*, *Clostridium*, Coprococcus, Lactobacillus, Bifidobacterium, and Enterococcus<br>Increase in *Escherichia coli*, LPS-producing *Klebsiella*, and *Haemophilus* | [50] |
| 7 | PBC | *Nov osphingoviumaromaticivorans*, *Lactobacillus delbrueckii*, *Toxoplasma gondii*, *Mycobacteria*, and retroviruses, though these associations are weaker than that for *E. coli* | [51] |

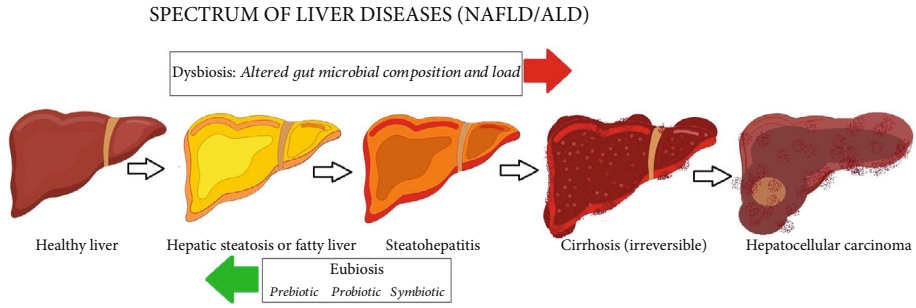


Figure 3: The sequelae of damage which can be potentiated by dysbiosis in the liver. The healthy liver goes through stages of fatty infiltration (hepatic steatosis), inflammation of the fatty liver (steatohepatitis), irreversible architectural damage (cirrhosis), and then finally at risk of malignancy (hepatocellular carcinoma).

*3.6. Microbe-Induced Inflammation.* Downstream effects of endotoxin translocation may include the induction of Toll-like receptors (TLR4) in the liver, with downstream activation of transcription factors inducing an inflammatory response [57]. Saturated fatty acids (SFA) such as palmitate can induce the production of IL-1$\beta$ and TNF-$\alpha$ by activation of proinflammatory signals through TLR4 that subsequently induce the production of ROS in hepatic infiltrating macrophages. This signaling ultimately leads to hepatic steatosis and insulin resistance in NAFLD [58]. Hepatic and serum TLR4 is significantly increased in NASH patients, and high serum levels of TLR4 are considered as a biomarker for liver fibrosis development [59]. Dormant hepatic stellate cells (HSCs), the main precursors for myofibroblasts in the liver, are the primary target through which TLR4 ligands promote fibrogenesis. In dormant HSCs, TLR4 activation not only upregulates chemokine secretion and induces chemotaxis of the Kupffer cells but also downregulates the transforming growth factor- (TGF-) beta pseudo receptor Bambi to sensitize HSCs to TGF-beta-induced signals and allow for unrestricted activation by the Kupffer cells [60–62].

## 4. Role of Microbial Metabolites

*4.1. SCFA.* SCFA involvement in NAFLD pathogenesis may be considered because of their potential contribution in the maintenance of body weight, intestinal homeostasis, and metabolism of glucose and lipids [63, 64]. Gut SCFAs are found to be increased in overweight adults, as compared to lean adults [65]. Faecal samples of NAFLD patients also showed increased amounts of SCFAs (propionate and acetate) and increased abundance of SCFA-producing bacteria, such as *Fusobacteriaceae* and *Prevotellaceae*, as compared to healthy controls [66]. SCFA supplementation improves diet-induced hepatic steatosis in murine models [67]. SCFA-supplemented diet helps in the prevention and reversal of high-fat diet- (HFD-) induced obesity and insulin resistance in mice by downregulating peroxisome proliferator-activated receptor (PPARg) present in liver and white adipose tissue [37].

*4.2. Choline.* Choline has multiple roles in the pathogenesis of NAFLD such as VLDL export, enterohepatic metabolism of bile, mitochondrial function, epigenetics, ER stress, and VLDL export, making it an essential nutrient [68]. It is a well-established fact that choline deficiency influences the development of NAFLD and NASH, validated by the use of a choline-deficient diet in the murine model of NASH [69]. Dysbiosis enhances choline conversion into methylamines that can potentially lead to choline deficiency causing NASH [70]. Choline deficiency contributes to the

pathogenesis of fatty liver disease via multiple mechanisms such as abnormal phospholipid synthesis, defective very low-density lipoprotein secretion, and modulation in enterohepatic bile circulation [71].

*4.3. TMA and TMAO.* Choline is metabolized to TMA by gut microflora, and later, TMA is metabolized to TMAO in the liver. Du et al. have found a correlation between high urinary excretion of TMAO with insulin resistance and NAFLD in mice [72].

*4.4. Amino Acids.* Phenylacetic acid, an AAA-derived microbial metabolite, has a strong correlation with hepatic steatosis in humans, inducing hepatic steatosis in both a human hepatocyte and in rodents, making it a causal factor in NAFLD pathogenesis.

*4.5. Ethanol.* In children with NASH as well as in adults with NAFLD, there are significantly more bacteria associated with increased alcohol levels in the blood in comparison with obese children without NASH [40, 73, 74].

*4.6. Role of Bile Acids.* Bile acids have been documented as important signaling molecules that affect host metabolism as well as immunity by activating a number of host receptors such as farnesoid X receptor (FXR) [75]. Bile acid-induced FXR activity can protect the small intestine by preventing bacterial overgrowth through its antibacterial action. Mice lacking FXR have a compromised gut barrier function validating its role [76]. In addition, FXR signaling is also critical for lipid and glucose metabolism evident from the fact that FXR-deficient mice show increased hepatic triglyceride level [77], glucose intolerance, and insulin resistance [78]. G-protein coupled bile acid receptor 1 (TGR5) is a cell surface receptor involved in multiple metabolic pathways. Compared to wild-type (WT) mice, TGR5-knockout (TGR5−/−) mice revealed exacerbated liver damage, high levels of proinflammatory factors, and higher M1 macrophage polarization, proving that TGR5 signaling attenuated liver steatosis as well as inflammation and inhibited NLRP3-mediated M1 macrophage polarization in NASH [79]. Figure 4 depicts the pathogenesis of NAFLD due to alteration in bile acid metabolism.

*4.7. Role in ALD.* Around the world, alcoholic liver disease is a foremost causal factor in alcohol-related morbidity and mortality [80]. This is because in heavy drinkers, the greatest burden of injury is experienced by the liver as it is the main location of ethanol metabolism. The clinical spectrum of alcoholic liver disease (ALD) includes alcoholic fatty liver, alcoholic steatohepatitis, alcoholic cirrhosis (Laennec's cirrhosis), and increased risk of hepatocellular carcinoma [81]. The pathomechanism of ALD involves complex interactions between the direct effects of alcohol and its toxic metabolites on various liver cells; however, there is solid proof of a causative link between the gut-liver axis to not only the progression of alcohol-induced liver disease but also to infections in ALD cirrhotic patients, both in patients and in experimental animal models [82].

Table 2 summarizes the changes caused by imbalance in various microbial metabolites as observed in various research studies.

## 5. Bacterial Overgrowth

Chronic alcohol ingestion causes dysbiosis in animals and humans due to small and large intestinal bacterial overgrowth [82–84]. Patients with chronic alcohol abuse showed a significantly higher number of anaerobic and aerobic bacteria in jejunal aspirates as compared to control subjects [85]. No obvious reason for this bacterial overgrowth is clear yet, but the impaired bile or intestinal dysmotility could be the cause of overgrowth [86]. In cirrhotic patients, SIBO is an imperative risk factor for hepatic encephalopathy occurrence, and probiotics VSL#3 decrease small intestinal bacterial overgrowth in cirrhotic patients [87–90].

*5.1. Dysbiosis.* Higher amount of *Proteobacteria*, *Prevotellaceae*, and *Veillonellaceae* and lower amount of *Bacteroidetes* were observed in the colon and faeces of patients with alcoholic cirrhosis as compared to noncirrhotic alcoholic patients or healthy subjects [68, 91–93]. Moreover, alcohol-fed animals had higher proportions of *Verrucomicrobia*, *Proteobacteria*, and *Actinobacteria* and lower proportions of *Firmicutes* such as Lactobacillus, *Pediococcus*, *Leuconostoc*, and *Lactococcus* as observed in various research studies [93–96].

*5.2. Leaky Gut.* In 1999, Mavrogeni et al. concluded that heavy drinkers get chronic liver injury due to "leaky gut." Alcohol causes epithelial cell death and mucosal ulcerations in the gut. Alcohol metabolism generates ROS that damage the cells damage via oxidative stress [97–100]. Acetaldehyde (one of the alcohol metabolites) forms DNA adducts that cause direct cellular damage and increase intestinal permeability by damaging tight junctions [91, 101–103]. Leaky gut in alcoholics is due to transepithelial leak (disrupted epithelial cells) and paracellular leak (disrupting TJ and cytoskeleton in between epithelial cell spaces [104]. Alcohol downregulated C-type lectins Reg3b and Reg3g in the small intestines and leads to SIBO and alcoholic steatohepatitis [92].

*5.3. Microbial Metabolites*

*5.3.1. BA.* Alcohol can affect the bile-acid metabolism, and, in turn, bile acids can alter intestinal bacteria. Alcohol exposure inhibits liver FXR leading to increased bile acid synthesis and inhibits intestinal FXR activation, which promotes bacterial overgrowth and dysbiosis. Alcohol decreases taurine-conjugated bile acid pool because alcohol causes Gram-negative bacterial overgrowth that functionally performs deconjugation [54, 102, 105–107].

*5.3.2. SCFA.* Butyrate maintains intestinal barrier function and alleviates gut leakage resulting in improvement in NAFLD and ALD. Inulin suppresses hepatic proinflammatory macrophages and activates anti-inflammatory macrophages that significantly reduce the inflammation in ALD [108–110].

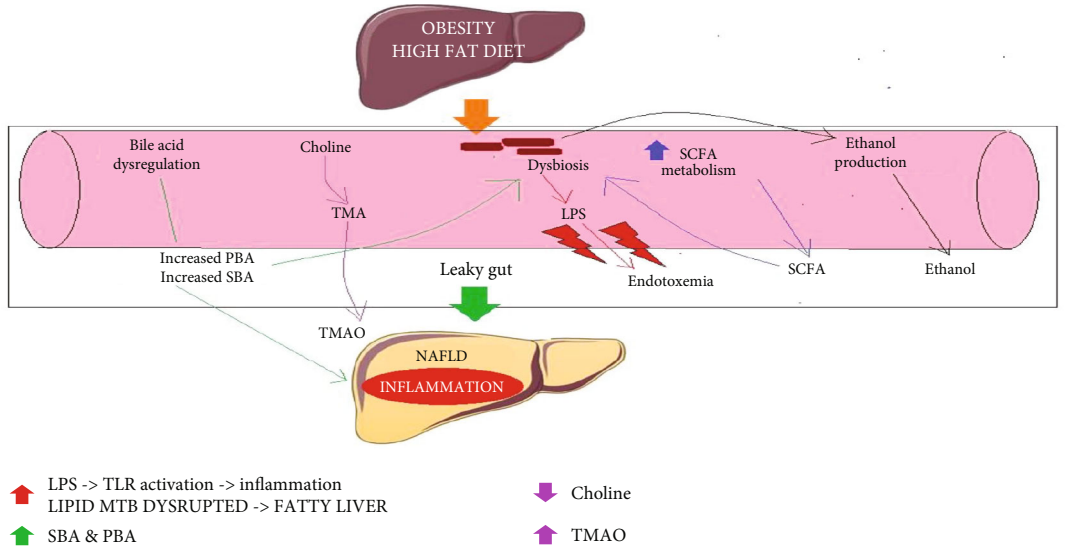


Figure 4: How dysbiosis alters bile acid metabolism, and resultant inflammation progressively leads to NAFLD (nonalcoholic fatty liver disease).

Table 2: Role of microbial metabolites.

| S. no. | Microbial metabolite | Key feature | Imbalance | References |
|---|---|---|---|---|
| 1 | SCFA | Maintenance of body weight, intestinal homeostasis, and metabolism of glucose and lipids | Increased amounts of SCFAs and increased abundance of SCFA-producing bacteria, such as Fusobacteriaceae and Prevotellaceae, are involved in NAFLD pathogenesis and obesity | [64, 82] |
| 2 | Choline | VLDL export, enterohepatic metabolism of bile, mitochondrial function, epigenetics, ER stress, and VLDL export, making it an essential nutrient | Influences the development of NAFLD and NASH | [83] |
| 3 | TMA & TMAO | Acts as an important stabilizer of protein folded state, and nucleic acid prevents protein denaturation and counteract effect of pressure and heat | High urinary excretion of TMAO causes insulin resistance and NAFLD. | [84] |
| 4 | Amino acids-phenylacetic acid | Dietary amino acids are the major fuel of small intestine mucosa particularly glutamate, glutamine, and aspartate which is the major oxidative fuel of the intestine | Hepatic steatosis in both human hepatocyte and rodents, making it a causal factor in NAFLD pathogenesis | [85, 86] |
| 5 | Ethanol | Bacterial intestinal flora is itself responsible for the production of endogenous ethanol through the fermentation of carbohydrates | It can induce leaky gut through disruption of epithelial-type junctions resulting in bacterial translocation | [40] |
| 6 | Bile acid | Bile acid-induced FXR activity can protect the small intestine by preventing bacterial overgrowth through its antibacterial action. FXR signaling is also critical for lipid and glucose metabolism | FXR deficiency causes compromised gut barrier function, glucose intolerance, insulin resistance, and increased hepatic triglyceride level | [76, 78] |

*5.3.3. Choline.* Alcoholics are known to be choline-deficient; however, choline supplementation did not stop the progression of ALD in ethanol-fed baboons [111].

*5.3.4. Tryptophan.* It plays a disease-protective role in ALD. Tryptophan metabolite, i.e., indole-3-acetic acid, stimulates IL-22 production and Reg3G expression and also reduces bacterial translocation to the liver in a mouse model of ethanol-induced liver disease [112].

*5.4. Host Immunity.* LPS and TLR4 have been anticipated as vital players in ALD pathogenesis. Chronic ingestion of alcohol leads to a strong elevation of portal and systemic levels of LPS in animal models and humans due to gut leak caused by

bacterial overgrowth and acetaldehyde direct cytotoxicity. Alcohol also affects mucosal immunity by suppressing antibacterial compounds secreting the Paneth cells resulting in fewer antibacterial compound secretion leading to bacterial overgrowth and endotoxin entrance [112, 113].

*5.5. Mycobiome.* A recent study of chronic alcohol feeding in a murine model shows intestinal fungal overgrowth associated with translocation of fungal products as evident by elevated plasma levels of 1,3-$\beta$-D-glucan, a component of the *Candida* cell wall. The Kupffer cells in the liver induce IL-1$\beta$ production by increased $\beta$-1,3-glucan that in turn increase alcohol-induced inflammation, steatosis, and hepatocyte injury by acting on hepatocytes [62, 114, 115].

## 6. Role in Cirrhosis

Cirrhosis is a chronic hepatic disease characterized by fibrosis and degeneration of normal liver cells into structurally abnormal nodules. Major risk factors of cirrhosis include ALD, NAFLD, viral hepatitis, autoimmune hepatitis, and biliary diseases. Imbalance in microbiota observed in cirrhotic patients has been depicted in Figure 5.

Cirrhosis patients have altered gut-liver axis related to gut and systemic inflammation associated with the severity of liver disease, damage to the gut barrier, and alterations in the composition as well as function of gut microbiota. Cirrhosis disrupts the architecture of the liver leading to a deficiency in proteins and disturbance of hepatic immune cell function. The cirrhosis-associated immune dysfunction allows for dysbiosis due to hepatic immunodeficiency as a result of persistent immune activation to PAMPs and DAMPs from a leaky gut [10]. Cirrhotic dysbiosis results in the relative abundance of Enterobacteriaceae (includes Gram-negative rods like *E. coli* and *Klebsiella*), *Enterococcaceae* (includes *Enterococcus faecalis* and *E. faecium*), and *Streptococcaceae* and reduces the advantageous microbiota such as *Lachnospiraceae* and *Ruminococcaceae* [60, 116]. Alterations in gut microbiota in cirrhosis can play an important role in the progression of disease from the outpatient to inpatient settings, and this can be countered by reducing unnecessary antibiotics and PPI use [95]. The intestinal mucosa of rats with cirrhosis shows a proinflammatory profile of immune dysregulation that coincides with the severity of cirrhosis; this diminished intestinal immune response occurs due to gut dysbiosis and leads to disturbed barrier function, promoting bacterial translocation [117]. Recently, studies using antibiotics like rifaximin, probiotics, prebiotics, and symbiotic defence are being done that prevent cirrhosis progression by modifying the gut microbiome. The importance of the gut microbiota in liver disease is evident by various studies depicting that several problems of serious liver disease, such as hepatic encephalopathy, are efficiently treated by the intonation of gut microbiome via the use of probiotics, prebiotics, and antibiotics [87].

## 7. Role in PSC

Primary sclerosing cholangitis (PSC) is a chronic disease leading to fibrotic scarring of the intrahepatic and extrahepatic bile ducts, causing considerable morbidity and mortality via the development of cholestatic liver cirrhosis, concurrent IBD, and a high risk of bile duct cancer.

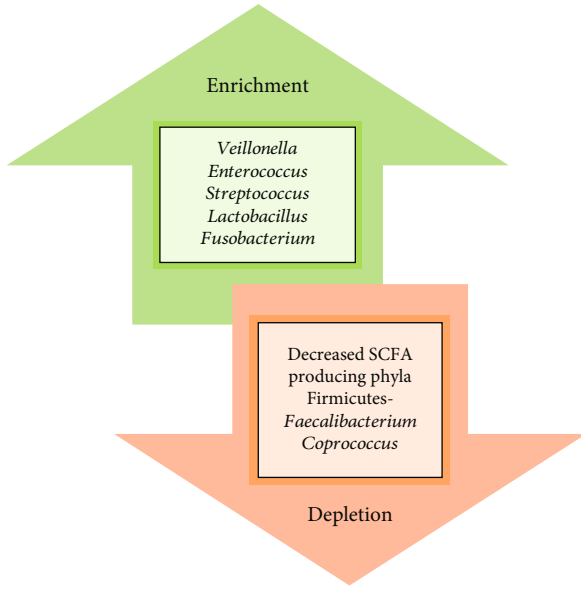


Figure 5: Imbalance in the microbiome that was found in the microbiome of cirrhosis. Faecal loads of liver cirrhosis patients showed proliferation in populations of pathogenic bacteria, such as *Enterobacteriaceae* and *Streptococci*, and depletion of *Firmicutes* leading to decreased short-chain fatty acid production (SCFA) [89].

Various genetic and environmental factors intervene to cause this complex genetic disease of bile ducts and bowel. It is now a well-acknowledged fact that the microbiome plays a vital role in the manifestation and progression of IBD [118, 119]. Similarly, new research has shown solid evidence about the role of altered gastrointestinal microbiome in the pathogenesis of PSC.

The role played by the gut microbiome had been long hypothesized, provided convincing evidence for this by demonstrating that SIBO, achieved using a blind jejunal loop, and induced cholangiographic alterations similar to PSC in rats. Additionally, previous studies of the faecal microbiome in PSC demonstrate that the overall bacterial community is distinct in PSC without any consistency with respect to alterations in specific microbe as compared to healthy controls. [120–122] had demonstrated that the microbiota of patients with PSC was characterized by decreased microbiota diversity, and a significant overpopulation of *Enterococcus*, *Fusobacterium*, and *Lactobacillus* genera. The *Veillonella* genus associated with other chronic inflammatory and fibrotic conditions was increased in PSC that observed a significant enhancement in *Barnesiellaceae* at the family level, and in Blautia and an unidentified *Barnesiellaceae* at the genus level associated with PSC [123, 124]. Various researches have confirmed that IBD has very little effect on the composition of the gut microbiota in PSC patients as microbial composition gets altered primarily by PSC.

Gut leak can clinically impact biliary inflammation in primary sclerosing cholangitis, observing increased levels of circulating marker bacterial translocation in PSC patients,

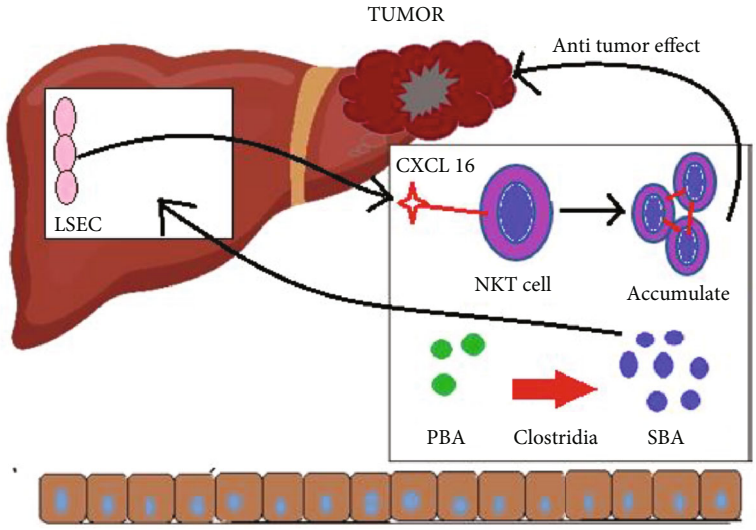


Figure 6: The role of Clostridium-mediated modulation of bile acids leading to stimulation of liver sinusoidal cells (LSEC) which produce chemokine CXLCL 16 that helps in recruiting NKT cells (natural killer T cells) that bring about antitumor surveillance.

and this high LPS trend was associated with poor prognosis measured by transplantation-free survival.

It has been difficult to find the causal link between the gut microbiome and PSC as most of the studies have been associational in the past. However, three studies have supported that dysbiosis, bacterial translocation across the gut barrier, and heightened immune responses (adaptive or innate) have significant roles in the pathogenesis of PSC. [125–127] study indicated three important findings about PSC: presence of *Klebsiella pneumonia* in the microbiota of patients with PSC, the role of K. pneumonia in disrupting the epithelial barrier to facilitate bacterial translocation and liver inflammatory responses, and that the PSC-derived microbiota revealed T helper 17 (TH17) cell responses in the liver and augmented susceptibility to hepatobiliary injuries. PSC patients have exhibited an imbalance between Th17 and T regulatory (Treg) responses and found the increased interleukin (IL)-17A levels in PSC, thereby supporting the role of Th17 responses [128–130].

*7.1. Role in PBC.* Primary biliary cirrhosis (PBC) is an autoimmune, cholestatic liver disease characterized by 3 main symptoms, i.e., chronic cholestasis, circulating antimitochondrial antibodies (AMA), and distinctive liver biopsy results of nonsuppurative destructive cholangitis and interlobular bile duct destruction [131, 132]. Perturbations in gut microbiota can lead to bacterial translocation of its products to the liver due to a leaky intestinal barrier, hence leading to chronic inflammation and fibrosis of the liver. Conversely, change in important metabolites of microbiome, i.e., bile acids, can influence the gut microbial diversity directly or indirectly via innate immunity [133].

There are many studies that have used 16S rRNA analysis to decipher the altered microbiota in patients with PBC. AMA, the cause of autoimmune origin, may be induced by rough mutants of the members of the Enterobacteriaceae. A study done by the UDCA treatment-naive group showed reduced microbial species richness along with distinct microbial diversity, and because the bile acids are essential regulators of gut microbiota, treatment with UDCA partially relieved the microbial dysbiosis. Their data suggested that the gut microbiota can be used as an innovative diagnostic biomarker and therapeutic target in PBC [134].

*7.2. Role in Hepatocellular Carcinoma.* Hepatocellular carcinoma (HCC) occurs in patients having underlying cirrhotic liver. Previous studies have investigated that the role of gut microbiome plays in its carcinogenesis as well as treatment. Liver cirrhosis and HCC patients had significant elevation in serum endotoxin levels suggesting that TLR-4 and the intestinal microbiota were needed only for HCC promotion by mediating increased proliferation, the expression of the hepatic mitogen epiregulin, and the prevention of apoptosis. Additionally, showed that treatment with probiotics mitigated gut dysbiosis and decreased liver tumor growth [135–137]. Figure 6 depicts the role of microbial modulation for antitumor surveillance.

A study found out that hepatic translocation of obesity-induced lipoteichoic acid (LTA), a Gram-positive gut microbial component, promotes obesity-related HCC by suppressing PGE2-mediated antitumor immunity and creates a tumor-promoting microenvironment [138]; compared with healthy controls, patients having primary HCC showed increased proinflammatory bacteria in their faecal microbiota, and the degree of dysbiosis (Ddys) had tendency to increase with its development [139]. Butyrate-producing bacteria belonging to families *Ruminococcus*, *Oscillibacter*, *Faecalibacterium*, *Clostridium*, and *Coprococcus* were decreased in patients suffering from early HCC, while LPS-producing *Klebsiella* and *Haemophilus* were increased as compared to controls [116]. The decrease in butyrate leads to damage of the gut barrier enhancing gut leak and HCC progression, whereas, LPS excess leads TLR4 activation and NF-$\kappa$B mediated inflammation through IL-1,6, TNF-$\alpha$ cytokines. Hence, the role of

dysbiosis in HCC progression could be a potential target of treatment indicating that the Kupffer cells were pivotal in activating the LPS-TLR4 axis, whereas according to the Kupffer cells, HSC, as well as hepatocytes, were sensitive to LPS activation via TLR4 [137, 140, 141]. Secondary bile acids such as DCA might play a vital role in oncogenesis, possibly through mTOR signal activation in hepatocytes. Deoxycholic acid is notorious for causing DNA damage. DCA provokes hepatic stellate cells (HSCs), which secretes tumor-promoting factors in the liver and enhances the development of HCC; alternatively, antibiotics against DCA-producing bacteria suppressed HCC progression [142]. *Clostridium* species modulates the bile acids to signal liver sinusoidal endothelial cells in order to produce the chemokine CXCL16 which recruited natural killer T (NKT) immune cells to perform antitumor surveillance of the liver and reducing cancer growth as depicted in Figure 6 [143].

*7.3. Role in Cholangiocarcinoma.* Cholangiocarcinomas are rare malignant tumors composed of cells that resemble those of the biliary tract. Due to the antimicrobial nature of bile, it was previously thought that the biliary tract is sterile in nature. However, recent evidences have suggested the existence of the biliary microbiome which is more diverse than the intestinal microbiome [144, 145].

Ulcerative colitis and primary sclerosing cholangitis (PSC) induce chronic biliary duct inflammation and thus are major risk factors of CCA. Gut barrier and endotoxemic inflammation play a major role in promoting CCA. For instance, a study showed that reduction in gut barrier function observed in animals suffering from PSC and colitis facilitated gut-derived bacteria and lipopolysaccharide to appear in the liver, inducing CXCL1 expression in hepatocytes through a TLR4-dependent mechanism and an accumulation of immunosuppressive CXCR2+ polymorphonuclear myeloid-derived suppressor cells (PMN-MDSC) that ultimately leads to CCA. Just like other liver disorders, dysbiosis has also been investigated in CCA [146]. According to the bacterial composition, it was significantly different in CCA as compared to control. Furthermore, the genus *Muribaculaceae* was most strongly associated with CCA and could be potentially used as a noninvasive tool for early diagnosis of CCA. Additionally, microbiota in a series of intrahepatic CCA which revealed that bacteria communities including *Lactobacillus*, *Actinomyces*, *Peptostreptococcaceae*, and *Alloscardovia* were more prevalent in gut microbiota from cases than controls. This study also demonstrated intrahepatic CCA biomarkers like elevated plasma tauroursodeoxycholic acid (TUDCA) and elevated *Ruminococcaceae* and IL-4 levels in patients with vascular invasion [147, 148].

## 8. Future Prospects

In the last decade, the research surrounding microbiome has accelerated to a great potential. We now know the innumerable species inhabiting our gut and how they are our metabolic factories as well as the origin of various intestinal and liver diseases. The future can hopefully bring more diagnostic and therapeutic modalities. *Clostridium*'s antitumor effect in hepatocellular carcinoma is very interesting and needs more in-depth research. The role of probiotics in disease prevention as well as treatment could be investigated more. The latest intriguing talk of the microworld is gut virome. Since we know how expertly bacteriophages carry the genome as vectors, discovery remains as to if gut virome could bring therapeutic breakthroughs for debilitating diseases like inflammatory bowel disease and autoimmune enteritis.

## 9. Conclusion

The significance of gut microbiota in the development of liver illnesses has been demonstrated by various studies done on microbiome and liver disease. Genesis and progression of liver disease are caused by a variety of factors such as bacterial overgrowth, dysbiosis, and disturbed intestinal barrier that results in leaky gut. In addition, the activation of Toll-like receptors in the liver by bacterial metabolites and microbial products contributes to the development of steatosis, inflammation, and fibrosis. The bile acid and SCFA pathways have provided an excellent explanation of how the gut microbiota gets affected by diet and, in turn, how this leads to the development and progression of liver disease. In order to create microbiota-targeted medicines for the treatment of complex liver diseases at its different stages, significant study in this topic is still required to elucidate other molecular and metabolic processes.

## Data Availability

All the data relevant to this research are available in the body of the manuscript as supporting figure and tables. We do not have any ethical or legal consideration for us not to make our data publicly available.

## Conflicts of Interest

The authors declare that they have no conflicts of interest.

## Authors' Contributions

Divya KP and Parneet Hari contributed equally to this work.

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