Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2024**; 29(2): 67
https://doi.org/10.31083/j.fbl2902067

Review

Gut Microbiome and Cancer: From Cancer Development to Therapeutics with a Special Focus on Hepatocellular Carcinoma

Sancharan Acharya[1], Chinnasamy Thirunavukkarasu[1,*]

[1]Department of Biochemistry and Molecular Biology, Pondicherry University, 605014 Puducherry, India
*Correspondence: tchinnasamy@gmail.com (Chinnasamy Thirunavukkarasu)
Academic Editor: Amedeo Amedei
Submitted: 11 November 2023 Revised: 15 December 2023 Accepted: 28 December 2023 Published: 6 February 2024

Abstract

The body of a human has a vast array of microorganisms termed the microbiome that impacts almost every function of the body. Gene-environment interactions play a major role in making us susceptible to cancer and the microbiome is such an environmental factor that we are exposed to from the very beginning of our lives to the very end. Increasing pieces of evidence are pointing towards an association of cancer and the microbiome. The bacteria inside our body might help us prevent some cancers as well as may increase the risk of carcinogenesis and treatment responses. Many studies are suggesting that tinkering with the microbiome might be a new way to treat and prevent many kinds of cancer. Although information on the roles of the microbiome in carcinogenesis is scant and almost no direct links have been found between these two yet. This review offers some of the recent evidences of the association between cancer and the microbiome, discuss the impact of gut bacteria on cancer and provide a detailed discussion on gut microbiota mediated therapeutic approaches with a special focus on Hepatocellular Carcinoma. The implementation of the new knowledge discovered in this subject calls for a great deal of research.

Keywords: cancer; gut microbiota; gut-liver axis; microbiome; cancer therapy; hepatocellular carcinoma; FMT

1. Introduction

Cancer, the deadly disease that sends shivers down the spine of whole humankind, involves abnormal cell growth that can spread throughout the body of an individual; however, not all cancers have the ability to spread itself or metastasize. Global Cancer Observatory (GCO) estimates the number of new cases of cancer inclusive of all kinds will go from 19,292,789 in 2020 to 28,887,940 in 2040. From ages 0–85+ years, including both sexes the numbers are estimated to increase by 59.2% from 2020 to 2040 alone in Asia. In Europe and North America, the rise in all kinds of cancer cases is estimated to be 21% and 37.9% respectively [1]. Cancer development is a slow and multistep process and the initiation depends on several factors. Some of the factors include diet, smoking, consumption of alcohol, physical inactivity whereas the other factors that are on the far side one's direct management embrace exposure to carcinogenic pollutants, chronic stress, radiation and microbiota within one's body [2]. In the process of development of cancer, gene-environment interactions play a key role. Exposure to certain environmental factors can influence the susceptibility of developing this deadly disease. Such an environmental factor is the microbiota present inside our body. Humans are often called 'superorganisms' due to the presence of a huge variety of microorganisms in our bodies. As the environment changes, the microbiota is subject to change throughout the life of an individual, although it stays quiet stable during the adult life [3]. Microbiota is related to every aspect of our body functions and alteration of which may result in several abnormalities. Every anatomical niche inside a human body shelters its own population of microbes even a tumor microenvironment has its own microbial population. The role of microbiota in cancer development was largely overlooked, until recently the attention of researchers shifted towards it. The arrival of next-generation sequencing techniques has made it relatively easy to study the epigenetic changes and mutations that occur throughout cancer development. Scientific communities from all over the world are trying to figure out the link between microbiota and the development of cancer which can lead us to new ways of preventing, detecting and treating cancer.

The sixth most common cancer kind worldwide is liver cancer, accounting for 830,200 fatalities worldwide in 2020 [4]. The most common primary liver cancer type is Hepatocellular Carcinoma (HCC) [5]. There are several risk factors that cause HCC, namely Hepatitis B (HBV) or Hepatitis C virus (HCV), diabetes, consumption of alcohol, metabolic-dysfunction associated steatotic liver disease (MASLD) and several other genetic diseases also [6,7]. HCC typically occurs from chronic liver disease (CLD) through stages like fatty liver disease, steatosis, steatohepatitis, fibrosis and cirrhosis [8]. HCC is often detected at advanced stages of the disease where the liver already shows symptoms of dysfunction and failure [5]. Out of all the HCC therapies available, one of the major options is surgical resection for primary or metastatic liver tumors, but the success rate depends on early-stage surgery where

chances of metastasis are less [9]. Where surgery is not an option immunotherapy, chemotherapy and targeted therapy are preferable. Sorafenib, a multi-kinase inhibitor having anti-proliferative and anti-angiogenic effects, is one of the first line treatment options. Because of their low cost, Sorafenib and Doxorubicin are the two primary drugs used to treat advanced HCC in under developed countries where instances of liver cancer are more [10,11]. In case of both primary and metastatic tumors; microwave ablation (MWA), irreversible electroporation (IRE), radiofrequency ablation (RFA), and high-intensity focused ultrasound (HIFU) are the minimal invasive therapies that are available for treatment [12,13]. Recently FDA has approved five new agents for HCC treatment as first line and second line therapies. Lenvatinib is approved as a line first treatment and other four second line treatment options are Regorafenib, Nivolumab, Pembrolizumab, and Cabozantinib [14]. Application of these drugs is dependent of the stage and dimensions of the tumor. Depending on the condition of the disease, recurrence of cancer and/or therapeutic resistance, combination therapy i.e., using two or more treatment options, is often preferable [15].

If HCC is detected early, there are many different treatment options available, and results are frequently positive, although early detection is very rare in this case. The biomarkers that are unique to HCC include des-gamma-carboxy prothrombin (DCP), alpha-fetoprotein (AFP), and Lens culinaris agglutinin A-reactive fraction of AFP (AFP-L3) [16,17]. Aldo-keto reductase family is one of the possible novel biomarkers that has been researched to diagnose HCC and forecast its prognosis [18]. Since gut microbiota is related to the development of liver diseases like cirrhosis/fibrosis and cancer, gut microbial changes may act as early indicators of HCC, where disease diagnosis will benefit from the non-invasiveness of gut microbiota [19]. Gut microbiota has been shown to be related with the efficacy of anti-cancer therapies as well as with the adverse effects of radiotherapy, immunotherapy and chemotherapy [20]. Combining the therapeutics approaches with antibiotics, probiotics or prebiotics to modulate the gut microbiota may prove to be fruitful in side effect management or combating cancer as a whole. In this regard, this review aims to explore recent research on the connection between cancer and the microbiome, to shed light upon recent microbiome mediated therapeutic approaches with a special focus on HCC and to point out the little explored or unexplored portions of this newly emerging field of science. We might be on the verge of the advent of a new paradigm in cancer research.

2. Microbiome and Its Connection with Human Physiology

An enormous number of microbes reside within the human body including bacteria, archaea, eukaryotes, and viruses. The collection of all microbes that reside on or within the human body is referred to as the human 'microbiota', including the skin, placenta, lung, saliva, oral mucosa, seminal fluid, mammary glands, uterus, ovarian follicles, conjunctiva, biliary tract, and gastrointestinal tract [21]. The term 'microbiome' refers to the combined genome of the microbiota [22]. The gastrointestinal (GI) tract has been estimated to shelter more than 10^{14} number of microorganisms. Compared to the human genome, the microbiome contributes more than 100 times as much genetic content [23]. In 2016, a study by Sender *et al.* [24], suggested that the total number of bacteria that are present inside the human body is estimated to be ~3.9 $\times$ 10^{13}, with a ratio of almost 1:1 with the total number of cells in the human body. The majority of these microorganisms are bacteria residing within the GI tract. The aggregate of bacteria, archaea, and eukarya residing in the GI tract is termed as the 'gut microbiota'. The microbiota has co-evolved with the host over the evolutionary time scale which formed a mutually beneficial relationship [25]. Recently, our capacity to scan the gut microbiota has been substantially enhanced by high-throughput and inexpensive sequencing techniques, such as targeting of the bacterial 16S ribosomal RNA (rRNA) gene and shotgun metagenomics [26].

The bacteria living in our guts are protected from their predators and also get a consistent supply of nutrients from our diets which help them survive. In return, the microbiota helps the host in various ways, such as harvesting energy [27], regulating host immunity [28], and maintaining the intestinal barrier, thus restricting harmful organisms from breaching the epithelium and causing illness [29]. The symbiotic bacteria produce disaccharides and monosaccharides by digesting glycans for the host's and their own source of energy. Symbiotic relationship with these microbes improves our ability to absorb nutrients from our diets and get the most energy out of it [30]. The variation of microbiota at levels of genus, species, and strain is enormous between human individuals [31]. This occurs due to environmental factors namely diet, lifestyle, health situation and host genetics [32]. The microbiota inside a human individual also varies over the lifespan of the individual and in response to diet, use of chemotherapeutics, antibiotics, stress, and several other factors [33–35]. Gene-environment interaction is the primary reason for human disease susceptibility, and it is now believed that the microbiome is an important factor also. Currently, it is understood that gut microbes primarily fall under the phylogenetic gates of Bacteroidetes, Firmicutes, Proteobacteria, Verrucomicrobia, Actinobacteria, Fusobacteria, and Cyanobacteria, the predominant bacteria being the first and second. The bulk of "good" bacteria in the gut of a human are Firmicutes and Cytophaga-Flavobacterium-Bacteroides [36,37].

'Gut dysbiosis' is referred to as a state where the gut microbial composition of the host gets unbalanced in comparison to a healthy individual. This might trigger inflam-

matory signaling pathways which can affect the immune system as a whole, rather than being limited to the gut environment. Gut microbiota dysbiosis is linked with many inflammatory and autoimmune conditions including rheumatoid arthritis, multiple sclerosis, type I diabetes, and inflammatory bowel disease [34]. Metagenomics is the tool that scientists use to study the microbiome. However, metagenomic studies are not enough to determine whether a certain microbiome difference causes a disease state or is itself a consequence of it. Thus, manipulating the microbiota in a precisely regulated manner is essential for finding out how the microbiota is connected to a particular disease. Because of this, gnotobiotic mouse models are essential for experiments in this field of research. Completely germfree laboratory mice can be raised maintained in specialized gnotobiotic facilities; if their foods are autoclaved and vital nutrients that the microbiota usually produces are given [38]. Germfree mice show metabolic anomalies such as hypoglycemia, reduced insulin and glycogen levels, as well as resistance to obesity even if it is provided with a high-fat diet. Studies have compared germ-free mice to genetically identical controls that have a complete but unidentified microbiota. Compared with controls, mice that are devoid of germs eat more, but are leaner and have around 35% less fat [39]. It can be said that, these experiments indicate that the host's capacity to obtain calories is enhanced by the gut microbiota. Additionally, the microbiota is crucial for regulation of the immune system and inflammatory reactions and germfree mice have been employed to show that [40]. Mice lacking transforming growth factor-1 display colorectal cancer and inflammation, which can be prevented by keeping them in a germ-free state [41]. A colitis phenotype is exhibited in IL-10 (interleukin 10, a potent immunosuppressive cytokine) knockout mice and it is reduced by maintaining them in a germ-free state [42]. So, it can be suggested that IL-10 has a primary function of the prevention of an unwarranted inflammatory response towards the commensal gut microbiota. The roles of microbiota in cellular energetics, immune response, and inflammation are very much relevant to cancer as these are recognized as the hallmarks of cancer [43]. Thus, many researches are shedding light upon how the microbiome can influence the host's susceptibility to various kinds of diseases including cancer.

Bile acids (BAs), short chain fatty acids (SCFAs), and other key metabolites are produced by the gut bacteria. Cholic acid (CA) and chenodeoxycholic acid (CDCA) are main components of primary BAs, whereas lithocholic acid (LCA) and deoxycholic acid (DCA) are key components of secondary BAs [44]. Conjugated-BAs can be created by mixing BAs with taurine or glycine. A sequence of liver enzymes produces primary BAs, which the gallbladder then excretes into the intestinal lumen. The generation of secondary BAs is significantly aided by the expression of bile salt hydrolase and 7-dehydroxylase by the gut microbiota [45]. The majority of BAs in the colon create enterohepatic circulation when they travel back to the liver via the portal vein system. BAs can facilitate lipid uptake and regulate energy metabolism. Additionally, bile acids play a significant role in immune modulation by mediating a number of downstream signal pathways. Microbes in the gut transform these chemicals into a variety of forms, considerably increasing their diversity and activity. SCFAs, as the name indicates, acidify the colon environment. That low pH promotes the development of helpful microbes while inhibiting disease colonization and improving mineral absorption. Furthermore, an acidic environment caused by SCFA synthesis reduces the quantity of secondary bile acids, that are shown to have negative impacts on gut health. SCFAs give colonic cells energy while also supporting in regeneration and maintaining optimal gut barrier impermeability. Butyrate does, in fact, induce the creation of tight connections between cells, forcing them to pack firmly together thereby rendering the gut increasingly impermeable [46]. Studying the gut microbiota's metabolites may therefore yield crucial information for aetiology and treatment of a disease. Via the biliary tract, the portal vein, and the systemic circulation, the gut and liver maintain close bidirectional connections that make up the gut-liver axis ,shown in the Fig. 1 [47]. Normal gut bacteria can collaborate with the host's immune system to form the gut barrier, which works to keep pathogens and toxins out and safeguard the body against sickness. However, microbial dysbiosis can disrupt gut barrier function, and a number of detrimental microbial related substances, along the gut-liver axis, reach the liver causing the development of HCC [48].

3. Influence of Microbiome on Carcinogenesis

Carcinogenesis or oncogenesis is the process through which normal cells turn into cancerous cells and causes the onset of the disease. This is a multistep process and is characterized by various changes at the cellular, genetic, and epigenetic levels. In this process of development of cancer, a key player is inflammation. A study in 2012, showed that IL-10 knockout mice with colitis have up to 100-fold higher levels of the *Enterobacteriaceae* family of bacteria in their colons compared with control mice without colitis. *Escherichia coli* and *Enterococcus faecalis* commensal bacteria strains were individually able to cause colitis when they were mono-associated with IL-10 mutant mice. However, only the *E. coli* strain was capable of causing colorectal cancer in the same mice after treatment with azoxymethane which is a procarcinogen. Therefore, in this case, carcinogenesis may not have been possible without inflammation, but it also wasn't necessary. The next step, then, was to determine which bacterial-triggered processes contributed to carcinogenesis. The polyketide synthases (pks) pathogenicity island, which is about 54 kb in size and codes for the enzymes needed to produce the genotoxin known as 'col-

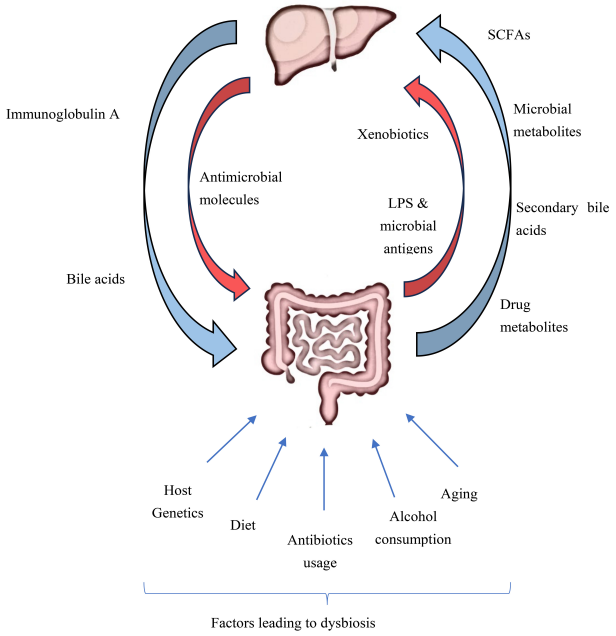

Fig. 1. The gut-liver axis. The gut-liver axis is the bidirectional interaction between the gut, its microbiota, and the liver due to a complex combination of signals generated through genetic, nutritional, and environmental variables. Short chain fatty acids (SCFAs), various microbial metabolites, secondary bile acids, and numerous drug metabolites produced in the gut by the gut microbiota aid in the regular operation of the liver. Several xenobiotic compounds, as well as microbial antigens and lipopolysaccharides (LPS) generated by the gut microbiota, might, nevertheless, have a deleterious impact on liver function. The liver also contributes to intestinal homeostasis by generating various bile acids and immunoglobulins. Although certain antibacterial compounds generated by the liver can impair proper intestinal function.

ibactin', was discovered through additional investigation. This colibactin was absent in the *E. faecalis* strain. The next objective was to show that colibactin is crucial for the development of cancer. To do that, a pks-deleted (Δpks) isogenic strain of *E. coli* was mono-associated with IL-10 knockout mice. Both the +pks strain and the Δpks strain mice promoted inflammation. But the Δpks strain was unable to induce carcinogenesis [49]. A study was conducted using RAG-2 knockout mice, where they were infected with *H. hepaticus* and a link between bacteria-mediated inflammation and DNA damage was found [50]. Activated macrophages and neutrophils infiltrated the inflammatory sites which boosted the synthesis of cytokines, chemokines, nitric oxide, superoxide, and other reactive species. This led to DNA and RNA damage and ended up causing colorectal cancer. Certain bacterial species can promote carcinogenesis by stimulating an inflammatory state through induction of proinflammatory toxins, increased generation of reactive oxygen species (ROS), and alterations in signaling pathways in human and mice model [51,52].

A well-recognized risk factor for the occurrence of cancer is obesity and is one of the most thoroughly researched causes of dysbiosis [39]. In the guts of both humans and mice, obesity has been linked to higher Firmicutes populations and lower Bacteroidetes populations [53]. Inflammation, along with many other factors contributes to obesity-associated cancer, and recent studies are suggesting that bacterial metabolites can also play a role in it. In the case of biliary cancer, some of the known cancer-causing gut bacteria include *Salmonella typhi* and *Helicobacter pylori.* [54]. *H. pylori* is associated with gastric adenocarcinoma and also cancer of mucosa-associated lymphoid tissue (MALT lymphoma). It has been categorized as a class I carcinogen by the World Health Organization (WHO) [55]. In the case of the development of colorectal cancer, there are many shreds of evidence suggesting that gut dysbiosis is a key player. The tumor microbiota and the adjacent healthy mucosal microbiota are distinctly different, and stool transplants from colorectal cancer patients compared to healthy controls, can cause the production of polyps, pro-carcinogenic signals, and can also change the local immunological environment in mice [56,57]. Gallbladder cancer and mucosa-associated lymphoid tissue (MALT) lymphomas provide examples of how certain bacterial infections might trigger cancer. Clonal expansion of T helper cells and B cells are the identifying characters of gastric MALT lymphoma. These cells react to antigens derived from *H. pylori* and regression occurs after the eradication of *H. pylori* [58]. There is no known microbiome for the pancreas. Recent studies suggest pancreatic cancer is promoted by inflammatory microbe-associated molecular patterns (MAMPs) and its receptor toll-like receptor 4 (TLR4) [59]. However, the mechanism through which the microbiota promotes pancreatic cancer remains unclear. The prevalence of skin cancer in mice deficient in bacterial MAMP receptors and germ-free mice is reduced which suggests that in skin carcinogenesis there may be a role for the microbiota [60–62].

Gut dysbiosis can promote cancer via long-distance mechanisms. The liver, which does not contain any known microbiome, is an example of it. Through bacterial metabolites and pro-inflammatory MAMPs that enter the liver through the portal vein, the gut microbiome may contribute to liver cancer [63]. This portal vein is responsible for the direct exposure of different components and metabolites from the gut microbiota to the liver. During the past decade a plethora of evidences are accumulating indicating the influence of gut-liver axis on the progression of liver disease from simple inflammation to fibrosis, cirrhosis and cancer as a major one [64]. Administration of clinically isolated strain of *Klebsiella pneumoniae* was shown to cause MASLD in mice model. This bacterium has also been reported to be associated with MASLD in human patients. Patients of HCC differ in their gut microbiota content from patients of liver cirrhosis without HCC. *Bacteroides spp.*

and *Ruminococcaceae* were found to be more abundant in HCC patients whereas *Bifidobacterium* abundance was lower [65]. Germ-free status in mice and non-absorbable antibiotics minimize hepatic inflammation and checks the growth of HCC [66].

In a study, the carcinogen 7, 12-dimethylbenz(a)anthracene was used to initiate oncogenesis in mice. HCC developed in those obese mice which were either leptin-deficient or were wild-type but provided with a high-fat diet, whereas cancer did not develop in genetically wild-type lean mice provided with a standard diet. Bacteria that were capable of transforming primary bile acids into DCA, were particularly overrepresented. Cluster IX of the genus *Clostridium* contains these bacteria. DCA being a carcinogen can cause DNA damage by free radical production and has been shown to be involved in liver and colorectal cancers. The obese mice had higher serum levels of DCA. DCA and *Clostridium* are functionally important, and to establish that some experiments were done. Firstly, when obese mice treated with 7,12-dimethylbenz(a)anthracene received a variety of antibiotic treatments, serum DCA levels were significantly reduced as well as the liver cancer phenotype. The antibiotics included Vancomycin, which kills Gram-positive bacteria including the overrepresented *Clostridium spp*. Secondly, two different strategies were used to diminish the production of DCA without the use of antibiotics. One of them was decreasing 7α-dehydroxylation activity using difructose anhydride III and the other one was stimulating bile acid secretion by ursodeoxycholic acid. The tumor phenotype was attenuated as a result of both [67].

4. Alteration of Microbiome During the Development of Cancer

Many studies have confirmed that as cancer develops in an organism; its normal microbiome gets affected. A study found that in the case of oral squamous cell carcinoma, three out of 40 studied microorganisms were elevated in the patients in comparison to healthy individuals [68]. The frequency of *Fusobacterium nucleatum* is increased in patients of colorectal cancer [69]. As mentioned in the previous section, it is well known that *H. pylori* is a cause of gastric carcinoma. It can also be said that the presence of *H. pylori* can indicate the risk of developing gastric cancer. So, as cancer progresses, the changes in microbiota can be detected as the studies throughout this review reveal. Discussed below are some possible mechanisms of transformation of the normal microbiome to cancer microbiome.

Microbes attach to their host cells with the help of adhesion molecules bound to their surfaces and their receptors present on the host cells [70]. Examples of such cell surface receptors include integrins, glycosaminoglycans, glycolipids, etc. Integrins are glycoproteins that are used by certain microbes such as *Treponema pallidum* [71]. Glycolipid receptors are used by *Mycoplasma hypopneumoniae*, glycosphingolipids are a type of glycolipid receptor which also act as a bacterial attachment site on cell surfaces. Studies have found that cell surface receptors of cancer cells differ significantly from the receptor found on normal cells. For example, fructose-containing glycopeptides are present on cancer cells surfaces more in number than that of normal cells. These alterations in cell surface receptors lead to alterations in normal microbe attachment to a cell. These changes enhance the attachment of certain microbes (which are not able to colonize in that specific site on normal cells surfaces) while it reduces or inhibits the attachment of other microbes which are actually present on normal cell surfaces. The electrical properties of cancer cells are also a factor in this regard. Cancer cells show more negatively charged surfaces than normal cells because they accumulate more negatively charged components [72,73]. This may lead to alterations in microbe attachment as well. Another important factor in this context is the heavily glycosylated, high molecular weight family of proteins called Mucins. Invading bacteria first interact with these mucins that line the epithelial cells of the host, causing inflammation. A transmembrane mucin glycoprotein called Mucin 1 (MUC1) is found on the surface of nearly all epithelial cells that interacts with invading microorganisms. This interaction has the potential to cause pro- or anti-inflammatory reactions. MUC1 functions as an immunomodulatory switch, acting as either pro- or anti-inflammatory during infection. The negatively charged extended sugar residues create a physical barrier, imparting an anti-adhesive characteristic on MUC1, preventing pathogen entry. Oligomers are formed by the chains of glycosyl residues, which give rise to a lubricating mucinous gel. This protects the epithelia from desiccation, pH changes, and microbial infection [74]. MUC1's heavily glycosylated extracellular domain functions as a barrier; yet, the intracellular cytoplasmic tail phosphorylation can activate downstream signaling pathways. MUC1 extracellular domain has the ability of bacterial attachment and thereafter getting shed from the epithelial surface. A signal might be triggered by this shedding that causes the cytoplasmic tail of MUC1 to be phosphorylated, controlling inflammatory reactions, epithelial cell adhesion, differentiation, and death. MUC1 therefore functions as a signaling receptor, sensing the external environment and activating internal signal transduction pathways. MUC1 is abundant on the mucosal surface of the stomach and is increased by *H. pylori* infection [75]. *H. pylori* has produced MUC1 oligosaccharide-specific adhesins and attaches to MUC1 on cultivated gastric epithelial cells. Despite this binding, there are fewer long-lasting adhesion events when MUC1-expressing gastric cells are cocultured with *H. pylori* because MUC1 is shed from the cell surface and covers the exterior of the bacterium. If the bacterial adhesins are deleted, the bacteria no longer adhere

Table 1. Changes in microbiota composition in case of various liver diseases in different organisms.

Organism	Disease	Location	Increase	Decrease	Reference
Balb/c mice - Female	CCl_4 induced fibrosis	Gut		*Clostridium leptum* *Clostridium coccoides*	Hurtado *et al*., 2011. [87]
C57BL/6J mice - Male	Western diet & CCl_4induced MASH	Gut	Erysipelotrichales	Bacteroidales Verrucomicrobiales	Carter *et al*., 2021. [88]
C57BL/6J mice - Male	HFD induced MASLD	Ileum	*Faecalibaculum*		Mu *et al*., 2021. [89]
		Cecum	*Escherichia-Shigella* *Faecalibaculum* *Fusobacterium* *Lachnospiraceae_XPB1014_group* *Ruminococcaceae* *F.* p-251-o5	*Barnesiella* *Faecalibacterium* *Parasutterella* *F. Muribaculaceae*	
		Colon	*Campylobacter* *Escherichia-Shigella* *Faecalibaculum* *Fusobacterium* *Ruminococcaceae_UCG-005*	*Allobaculum* *Alloprevotella* *Bacteroides* *Barnesiella* *Faecalibacterium* *Parasutterella* *F. Muribaculaceae*	
Sprague-Dawley rats-Male	CCl_4 induced cirrhosis	Left liver lobe & mesenteric lymph nodes (MLNs)	*Pasteurellaceae* *Erysipelotrichaceae* *Clostridiaceae* *Enterobacteriaceae* *Sutterellaceae* *Pseudoflavonifractor* *Clostridium XIVb* *Odoribacter* *Desulfovibrio* *Escherichia-Shigella* *Parasutterella*	*Acidaminococcaceae* *Paraprevotellaceae* *Bacteroidaceae* *Desulfovibrionaceae* *Prevotellaceae* *Akkermansia* *Parabacteroides* *Alloprevotella* *Bacteroides*	Shi *et al*., 2017. [90]
Sprague-Dawley rats-Male	CCl_4 induced cirrhosis	Ileocecal& MLNs	*Erysipelotrichia* *Betaproteobacteria* *Coprococcus* *Sutterella* *Candidatus Arthromitus*	*Desulfovibrio* *Ruminococcus* *Allobaculum*	Santiago *et al*., 2019. [91]

Table 1. Continued.

Organism	Disease	Location	Increase	Decrease	Reference
C57BL/6 mice- Male	HFD induced MASLD	Gut	Firmicutes Actinobacteria Verrucomicrobia Proteobacteria *Adlercreutzia* *Coprococcus* *Dorea* *Ruminococcus*	Bacteroidetes Tenericutes *Turicibacter* *Anaeroplasma*	Velázquez *et al*., 2019. [92]
C57BL/6 mice- Male	HFD induced steatosis (60% fat- Lard)	Gut	*Lactobacillus* *Clostridium coccoides* *Bifidobacterium* *Clostridium leptum*	*Enterobacteriaceae*	Gauffin Cano *et al*., 2012. [93]
Sprague-Dawley rats- Male	HFD induced steatosis (45% fat- Lard)	Gut	Firmicutes	Bacteroidetes	Mei *et al*., 2015. [94]
C57BL/6 mice- Male	HFD induced steatosis (45% fat- Lard)	Gut	Firmicutes	Bacteroidetes *Prevotella*	Seo *et al*., 2015. [95]
C57BL/6J mice - Male	HFD induced steatosis (60% fat- Lard)	Gut	Firmicutes Proteobacteria	Bacteroidetes Actinobacteria	Wang *et al*., 2015. [96]
Sprague-Dawley rats- Male	HFD induced steatosis (60% fat- Lard)	Gut	Firmicutes Verrucomicrobia *Akkermansia* *Helicobacter*	Bacteroidetes Proteobacteria *Bacteroides*	Monteiro *et al*., 2016. [97]
Sprague-Dawley rats- Male	HFD induced steatosis (45% fat- Lard)	Gut	*Bacteroides* *Prevotella* *Lactobacillus* *Faecalibacterium* *Blautia* *Sutterella* *Escherichia*	*Oscillospira* *Ruminococcus* *Clostridium*	Tian *et al*., 2016. [98]

Table 1. Continued.

Organism	Disease	Location	Increase	Decrease	Reference
Sprague-Dawley rats-Male	HFD induced steatosis (45% fat- Lard)	Gut	Proteobacteria	*Spirochaetae*	Feng *et al*., 2017. [99]
			Actinobacteria	*Quinella*	
			Collinsella	*Treponema*	
			Deferribacteres		
			Gemella		
			Streptococcus		
			Elusimicrobium		
C57BL/6J mice - Male	HFD induced steatosis (60% fat- Lard)	Gut	*Helicobacter*	Bacteroidetes	Porras *et al*., 2017. [100]
			Firmicutes	Bacteroidia	
			Proteobacteria	Betaproteobacteria	
			Bacilli	Erysipelotrichi	
			Clostridia		
			Deltaproteobacteria		
C57BL/6J mice - Male	HFD induced steatosis (60% fat- Lard)	Gut	Firmicutes	Bacteroidetes	Xu *et al*., 2017. [101]
			Helicobacter marmotae		
			Odoribacter		
			Anaerotruncus		
Sprague-Dawley rats-Male	HFD induced steatosis (60% fat- Lard)	Gut	Proteobacteria	Bacterioidetes	Chen *et al*., 2018. [102]
			Verrucomicrobia	Tenericutes	
C57BL/6J mice - Male	HFD induced steatosis (30% fat- Lard)	Gut	Saccharibacteria	Deltaproteobacteria	Ye *et al*., 2018 [103]
			Firmicutes	Bacteroidetes	
			Proteobacteria	*Porphyromonadaceae*	
			Bacilli		
			Ruminococcaceae		
			Helicobacteraceae		
			Coriobacteriaceae		
			Lactobacillaceae		
BALB/c mice	HFD induced steatosis (45% fat- Lard)	Gut	Firmicutes	Bacteroidetes	Duan *et al*., 2019. [104]
			Allobaculum sp.	*Prevotellaceae*	
			Lachnoclostridium	*Rikenellaceae*	
			Pseudomonas	*Bacteroidales*	

Table 1. Continued.

Organism	Disease	Location	Increase	Decrease	Reference
Wistar rats- Male	HFD induced steatosis (45%) cocoa butter	Gut	*Prevotella* *Akkermansia*	*Ruminococcus* *Oscillospira* *Clostridium*	Tian *et al*., 2016. [98]
C57BL/6 mice - Male	HFD induced steatosis (60%)	Gut	Firmicutes *Lactobacillales*	Bacteroidetes	Ishioka *et al*., 2017. [105]
C57BL/6J mice	HFD induced steatosis (60%)	Gut	Tenericutes Actinobacteria	Cyanobacteria	Xu *et al*., 2017. [101]
C57BL/6J mice - Male	HFD induced steatosis (38%) Milk fat	Gut	*Dorea* *Sutterella*	*Ruminococcus* *Bifidobacterium* *Akkermansia* *Parabacteroides*	Natividad *et al*., 2018. [106]
Human patients	Cirrhosis + HCC	Gut	*Bacteroidetes* *Ruminococcaceae*	*Bifidobacterium*	Ponziani *et al*., 2019. [107]
Human patients	Cirrhosis + HCC	Gut	Actinobacteria *Gemmiger* *Parabacteroides*	Verrucomicrobia	Ren *et al*., 2019. [108]
Human patients	HBV + HCC	Gut	*Escherichia-Shigella* *Enterococcus*	*Faecalibacterium* *Ruminococcus* *Ruminoclostridium*	Liu *et al*., 2019. [109]
Human patients	HCC	Gut	Fusobacteria *Sarcina* *Blautia*	Verrucomicrobia	Zheng *et al*., 2020. [110]
Human patients	Early HCC vs. late HCC	Gut	Enterococcaceae *Enterococcus* *Enterobacteriaceae*	Actinobacteria *Bifidobacteriaceae* *Bifidobacterium* *Lachnospiraceae* *Peptostreptocpccaceae* *Clostridales* *Coriobacteriaceae* *Christensenellaceae*	Zhang *et al*., 2021. [111]

HFD, high-fat diet; MASLD, non-alcoholic fatty liver disease; HCC, Hepatocellular Carcinoma; HBV, hepatitis B virus.

to the cells. MUC1 is not lost in this situation, but steric hindrance prevents non-MUC1-binding ligands from adhering to the cell surface [76]. Mice missing MUC1 had a fivefold increase in *H. pylori* colonization within one day of infection and developed atrophic gastritis with parietal cell loss [77]. According to one research, MUC1 is an intestinal receptor for enteroaggregative *E. coli* and interacts with the bacterial adherence fimbriae to promote attachment. Furthermore, it has been demonstrated that enteroaggregative *E. coli* infection increases MUC1 expression in inflamed human intestinal tissues [78]. In the event of *E. coli* infection, MUC1 works as a proinflammatory molecule by enabling *E. coli* access into gastric epithelial cells. The gut bacteria and the host epithelial mucus layer both play important roles in the large intestine's maintenance and defense. According to an increasing body of evidence, the breakdown of the gut's protective mucosal barrier plays an important part in the onset of colorectal cancer [79]. The disruption of the colonic barrier could increase colonocyte exposure to toxins from the colonic environment, hence boosting inflammatory processes and the generation of ROS, which can lead to carcinogenesis.

The immune response plays a major role in the colonization of the microbiome in the human body. The immune system discriminates between pathogenic and non-pathogenic bacteria using TLRs. For example, the bacteria *Bacteroides fragilis* produce a symbiotic factor that causes immunologic tolerance via the TLR2 receptor on the helper T cells [80]. A recent study has also established a correlation between TLR4 levels and lung cancer malignancy. In that study, TLR4 and TLR9 expression have been shown to increase in lung cancer [81]. Activation of certain TLR mediated pathways increase acute inflammation as well as wound healing and epithelial proliferation. If due to an altered microbiota the inflammation becomes chronic then this can lead to cancer. So, the expression of TLRs can alter the microbiota during cancer by mounting immune responses against certain bacteria.

Growth promoting hormones are always associated with the transformation of a normal cell to a cancerous one. Several studies have shown that these hormones are related to cancer cell proliferation in animal models as well as in cancer cell lines [82]. A study showed that hormones can alter the normal microbiome. Ovariectomized rats were compared with normal rats to see the differences in vaginal microbiota. Indeed, significant differences were found in the microfloral compositions of the two rat groups [83]. Another study showed that human gut microbiota can metabolize estrogen thus altering the hormone level in the body [84]. It is known that estrogen through estrogen receptors can drive neoplastic growth. Estrogen concentration is directly related to increasing the risk of breast cancer. As tumorigenesis progresses and the mass of the solid tumor increases, hypoxic conditions are generated due to an insufficient supply of oxygen. This condition can be favourable for the growth of certain bacteria over others [85]. Studies have revealed that more than 30 different types of intestinal microorganisms that are present in individuals with HCC might change in the early stages of the disease, demonstrating the importance of the gut microbiota in the formation and progression of HCC through various stages from a simple liver disease [86]. Alteration of gut microbiota associated to various liver diseases including liver cancer is show in Table 1 (Ref. [87–111]). Some of the above-mentioned mechanisms by which the eubiotic gut gets altered into dysbiotic gut is shown in the Fig. 2.

5. Mechanisms of Cancer Development

Microbiome can directly or indirectly promote cancer by various mechanisms. The immune system detects microbes by pattern recognition receptors (PRRs). These control the microbial population in our body by initiating the innate immune response and by producing antimicrobial substances. These substances not only kill cancer-promoting bacteria and suppress cancer, but can also prevent cells from dying thus trigger inflammation which is a major factor of carcinogenesis [112]. The microbiota modulates the development of cancer by releasing genotoxins which are carcinogenic in nature. Fig. 3 summarizes the mechanisms through which microbes may promote carcinogenesis.

Microbiome promotes cancer by stimulating cytokine and chemokine production through inflammation. TLRs are a kind of PRRs which sense the MAMPs and mount immune responses leading to inflammation. TLR4 is the receptor for sensing bacterial lipopolysaccharides (a constituent of Gram-negative bacteria's cell wall). Mice which are deficient of TLR4 show reduced tumor development as compared to controls, which suggest that TLR4 has some role in tumor development [113]. A similar kind of receptor named TLR2 senses peptidoglycan and lipoteichoic acid on the bacterial cell wall. It has been shown that this TLR2 promotes the development of gastric cancer [114]. TLRs promote cancer through myeloid differentiation primary response 88 (MYD88) pathway which in turn triggers the nuclear factor-κB (NF-κB) and signal transducer and activator of transcription 3 (STAT3) signaling pathways [113–115]. TLR2 present on the surface of Treg cells when senses 'polysaccharide A' present on the cell wall of *Bacteroides fragilis*, it causes immunogenic tolerance, and thus these bacteria can live within our gut. But when polysaccharide A is lacking from the cell wall of *B. Fragilis*, no tolerance is generated and T helper 17 response eliminates the bacteria from the system. This is an example of the mechanism of discriminating between 'good' and 'bad' bacteria by our immune system [80]. Another example showing the importance of the TLR signaling pathway in carcinogenesis is from TLR5 signaling. TLR5 is responsible for the recognition of bacterial flagellin. To confirm that the microbiome can alter the metabolism of an organism, a study showed that, TLR5 knockout mice showing symptoms of metabolic

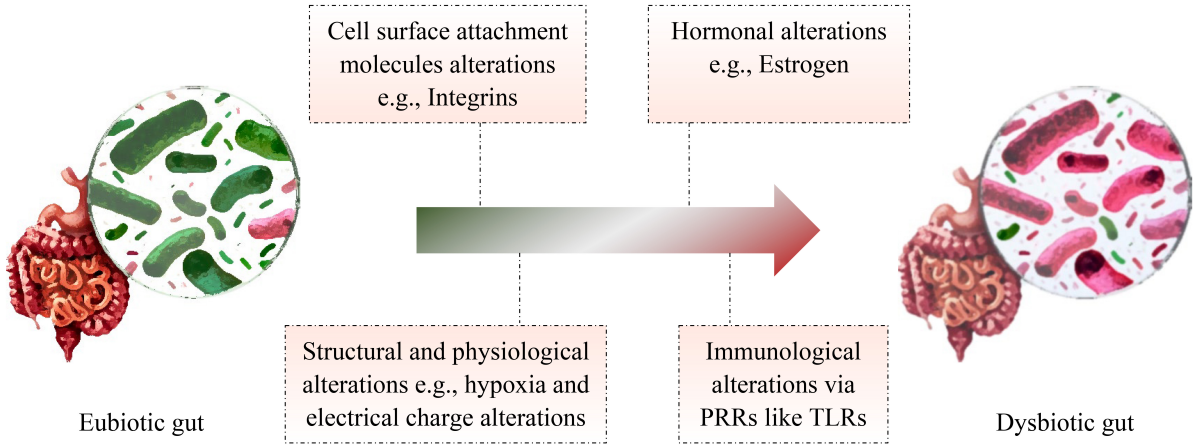

Fig. 2. Some of the possible mechanisms responsible for the alteration of eubiotic gut into dysbiotic gut. Alterations in cell surface attachment molecules, structural and physiological changes such as hypoxia and electrical charge changes, immunological changes via pattern recognition receptors (PRRs) such as toll-like receptors (TLRs), and hormonal changes can all contribute to gut dysbiosis.

disorders such as hyperphagia had significant changes in their microbiome. As the microbiota from these mice were transplanted into germ-free mice which were wild-type, the symptoms developed in the later [116]. Like TLRs, NOD-like receptors (NLRs) are also a kind of PRRs that have a nucleotide-binding oligomerization domain or NOD at its center. NOD2 is an NLR that senses muramyl dipeptide which is derived from peptidoglycan and is present on the cell wall of both Gram-negative and Gram-positive bacteria. The deficiency of NOD2 in mice leads to an increased incidence of colorectal cancer. NOD2 is very important for bacterial immunity because studies show that NOD2 knock-out mice are very much susceptible to bacterial infections. Recently a study showed that NOD2 deficiency promotes dysbiosis which eventually causes cancer [117].

Bacteria can contribute towards carcinogenesis via specific toxins. These toxins can either produce chronic inflammation which generates reactive oxygen species (ROS), thus causing genomic instability, or can directly damage DNA, both of which promote the development of cancer. Two examples of bacterial genotoxins are cytolethal distending toxin (CDT) produced by gram-negative bacteria and colibactin produced by the members of the Enterobacteriaceae family. Both of these toxins can induce genomic instability by damaging DNA directly causing double-strand DNA damage which activates the ATM-CHK2 signaling pathway [118–120]. The bacteria present in the lumen can establish direct contact with the host cells if the function of the barrier somehow gets altered and thus can deliver toxins directly. The most studied genotoxin is Cytolethal Distending Toxin (CDT) and is produced by several bacteria including *Helicobacter sp.* and *E. coli* [119]. CDT is made up of 3 subunits namely CdtA, CdtB and CdtC. CdtA and CdtC subunits bind to the host cell-surface and CdtB is delivered into the cytoplasm. The CdtB subunit exhibits DNase activity and induces double-strand DNA breaks. Thus, CDT arrests the host cells in the G2/M phase of the cell cycle, resulting in enlarged cells [120]. Along with genotoxins, metabolites that are derived from bacteria may cause genomic instability. *Enterococcus faecalis* can promote colorectal cancer in IL-10 knock-out mice by generating a hefty amount of superoxide which causes double-strand DNA damage and instability of chromosomes. ΔmenB, a mutant strain of *E. Faecalis* which cannot produce extracellular superoxide, is not able to promote the development of cancer in IL-10 knockout mice [121].

The microbiome is responsible for the fermentation of proteins as well as carbohydrates inside our gut. Ammonia, phenols, nitrosamines, sulfides, etc are generated via protein fermentation by microbes mainly in the distal colon which are toxic and potential carcinogens [122]. Microbiota plays key roles in bile acid metabolism via many kinds of hydrolases, thereby changing bile acid composition in our gut. A study suggesting how a high-fat diet can increase the levels of DCA which is a secondary bile acid and can lead to cancer has been discussed in section 3. On the other hand, short-chain fatty acids are generated as a result of the fermentation of carbohydrates such as butyrate. Cancer preventing the role of butyrate as a prebiotic will be discussed in section 7.1 of this review. Lastly, alcohol metabolism is also related to microbiota which is a major causative agent of cancer worldwide. Alcohol is metabolized into acetaldehyde and ROS is also generated in this process, both acetaldehyde and ROS contributes to cancer. Germfree mice have a significantly lower level of acetaldehyde compared to normal mice which indicates that there might be a relation between microbiota and acetaldehyde production [123].

From cholesterol, Bile acids (BAs) are made. The enterohepatic circulation of BAs plays a crucial part in preserving the gut-liver axis' homeostasis. The transformation, conjugation, reabsorption, and deconjugation of primary BAs into secondary BAs are all processes that the gut microbiota participates in throughout the metabolism of BAs. By altering the content and quantity of BAs, important bile acid metabolic stages can affect homeostasis [124]. When BAs build up to large concentrations, they directly impact liver cells [125]. The breakdown of BA hemostasis is seen as a negative aspect. Through fibrosis, oxidative stress, and resistance to apoptosis, the altered BA metabolism can encourage carcinogenesis [126]. Secondary BAs encourage hepatic inflammation and carcinogenesis in MASLD-related HCC via the mTOR signaling pathway [127]. Shen *et al.* [128] in mouse model discovered that in case of both *in vitro* and *in vivo* studies, reducing gut bile salt hydrolase (BSH)-rich bacteria (i.e., *Bacteroidales Clostridiales, Lactobacillales, Bifdobacteriales*) significantly reduced serum conjugated DCAs, a result that may be linked to the development of HCC. SCFAs exhibit metabolic and immunologic effects on carcinogenesis, similar to BAs. Acetate, propionate, and butyrate make up the majority of SCFAs, which are by-products of gut microbiota's colonic fermentation of dietary fiber [129]. Through G-protein-coupled receptors GPR43 and GPR41, SCFAs affect the genes involved in fatty acid oxidation, ROS genesis, lipogenesis, and insulin sensitivity to change metabolism [130,131]. By improving epithelial integrity, SCFAs reduce systemic endotoxemia. Additionally, SCFAs prevent histone deacetylases (HDAC), which has an impact on gene transcription. In immunomodulation, SCFAs have a complex role to play [132]. The fermentation of glucose in the intestines is able to make ethanol. *Klebsiella pneumonia*, *Saccharomyces cerevisiae* and *Candida spp.* are among the organisms that have the ability to create endogenous ethanol [131]. The prevalence of ethanol-producing bacteria is higher in MASLD and obese patients, and it has been discovered that serum ethanol levels are much higher in these patients than in healthy individuals, even in the absence of alcohol consumption [133,134]. The well-known carcinogen ethanol interacts with other risk factors in the liver to cause cancer. It has been determined that increased free radicals and ROS caused by the metabolism of alcohol, are crucial factors in the development of hepatocarcinogenesis. In the development of HCC, Hepatitis B and C virus have a major role to play. Compared to healthy controls, patients with persistent liver cirrhosis, HBV infection and HCC had less dysbiosis, notably a reduced abundance of Firmicutes and a greater abundance of Bacteroidetes. In the meantime, persistent HBV infection was associated with an increase in genes involved in glycan production, metabolism, and lipid metabolism. In comparison to healthy controls, individuals with HCV and HBV infection showed greater plasma levels of lipopolysaccharides (LPS), IL-6, sCD14 generated upon LPS activation of monocytes, and intestinal fatty acid binding protein [134].

6. Gut Microbiota as a Non-Invasive Marker for Cancer

A biomarker is an indicator of an organism's or disease's presence, severity, or a physiological condition. Biomarkers, in cancer biology, are used as diagnostic tools to identify diseases, prognostic markers to forecast outcomes, and predictive markers to forecast the effects of therapy. Certain of these markers have prompted paradigm shifts in patient management in favor of personalized therapy. The potential of a few metagenomic indicators for cancer diagnosis will be discussed in this section.

New evidence points to dysbiosis of the gut microbiota to be used as a potential non-invasive tool for the early detection of a number of malignancies. Even though *Helicobacter pylori* infection is linked to 70% of gastric cancer, this bacterium is not a useful screening sign. In fact, only 1–4 percent of those with *H. pylori* infection go on to acquire gastric cancer. *Faecalibacterium, Desulfovibrio, Escherichia*, or *Oscillospira* were intriguingly found by Liu *et al.* [135] as fecal biomarkers to accurately predict gastric cancer with a 90% or higher rate of success. Patients with cancer in other parts of their bodies have been reported to have gut microbiota dysbiosis. A gut microbiota imbalance has been linked to breast cancer in increasing numbers of studies [136]. One potential application of the gut microbiota may be as an important biomarker in breast cancer research, according to several studies that found that women with breast cancer had a variable composition of gut microbiota, with elevated levels of *Faecalibacterium*, *Ruminococcaceae, and Clostridiaceae*, and decreased levels of *Lachnospiraceae and Dorea* in comparison to paired healthy controls [137]. In a study by Zhuang *et al.* [138] comparing the gut microbiota of 30 people with lung cancer to 30 healthy controls, it was discovered that controls had higher concentrations of the bacterial phylum Actinobacteria and the genus *Bifidobacterium*, while lung cancer patients had elevated levels of *Enterococcus*, suggesting that these bacteria could be used as potential biomarkers for the disease. One very interesting study by Bhandari *et al.* [139] showed a strong relationship between the volatile metabolites in exhaled breath and the fecal microbiota, as they varied between cancer patients and healthy controls. Since gastric cancer has been linked to changes in the volatile metabolic profiles and dysregulation of the gut microbiota, its composition, and the associated metabolic pathways, the exhaled breath analysis and fecal microbiome analysis were combined, and they may now be used as non-invasive diagnostic and screening tools for the disease.

Ren *et al.* [108] showed that transition of cirrhosis to early HCC with cirrhosis increased fecal microbial diversity. Actinobacteria, as opposed to cirrhosis, were more prevalent in early HCC. In contrast, early

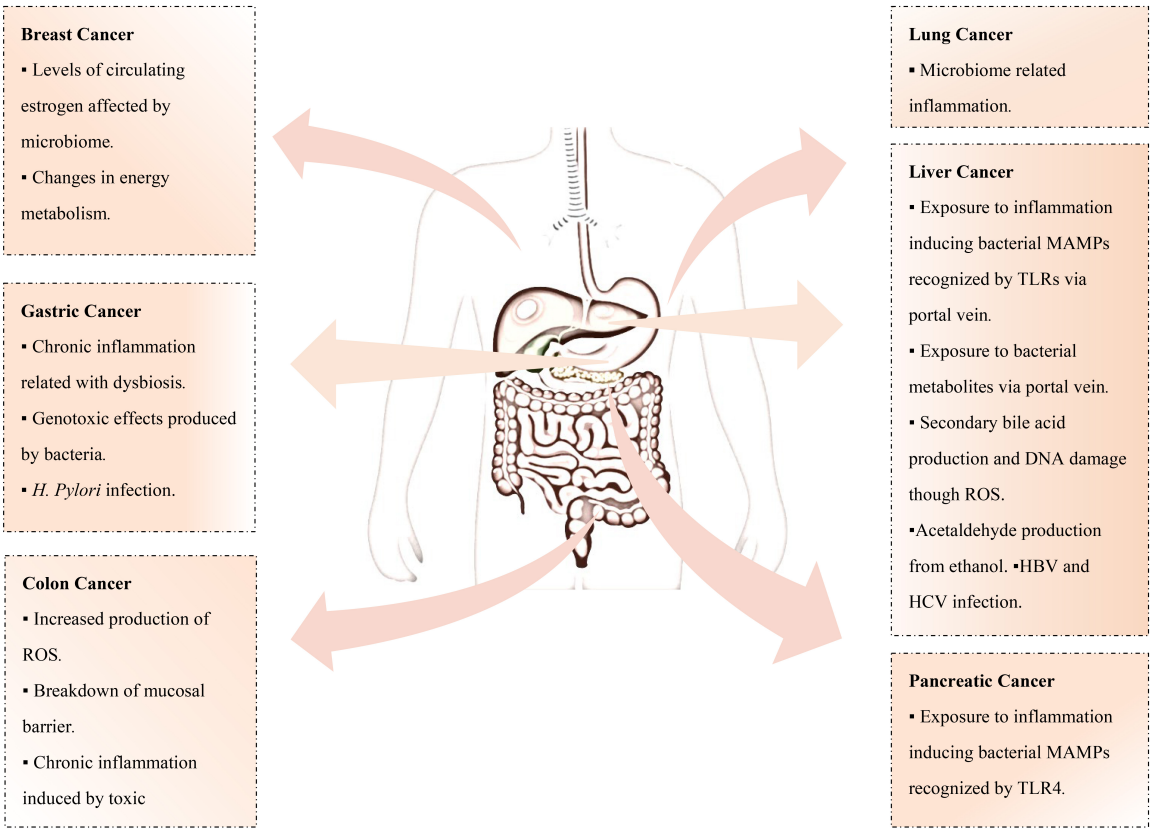

Fig. 3. Mechanisms of carcinogenesis by human microbiota. Changes in hormones and energy metabolism, for example, can cause breast cancer. Chronic inflammation and genotoxic chemicals can cause lung, stomach, and colon cancer. *H. pylori* infestation can also result in stomach and colon cancer. Toll-like receptors (TLRs) identify microbe-associated molecular patterns (MAMPs), which can cause liver and pancreatic cancer. Bacterial metabolites, secondary bile acids, ROS production, acetaldehyde formation from ethanol, and hepatitis B and C virus infection can all cause liver cancer.

HCC was enriched in 13 taxa, including *Gemmiger* and *Parabacteroides*. In early HCC compared to controls, butyrate-producing genera were downregulated whereas LPS-producing genera were upregulated. Through fivefold cross-validation on a random forest model, the ideal 30 microbiological markers were found, and they produced an area under the curve of 80.64% between 75 early HCC and 105 non-HCC samples. Gut microbial indicators confirmed a substantial propensity for early and even advanced HCC [108]. According to Komiyama *et al*. [140], the microbiota that is associated with tumors includes Actinobacteria, Bacteroidetes, Firmicutes, and Proteobacteria. *Ruminococcus gnavus* was also discovered to be a distinctive taxon for people with viral hepatitis-related HCC. Despite the fact that the level of dysbiosis was independent to the HCC stage, Ni *et al*. [141] discovered that patients with HCC had more pro-inflammatory gut bacteria and dysbiosis than healthy controls. However, other researchers have noted links between the HCC stage, gut microbiota alterations, and dysbiosis. *Escherichia coli* counts in the feces were greater in patients with HCC, according to a prospectively matched analysis of 30 cirrhotic patients reported by Grat *et al*. [141] which had a sensitivity of 66.7% and a specificity of 73.3% when predicting the existence of HCC based on *Escherichia coli* counts. Piero *et al*. [142] used a comparable sequencing apparatus to study 407 patients. Comparing the HCC group to cirrhotic individuals without HCC, the HCC group had a three-fold increase in *Erysipelotrichaceae* and a five-fold drop in the *Leuconostocaceae*. Patients with HCC had significantly lower levels of the *Lachnospiraceae* bacteria *Fusobacterium* and *Dorea*, but *Odoribacter* and *Butyricimonas* were reported to be more significantly enriched in HCC.

One critical point to consider while conducting these gut microbiota based biomarker researches is; age, gender, BMI, food, and antibiotic use are some of the variables that affect the gut microbiome's inter-individual variance and macro- and microscopic morphological variability. So, the research outcome may not be the same in every case, and further research is necessary to standardize these in the hope for developing a potential gut microbiota based biomarker for cancer.

7. Gut Microbiota Targeted Cancer Therapeutics

Bacteria plays dual role in cancer by supporting the tumor growth or by suppressing it. Keeping this in mind, modulating the microbial community inside the gut might be beneficial in prevention or treatment of cancer. To accomplish this goal, multiple approaches (shown in Fig. 4) have been taken into consideration such as antibiotics, fecal microbiota transplantation (FMT), probiotics, prebiotics, synbiotics, nanoparticles and bacteriophages.

7.1 Probiotics, Prebiotics and Synbiotics

Live microorganisms known as probiotics are meant to improve or restore the microbiota in the gut in order to promote health. Probiotics are generally considered to be safe to consume, however they can cause bacterial-host interactions that have negative side effects [143]. Researchers have shown that, *Bifidobacterium* probiotics when administered orally followed by the anti-CTLA-4 drug Ipilimumab can check colitis without hampering the efficacy of the drug in mouse models [144]. Irinotecan, a topoisomerase I inhibitor, is used as an anti-cancer drug for colon and lung cancer. Bacterial β-glucuronidase extensively deconjugate SN-38G in the intestinal lumen regenerating SN-38 which is responsible for the onset of diarrhea. The severity of diarrhea can be lowered by supplementation of *Bifidobacterium bifidum* with *Lactobacillus acidophilus* during pelvic radiotherapy [145]. Diverse gut microbiota based approaches have been taken to control Irinotecan-induced-diarrhea by administering antibiotics or supplementation of probiotics. The widely available probiotic VSL#3 has been shown to reduce the degree of liver disease and hospitalization in cirrhotic individuals [146]. Prohep, a probiotic blend made up of *Escherichia coli* Nissle 1917, *Lactobacillus rhamnosus* GG, and VSL#3, can effectively block angiogenesis, regulate the subset of $CD_4{}^+$ T cells, and enhance SCFA-producing bacteria, resulting in a 40% reduction in tumor weight and size in mice [147]. By influencing host-mediated epigenetic regulation, probiotics can also lower the incidence of HCC. *Lactobacillus acidophilus* and *Bifidobactrum bifidioum* have been shown by Heydari *et al*. [147] to adversely affect oncogenic microRNAs expression in HCC cancer mice. According to Mihailovi *et al*. [148], the probiotic *Lactobacillus paraplantarum* BGCG11 can lessen DNA damage and boost Akt activity, which may prevent cell carcinogenesis. Supplementing with probiotics can prevent the growth of HCC by reducing liver inflammation brought on by TLR. Probiotic treatment improved intestinal homeostasis, decreased exotoxin levels, and suppressed tumor cell growth in the DEN-induced HCC model [149]. Additionally, *Lactobacillus plantarum* can stop the development of liver cirrhosis by drastically reducing the expression of CXCL9, TLR4 and phosphatidylinositol 3, 4, and 5 trisphosphate RAC exchanger 2 (PREX-2) [150]. Probiotic treatment also increased the expression of a number of anti-inflammatory cytokines, such as IL-27, IL-13, and IL-10. In mice fed a specific probiotic combination, downregulation of angiogenic factors and receptors, including vascular endothelial growth factor A (VEGFA), Fms related receptor tyrosine kinase 1, Angiopoietin- 2 (ANGPT2), and kinase insert domain receptor, was seen [147]. All probiotic species do not, however, exhibit identical immunomodulatory effects on the gut microbiota. Consider the several *Lactobacillus spp.* strains that have been linked to both pro- and anti-obesity actions [151].

Prebiotics are substances present in food which foster the growth or activity of beneficial microorganisms. Prebiotics have the potential to alter the composition of the gut microbiome [152]. Pure polyphenols and polyphenol-rich meals, together with conventional diets, have been proven to confer health advantages via maintaining the gut's beneficial microbiota [153]. By modulating the immune system, polyphenols are known to exhibit chemopreventive effects in HCC [154]. Tea phenols may contribute to maintaining excellent gastrointestinal health since they have been shown to have beneficial effects on the population of gut microbes and to suppress harmful bacteria [155]. Additionally, tea polyphenols are a powerful substitute for HCC chemoprevention and treatment [156]. One of the most prevalent non-digestible oligosaccharides that have been recognized as having a functional role in nature is lactulose [157]. Lactulose administration speeds up the regeneration of the liver after hepatectomy in rats, which may be the result of reducing oxidative stress and inflammation [158]. After interventional therapy, lactulose, when taken orally, could balance out the imbalance of the antioxidant and oxidative systems in patients with HCC who also have hepatocirrhosis and hypersplenism, lessen liver injury, and enhance antitumor immunity and prognosis [159]. The use of Cordyceps sinensis polysaccharides (CSP) had an effect on the differentiation of T helper cells through upregulation of TLR and NF-κB components in mice treated with Cyclophosphamide. The SCFA level was increased and the gut microbiota composition was affected as well. Thus, to alleviate the side effects of Cyclophosphamide, CSP was put forward as a prebiotic [160]. In melanoma patients, Ipilimumab efficacy was shown to be increased after anti-CTLA4 treatment followed by an increase in *Bacteroides fragilis* abundance [161].

A synbiotic is described as a "mixture of probiotics and prebiotics that beneficially affects the host by improving the survival and activity of beneficial microorganisms in the gut" [152]. The major prebiotics used to make symbiotic formulations include oligosaccharides like fructooligosaccharide (FOS), xyloseoligosaccharide (XOS), inulin, natural sources of prebiotics like chicory and yacon roots, etc. The used probiotic strains are *Lacbobacillus spp.*, *Bifidobacteria sp.*, *S. boulardii*, *B. coagulans*, etc. Individuals who consume synbiotics are said to experience the following health benefits: (1) Higher numbers of *lactobacilli* and *bifidobacteri* and a healthy gut flora, (2) im-

provement in cirrhotic patients' liver function, (3) improved immunomodulating ability [162,163]. In a study by Tang *et al*. [164], there were eight Randomized controlled trials (RCTs) with 445 participants total. In hepatopancreatobiliary cancer patients, supplementation with probiotics or synbiotics considerably decreased the incidence of postoperative infection; probiotics and synbiotics were equally efficient in doing so. Probiotics or synbiotics can also shorten hospital stays and the amount of time spent on antibiotics. Hepatic tumors and liver cirrhosis are frequently the last stages of a chronic liver disease. The most common form of treatment is surgery, either liver resection (LR) or liver transplantation (LT). Protocols are not present for usage of Pro-/synbiotics in the therapy for LR and LT according to the most recent recommendations of the American Association for the Study of Liver Disease (AASLD) and European Association for the Study of the Liver (EASL), whose benefits are still being debated [165].

7.2 Antibiotics

Antibiotics can kill bacteria or inhibit their growth by checking DNA transcription, synthesis of proteins and various other processes. Antibiotics are typically used to eradicate harmful bacteria and regulate the microbiota in the stomach [166]. Antibiotic exposure affects a sizable fraction of cancer patients. Different cancer kinds have different antibiotic prescription rates, with patients of lung cancer receiving more frequent and more extensive prescriptions than those of melanoma. It is unknown to what extent this variation contributes to the substantially superior outcomes of immunotherapy in melanoma [167]. Significant changes in the microbiota's composition result in increased microbiota dysbiosis and decreased immunotherapeutic effectiveness, both of which are directly related to cancer. These changes are caused by the widespread use of broad-spectrum antibiotics, which breeds antibiotic resistance. A dysbiosis of the intestinal microbiota caused by cirrhosis results in an increase in immunosuppressive bacteria and a decrease in helpful bacteria which may eventually lead to cancer [168]. In the context of immune checkpoint inhibitor (ICI) medication, a rising body of evidence points to the host microbiome—which is commonly affected by antibiotic treatment—as a significant outcome predictor. Patients who received ICIs and tyrosine kinase inhibitors (TKIs) for various cancer types had poorer survival rates when taking antibiotics [169]. A reduction in *Bifidobacterium* and an increase in gram-negative bacteria like *Escherichia coli* and *Bacteroides spp.*, have been observed in studies using mice models, which is likely a factor in the development of HCC [170]. Intestinal dysbiosis and bacterial translocation are common in patients with advanced chronic liver disease (ACLD), which may induce impaired immune function via the gut-liver axis [171]. To check the early effects of antibiotics on HCC patients, Pinato *et al*. [169] studied 4098 patients of HCC and concluded quite an intriguing result. Patients receiving treatment with tyrosine kinase inhibitors and immune checkpoint inhibitors, and placebo all showed worse outcomes when exposed to antibiotics early. This highlights the distinction between hepatocellular carcinoma and other malignancies considering the intricate interactions between cirrhosis, cancer, infection risk, and the pleiotropic effects of this disease's molecular therapies. Anti-PD-1, anti-PD-L1, and anti-CTLA-4 drugs were among the immunotherapy substances that were investigated. Bevacizumab, Cabozantinib, Ramucirumab, Sorafenib, Lenvatinib, and Regorafenib were among the TKIs and VEGF inhibitors investigated [169]. A probable reason for why antibiotics had an impact on the poor prognosis of HCC patients receiving ICIs is because they disrupted the immunosuppressive relationship. Due to the extensive recruitment of myeloid suppressor cells and macrophages, HCC has an immunosuppressive tumor microenvironment that is unique from that of lung and melanoma malignancies [172]. According to Singh *et al*. [173], Vancomycin can reduce secondary BAs and SCFAs, which can prevent the growth of liver cancer in mice with TLR5 deficiency that are administered insulin. However, due to its potential negative effects, it is not advised for use in the treatment of HCC. Additionally, Norfloxacin treatment effectively decreased the recurrence of spontaneous bacterial peritonitis in liver cirrhosis and preferentially removed aerobic gram-negative bacilli from fecal flora [174]. Norfloxacin treatment has a significant drawback in that drug resistance can quickly arise, making it challenging to meet the long-term demand for HCC prophylaxis [175]. Furthermore, Fujinaga *et al*. [176] discovered that Rifaximin can dramatically lessen liver fibrosis by suppressing the LPS-TLR4 signaling pathway, lowering portal endotoxins, and reducing intestinal permeability. The lack of significant adverse effects on the gut flora of Rifaximin is a benefit. Since Rifaximin has not been associated with any clinically significant drug resistance, unlike Norfloxacin, it may be appropriate for long-term use [8]. However, further research is still needed to determine how Norfloxacin and Rifaximin affect the growth of HCC. Due to their anti-infection and anti-cancer actions, antibiotics are frequently employed as adjuvant medications in the course of surgical treatment, radiation, immunotherapy, and chemotherapy of malignancies [177]. Antibiotic resistance and its negative effects on the reproductive system are a growing worry, though. antibiotics, by disrupting the gut flora, can also lessen the effectiveness of surgery, radiation, chemotherapy, and immunotherapy when used in combination [178]. It makes sense to utilize probiotics and prebiotics to lessen the side effects of antibiotics in cancer treatments because the procancerous effects of antibiotics are primarily brought on by their detrimental influence on gut flora.

7.3 Fecal Microbiota Transplantation

To restore eubiosis, FMT has been shown to be the quickest amongst all the approaches. Along with different bacterial strains, feces also contain proteins, bile acids and bacteriophages which have significant role in microbiota modulation [179]. FMT, which got its start in Traditional Chinese Medicine (TCM) more than 1700 years ago, is now regarded as a legitimate technique for altering the flora in the gut to cure disease [180]. To re-establish fresh intestinal flora and treat both intestinal and extraintestinal disorders, fecal microbiota transplantation involves transferring fecal samples from healthy people to the patient's gastrointestinal tract in a number of ways [181]. It can be given either through the lower gastrointestinal system, such as by colonoscopy or enema, or through the upper gastrointestinal tract, such as the duodenal tube or oral capsules [182,183]. FMT has grown quite mature and drawn more attention over the past ten years [184]. FMT is safe and simple to use, however after certain patients died from the therapy, questions have been raised. Even though *E. coli* is naturally present in the feces of healthy donors, it is the cause of death in the patient who received FMT [185]. As evident from the previous example. developing efficient and secure microbiome-based therapeutics requires identifying such harmful species and comprehending processes that encourage their cohabitation [186]. In a MASH mouse model established by a high-fat diet, Zhou *et al*. [187] demonstrated that FMT not only raises the amount of butyrate and lowers the endotoxin levels, but also enhances intrahepatic immunity. In addition, Wang *et al*. [188] hypothesized that FMT would mitigate systemic inflammatory response and prevent intestinal mucosal barrier degradation in animals with hepatic encephalopathy. Furthermore, immunocompromised individuals with *Clostridium difficile* infection who got FMT showed no illnesses, proving the effectiveness of FMT in clinical practice [189]. There hasn't been any research done on how FMT directly affects the growth and development of HCC. FMT may control irregularities in the intestinal flora and lessen the production of cytotoxins to prevent the development of HCC in people with hepatitis B cirrhosis [190]. Additionally, FMT can alter the gut microbiome to prevent colitis and toxicity linked to ICI [191], suggesting that other mechanisms like the immunological microenvironment may also be at play in FMT's influence on HCC. Very few researches have been conducted on the role and mechanism of FMT in HCC treatment and additional research is required to demonstrate the safety of FMT in patients with HCC.

7.4 Nanomaterials as Modulator of Gut Microbiota

In molecular biology and medicine, nanoparticles with distinctive optical features, simple surface chemistry, and the right size scale are sparking a lot of interest. Noble metal nanoparticles' increased light scattering and absorption caused by surface plasmon resonance (SPR) has enormous potential for cancer diagnosis and therapy. Imaging and cancer detection at the molecular level are made possible by the conjugation of nanoparticles to ligands that are selectively targeted to biomarkers on cancer cells [192]. Since nanomaterials are effective at preventing cancer, it has been hypothesized that they can also change the microenvironment of cancer by affecting the microbiota that causes it and its metabolites as well. The body tissue of *Eudynerus crypticus* was found to significantly accumulate copper nanoparticles (CuNPs) and change the composition and diversity of the gut microbiota, particularly of bacterial species. In the guts of *E. crypticus*, the CuNPs also dramatically decreased the variety and enrichment of antibiotic-resistance genes [193]. In several consumer goods, including whitening agents, meals, pharmaceuticals, and personal care items, Titanium dioxide nanoparticles (TiO_2NPs) are used as an essential component. It was discovered that the TiO_2NPs can have a potent antibacterial effect on both the gut microbiota and the skin microbiome, including *Staphylococcus aureus* [194]. The production of ROS, which in turn damages the microbial cell wall or cytoplasmic membrane, was the postulated mechanism for the toxicity of TiO_2NPs [195]. When compared to the control group, adult male mice fed with TiO_2NPs had different microbiota compositions, including less diversity of *Bifidobacteria*. The microbial abundance was considerably changed by feeding mice a diet based on TiO_2NP, with *Proteobacteria/Bacteroides* levels rising and *Prevotella* levels falling [195]. In the duodenum, curcumin-inulin nanoparticles can serve two purposes. The release of 90% curcumin and the prebiotic activity of inulin may be important in the development of future cancer therapies [196]. Additionally, nanoparticles may be able to supply a complex of nanomaterials and prebiotics, which in turn aids in controlling the beneficial bacterial metabolism and has recognized anti-cancerous properties. Using stimulus-responsive discharge processes, nanomaterial/prebiotic complexes offer a unique way to deliver targeted prebiotics to certain microbial species in the gastrointestinal system or to target specific microbial species [197]. In comparison to the control group, mice given Zn-based nanomaterials had higher abundances of *Bifidobacteria, Lactobacillus, Clostridia*, and SCFAs in their feces. Additionally, compared to the control group, the elevated amounts of SCFAs enhanced the induction of anti-inflammatory activity [198]. Thus, the gut microbiota and also the metabolites produced by it can be affected by nanoparticles. Since changes in microbial metabolite levels are associated with a variety of physiological circumstances, nanomaterials may be used to change the amounts of bacteria that cause cancer and the metabolites they produce to cure a variety of cancers. Tumor-associated bacteria and the metabolic products they produce offer a potential target for interference that can distinguish tumorous tissues from healthy tissues with ease. To release the medicine at the distal tumor site, tumor-associated bac-

teria generate compounds that catalyze the breakdown of Doxorubicin-loaded nanomaterials. For instance, a nanogel system based on nanomaterials was created to neutralize bacterial lipase and release Doxorubicin into the tumor microenvironment. Furthermore, in vitro testing demonstrated that H22 hepatic cancer cell cytotoxicity was triggered by the release of doxorubicin by bacterial lipase [199]. By combining ginsenoside Rg3 with Fe@Fe_3O_4 nanoparticles, which have a fantastic coupling effect, a new kind of nanomedicine has been created by Ren *et al*. [200]. Ginsenoside Rg3 nanoparticle conjugation dramatically increases the survival of HCC mice in the DEN-induced spontaneous HCC model. According to more research, NpRg3 treatment dramatically reduces the growth of HCC and prevents its metastasis to the lungs. Notably, NpRg3 slows DEN-induced changes in gut microbial composition and ileocecal shape by more than 12 weeks during the development of HCC. NpRg3 treatment increases the abundance of Bacteroidetes and Verrucomicrobia but decreases Firmicutes in terms of bacterial composition and gene function [200]. In dystrophin-utrophin double knockout (DKO) mice fed normal chow (NC) (MASH model), SMAPoTN treatment reduced MASH, while in DKO mice fed a high fat diet (HCC model), SMAPoTN treatment stopped the development of HCC. Through a mechanism related to the decrease in ROS, SMAPoTN, which was created utilizing redox polymers containing antioxidant nitroxide radicals, prevented inflammation and fibrosis in the livers. Additionally, the study discovered that the SMAPoTN treatment may enhance several probiotic-related bacteria, such as lactate-producing *Lactobacillaceae*, which are known to support healthy intestinal barrier function [201]. Nanoparticles can therefore be employed to both directly destroy cancer cells and modify the gut microbiome.

7.5 Bacteriophages

Bacteriophages or phages are a group of prokaryotic viruses that can be icosahedral (T4, T7) or filamentous (M13), or both. When they infect a bacterial host cell, they can start a lytic or lysogenic cycle [202]. Bar *et al*. [203] in the year 2008 demonstrated that phages can be used in the form of tailored drug-carrying nanoparticles. Filamentous bacteriophages were chemically and genetically altered to show a ligand that confers host specificity. Chemical conjugation was used to load the phages with a sizable payload of a lethal medication. The drugs used were, doxorubicin coupled to genetically altered cathepsin-B sites on the phage coat, hygromycin covalently bonded to the phages, anti-ErbB2 and anti-ERGR antibodies as targeting moieties. Endocytosis, intracellular breakdown, and drug release from phage nanomedicines targeted by certain antibodies to receptors on cancer cell membranes resulting in growth suppression was demonstrated [203]. Cancer-causing microorganisms can also be lysed by bacteriophages. *Fusobacterium nucleatum*, a source of cancer, can be eliminated by bacteriophages derived from human saliva. The bacteriophage based on human saliva was created to make chemistry-based connections to nanomaterials simpler, which led to improved nanomaterials that target *F. nucleatum* sites in colorectal cancer [204]. Additionally, the bacteriophages are extremely specialized and could kill only one type of bacterial species while sparing others. The bacteriophage based on human saliva, for instance, showed very little inhibition against five different bacterial strains. The virus had no effect on the strain of *Clostridium butyricum*, which can inhibit the formation of colorectal cancer and secretes short-chain fatty acids. The use of phages in the treatment of gastrointestinal and chronic liver disease has been the subject of numerous clinical trials and case reports [205]. Dextran sulfate sodium (DSS)-induced colitis was not observed in mice who received phage against adherent-invasive *E. coli* [206]. Phage therapy for alcoholic liver disease has produced encouraging outcomes. The intestine cytolytic strain of *E. faecalis* could be destroyed by four phages found in sewage. When these phages were administered intragastrically to $Atp4a^{Sl/Sl}$ mice, the liver damage, steatosis, and inflammation brought on by prolonged ethanol consumption were considerably reduced [207].

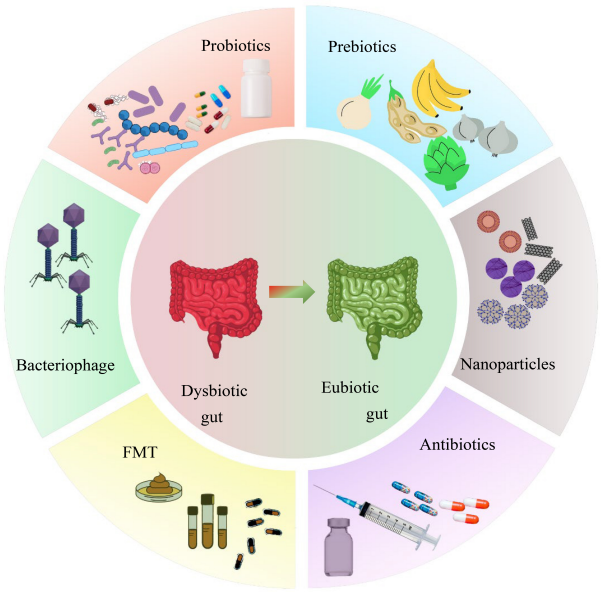

Fig. 4. Therapeutic approaches to restore eubiosis in a dysbiotic gut. There are several approaches to restoring intestinal eubiosis. Probiotics and prebiotics are being utilized to target gut microbiota restoration and have been the subject of current research, including clinical trials. Different types of nanoparticles are being studied in this area. Antibiotics are employed in this respect, with different effectiveness when administered alone or in combination with all of the aforementioned. Another promising technique is fecal microbiota transplantation (FMT). Bacteriophages may potentially be utilized to target eubiosis restoration/maintenance as a unique method.

8. Summary

Researchers from all over the world are conducting a sizable number of studies to learn more about the relationship between the microbiome and cancer. However, very little is known about how the microbiome really causes cancer. The majority of these studies are concentrated on identifying the evidence of the microbiome's link with cancer. The development of this field of study has led to the discovery of numerous previously unknown fresh insights. Clarification of the link between the microbiome and cancer has prompted researchers to concentrate on how to alter gut microbiota in order to restore eubiosis for the treatment of other diseases in addition to cancer, as well as the potential function of microbiota as a biomarker to detect cancer at an early stage. By altering the gut microbiome, which is a topic of intense research right now, antibiotics may be utilized to treat cancer. Antibiotics can be harmful to our health when used excessively, but when used carefully and selectively against specific microbial populations, they can improve treatment outcomes. However, there also exists evidence indicating that using antibiotics excessively can have the opposite effect, making cancer therapy less effective for patients. Bacteriophages that have been demonstrated to be just as effective as antibiotics are now being tested for the treatment of several diseases by modifying the microbiota, and this also applies to the treatment of cancer. Without disrupting the populations of commensal bacteria that are not bacteriophage targets, these viruses destroy bacteria very selectively. Presently, phage display is being considered as a cancer therapy strategy. Phage particles that display a specific peptide of its surface may be used to identify cell-specific targeting molecules, identify cancer cell surface biomarkers, identify anti-cancer peptides, and develop peptide-based anticancer therapy [208]. Prebiotics, probiotics, and synbiotics are already being used successfully to alter the composition of the gut microbiota in order to prevent or treat cancer. Probiotics that are sold commercially are openly available and accessible to everyone on the market. Cancers can be identified using tumor microbiota signatures unique to that tumor, and they can be targeted to stop cancer from progressing and enhance treatment outcomes. Using the drug-loaded stimulus-responsive nanocarriers outlined in section 7.4, it is being investigated whether certain known bacteria that reside in particular tumors can be utilized for targeted therapeutics or can be genetically modified to either directly destroy malignant cells or create an anti-tumor immune milieu.

9. Conclusion and Future Perspective

From simple food digestion and energy metabolism to memory and depression, gut microbiota is linked to practically every facet of human physiology. Future prospects for the study of the microbiome are very bright. Although the processes by which these two interact are largely unclear, evidence has already shown a connection between gut microbiota and cancer. Modulation of the gut microbiota may be a viable method to treat cancer. However, because the microscopic organisms are linked to other physiological functions, attempting to alter their composition in the gut can also result in additional health complications. To have a thorough understanding of how our gut microbiota and all of the physiological features are interconnected, critically designed innovative researches are required. To use the research from this sector for true human benefit, carefully monitored clinical studies are needed. The research on the relationship between gut microbiota and cancer has a number of limitations. A majority of the microorganisms found inside the human body cannot yet be grown under culture conditions that can support their growth. Gnotobiotic mice are used to explore the relationship between the microbiome and cancer, however these models lack the microbiota that would make up a person's genuine microbiome. Although FMT suggests a viable method for altering the gut microbiota to restore eubiosis, more thorough research on the mechanisms and adverse effects is required. Prior to patient administration, careful characterization of all the microorganisms contained in the fecal sample is crucially required. The precise identification of the mediators by which bacteria induce cancer is extremely important for therapies. Meta-transcriptomic and metabolomic investigations must be employed more to identify these carcinogenic substances and their mechanisms of action, because metagenomics does not assess microbial gene expressions. By using corresponding diets and genetically modified bacteria strains with or without specific enzyme coding genes, it is possible to either raise or decrease the quantities of substances that promote tumor growth. Applications of the information gained from these studies on cancer prevention, detection and treatment are beyond imagination. The potential of microbiota getting used as a detector of cancer together with uses in treatment and surveillance is never-ending. Many questions remain unanswered as the field advances at an astounding rate, including whether early colonization by carcinogenic microbes can result in the later development of cancer, how long it takes for cancer to manifest after carcinogenic bacteria have colonized the body, and whether altering the microbiota can reduce the risk of cancer in humans. This area of cancer research offers great promise and has the ability to usher in a new era of cancer research, however, it is merely in its infancy right now and plenty of effort and hard work awaits.

Author Contributions

SA- designed the study and wrote the manuscript. CT- provided help and advice on the review writing. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

The author, Sancharan Acharya, gratefully acknowledges the UGC, India, for the University fellowship.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Cancer Tomorrow. Available at: https://gco.iarc.fr/tomorrow/en/dataviz/bars?types=0&sexes=0&mode=population&group_populations=0&multiple_populations=1&multiple_cancers=1&cancers=39&populations=903_904_905_908_909_935&apc=cat_ca20v1.5_ca23v-1.5&group_cancers=1 (Accessed: 3 August 2023).

[2] Dietert RR, Dietert JM. The Human Superorganism: Microbes for Freedom vs. Fear. Preprints.org. 2023. (preprint)

[3] Rodríguez JM, Murphy K, Stanton C, Ross RP, Kober OI, Juge N, *et al*. The composition of the gut microbiota throughout life, with an emphasis on early life. Microbial Ecology in Health and Disease. 2015; 26: 26050.

[4] Liver cancer statistics. World Cancer Research Fund International. Available at: https://www.wcrf.org/cancer-trends/liver-cancer-statistics/ (Accessed: 3 August 2023).

[5] Balogh J, Victor D, 3rd, Asham EH, Burroughs SG, Boktour M, Saharia A, *et al*. Hepatocellular carcinoma: a review. Journal of Hepatocellular Carcinoma. 2016; 3: 41–53.

[6] Sia D, Villanueva A, Friedman SL, Llovet JM. Liver Cancer Cell of Origin, Molecular Class, and Effects on Patient Prognosis. Gastroenterology. 2017; 152: 745–761.

[7] Zhang C, Yang M, Ericsson AC. Antimicrobial Peptides: Potential Application in Liver Cancer. Frontiers in Microbiology. 2019; 10: 1257.

[8] Yu LX, Schwabe RF. The gut microbiome and liver cancer: mechanisms and clinical translation. Nature Reviews. Gastroenterology & Hepatology. 2017; 14: 527–539.

[9] Orcutt ST, Anaya DA. Liver Resection and Surgical Strategies for Management of Primary Liver Cancer. Cancer Control: Journal of the Moffitt Cancer Center. 2018; 25: 1073274817744621.

[10] Colagrande S, Regini F, Taliani GG, Nardi C, Inghilesi AL. Advanced hepatocellular carcinoma and sorafenib: Diagnosis, indications, clinical and radiological follow-up. World Journal of Hepatology. 2015; 7: 1041–1053.

[11] Guiu B, Assenat E. Doxorubicin for the treatment of hepatocellular carcinoma: GAME OVER!. Annals of Translational Medicine. 2020; 8: 1693.

[12] Li D, Kang J, Golas BJ, Yeung VW, Madoff DC. Minimally invasive local therapies for liver cancer. Cancer Biology & Medicine. 2014; 11: 217–236.

[13] Dodd GD, 3rd, Soulen MC, Kane RA, Livraghi T, Lees WR, Yamashita Y, *et al*. Minimally invasive treatment of malignant hepatic tumors: at the threshold of a major breakthrough. Radiographics: a Review Publication of the Radiological Society of North America, Inc. 2000; 20: 9–27.

[14] Bteich F, Di Bisceglie AM. Current and Future Systemic Therapies for Hepatocellular Carcinoma. Gastroenterology & Hepatology. 2019; 15: 266–272.

[15] Cidon EU. Systemic treatment of hepatocellular carcinoma: Past, present and future. World Journal of Hepatology. 2017; 9: 797–807.

[16] Toyoda H, Kumada T, Tada T, Sone Y, Kaneoka Y, Maeda A. Tumor Markers for Hepatocellular Carcinoma: Simple and Significant Predictors of Outcome in Patients with HCC. Liver Cancer. 2015; 4: 126–136.

[17] Zhao YJ, Ju Q, Li GC. Tumor markers for hepatocellular carcinoma. Molecular and Clinical Oncology. 2013; 1: 593–598.

[18] DiStefano JK, Davis B. Diagnostic and Prognostic Potential of AKR1B10 in Human Hepatocellular Carcinoma. Cancers. 2019; 11: 486.

[19] Veziant J, Villéger R, Barnich N, Bonnet M. Gut Microbiota as Potential Biomarker and/or Therapeutic Target to Improve the Management of Cancer: Focus on Colibactin-Producing *Escherichia coli* in Colorectal Cancer. Cancers. 2021; 13: 2215.

[20] Huang J, Liu W, Kang W, He Y, Yang R, Mou X, *et al*. Effects of microbiota on anticancer drugs: Current knowledge and potential applications. EBioMedicine. 2022; 83: 104197.

[21] Marchesi JR, Ravel J. The vocabulary of microbiome research: a proposal. Microbiome. 2015; 3: 31.

[22] Prescott SL. History of medicine: Origin of the term microbiome and why it matters. Human Microbiome Journal. 2017; 4: 24–25.

[23] Thursby E, Juge N. Introduction to the human gut microbiota. The Biochemical Journal. 2017; 474: 1823–1836.

[24] Sender R, Fuchs S, Milo R. Are We Really Vastly Outnumbered? Revisiting the Ratio of Bacterial to Host Cells in Humans. Cell. 2016; 164: 337–340.

[25] Bäckhed F, Ley RE, Sonnenburg JL, Peterson DA, Gordon JI. Host-bacterial mutualism in the human intestine. Science (New York, N.Y.). 2005; 307: 1915–1920.

[26] Poretsky R, Rodriguez-R LM, Luo C, Tsementzi D, Konstantinidis KT. Strengths and limitations of 16S rRNA gene amplicon sequencing in revealing temporal microbial community dynamics. PloS One. 2014; 9: e93827.

[27] den Besten G, van Eunen K, Groen AK, Venema K, Reijngoud DJ, Bakker BM. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. Journal of Lipid Research. 2013; 54: 2325–2340.

[28] Gensollen T, Iyer SS, Kasper DL, Blumberg RS. How colonization by microbiota in early life shapes the immune system. Science (New York, N.Y.). 2016; 352: 539–544.

[29] Gill SR, Pop M, Deboy RT, Eckburg PB, Turnbaugh PJ, Samuel BS, *et al*. Metagenomic analysis of the human distal gut microbiome. Science (New York, N.Y.). 2006; 312: 1355–1359.

[30] Ley RE, Hamady M, Lozupone C, Turnbaugh PJ, Ramey RR, Bircher JS, *et al*. Evolution of mammals and their gut microbes. Science (New York, N.Y.). 2008; 320: 1647–1651.

[31] Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, *et al*. A human gut microbial gene catalogue established by metagenomic sequencing. Nature. 2010; 464: 59–65.

[32] Li J, Jia H, Cai X, Zhong H, Feng Q, Sunagawa S, *et al*. An integrated catalog of reference genes in the human gut microbiome. Nature Biotechnology. 2014; 32: 834–841.

[33] Zwielehner J, Lassl C, Hippe B, Pointner A, Switzeny OJ, Remely M, *et al*. Changes in human fecal microbiota due to chemotherapy analyzed by TaqMan-PCR, 454 sequencing and PCR-DGGE fingerprinting. PloS One. 2011; 6: e28654.

[34] Jostins L, Ripke S, Weersma RK, Duerr RH, McGovern DP, Hui KY, *et al*. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature. 2012; 491: 119–124.

[35] Wostmann BS. The germfree animal in nutritional studies. Annual Review of Nutrition. 1981; 1: 257–279.

[36] Yu Z, Morrison M. Improved extraction of PCR-quality community DNA from digesta and fecal samples. BioTechniques. 2004; 36: 808–812.

[37] Jandhyala SM, Talukdar R, Subramanyam C, Vuyyuru H, Sasikala M, Nageshwar Reddy D. Role of the normal gut microbiota. World Journal of Gastroenterology. 2015; 21: 8787–8803.
[38] Al-Asmakh M, Zadjali F. Use of Germ-Free Animal Models in Microbiota-Related Research. Journal of Microbiology and Biotechnology. 2015; 25: 1583–1588.
[39] Liu BN, Liu XT, Liang ZH, Wang JH. Gut microbiota in obesity. World Journal of Gastroenterology. 2021; 27: 3837–3850.
[40] Kamada N, Seo SU, Chen GY, Núñez G. Role of the gut microbiota in immunity and inflammatory disease. Nature Reviews. Immunology. 2013; 13: 321–335.
[41] Engle SJ, Ormsby I, Pawlowski S, Boivin GP, Croft J, Balish E, *et al*. Elimination of colon cancer in germ-free transforming growth factor beta 1-deficient mice. Cancer Research. 2002; 62: 6362–6366.
[42] Sellon RK, Tonkonogy S, Schultz M, Dieleman LA, Grenther W, Balish E, *et al*. Resident enteric bacteria are necessary for development of spontaneous colitis and immune system activation in interleukin-10-deficient mice. Infection and Immunity. 1998; 66: 5224–5231.
[43] Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011; 144: 646–674.
[44] Di Ciaula A, Garruti G, Lunardi Baccetto R, Molina-Molina E, Bonfrate L, Wang DQH, *et al*. Bile Acid Physiology. Annals of Hepatology. 2017; 16: s4–s14.
[45] Wahlström A, Sayin SI, Marschall HU, Bäckhed F. Intestinal Crosstalk between Bile Acids and Microbiota and Its Impact on Host Metabolism. Cell Metabolism. 2016; 24: 41–50.
[46] Parada Venegas D, De la Fuente MK, Landskron G, González MJ, Quera R, Dijkstra G, *et al*. Short Chain Fatty Acids (SCFAs)-Mediated Gut Epithelial and Immune Regulation and Its Relevance for Inflammatory Bowel Diseases. Frontiers in Immunology. 2019; 10: 277.
[47] Tripathi A, Kar SK, Shukla R. Cognitive Deficits in Schizophrenia: Understanding the Biological Correlates and Remediation Strategies. Clinical Psychopharmacology and Neuroscience: the Official Scientific Journal of the Korean College of Neuropsychopharmacology. 2018; 16: 7–17.
[48] Sidhu M, van der Poorten D. The gut microbiome. Australian Family Physician. 2017; 46: 206–211.
[49] Arthur JC, Perez-Chanona E, Mühlbauer M, Tomkovich S, Uronis JM, Fan TJ, *et al*. Intestinal inflammation targets cancer-inducing activity of the microbiota. Science (New York, N.Y.). 2012; 338: 120–123.
[50] Mangerich A, Knutson CG, Parry NM, Muthupalani S, Ye W, Prestwich E, *et al*. Infection-induced colitis in mice causes dynamic and tissue-specific changes in stress response and DNA damage leading to colon cancer. Proceedings of the National Academy of Sciences of the United States of America. 2012; 109: E1820–E1829.
[51] Boleij A, Hechenbleikner EM, Goodwin AC, Badani R, Stein EM, Lazarev MG, *et al*. The Bacteroides fragilis toxin gene is prevalent in the colon mucosa of colorectal cancer patients. Clinical Infectious Diseases: an Official Publication of the Infectious Diseases Society of America. 2015; 60: 208–215.
[52] Kostic AD, Chun E, Robertson L, Glickman JN, Gallini CA, Michaud M, *et al*. Fusobacterium nucleatum potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment. Cell Host & Microbe. 2013; 14: 207–215.
[53] Ley RE, Turnbaugh PJ, Klein S, Gordon JI. Microbial ecology: human gut microbes associated with obesity. Nature. 2006; 444: 1022–1023.
[54] Huang Y, Fan XG, Wang ZM, Zhou JH, Tian XF, Li N. Identification of helicobacter species in human liver samples from patients with primary hepatocellular carcinoma. Journal of Clinical Pathology. 2004; 57: 1273–1277.
[55] Ishaq S, Nunn L. Helicobacter pylori and gastric cancer: a state of the art review. Gastroenterology and Hepatology from Bed to Bench. 2015; 8: S6–S14.
[56] Gao Z, Guo B, Gao R, Zhu Q, Qin H. Microbiota disbiosis is associated with colorectal cancer. Frontiers in Microbiology. 2015; 6: 20.
[57] Wong SH, Zhao L, Zhang X, Nakatsu G, Han J, Xu W, *et al*. Gavage of Fecal Samples From Patients With Colorectal Cancer Promotes Intestinal Carcinogenesis in Germ-Free and Conventional Mice. Gastroenterology. 2017; 153: 1621–1633.e6.
[58] Wotherspoon AC, Doglioni C, Diss TC, Pan L, Moschini A, de Boni M, *et al*. Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of Helicobacter pylori. Lancet (London, England). 1993; 342: 575–577.
[59] Ochi A, Nguyen AH, Bedrosian AS, Mushlin HM, Zarbakhsh S, Barilla R, *et al*. MyD88 inhibition amplifies dendritic cell capacity to promote pancreatic carcinogenesis via Th2 cells. The Journal of Experimental Medicine. 2012; 209: 1671–1687.
[60] Sacksteder MR. Occurrence of spontaneous tumors in the germfree F344 rat. Journal of the National Cancer Institute. 1976; 57: 1371–1373.
[61] Swann JB, Vesely MD, Silva A, Sharkey J, Akira S, Schreiber RD, *et al*. Demonstration of inflammation-induced cancer and cancer immunoediting during primary tumorigenesis. Proceedings of the National Academy of Sciences of the United States of America. 2008; 105: 652–656.
[62] Mittal D, Saccheri F, Vénéreau E, Pusterla T, Bianchi ME, Rescigno M. TLR4-mediated skin carcinogenesis is dependent on immune and radioresistant cells. The EMBO Journal. 2010; 29: 2242–2252.
[63] Tripathi A, Debelius J, Brenner DA, Karin M, Loomba R, Schnabl B, *et al*. The gut-liver axis and the intersection with the microbiome. Nature Reviews. Gastroenterology & Hepatology. 2018; 15: 397–411.
[64] Naggie S, Ramers CB. Sustained Virologic Response in People Who Inject Drugs and/or Who Are on Opioid Agonist Therapy: Is 90% Enough? Hepatology Communications. 2019; 3: 453–455.
[65] Yuan J, Chen C, Cui J, Lu J, Yan C, Wei X, *et al*. Fatty Liver Disease Caused by High-Alcohol-Producing Klebsiella pneumoniae. Cell Metabolism. 2019; 30: 1172.
[66] Mishra R, Rajsiglová L, Lukáč P, Tenti P, Šima P, Čaja F, *et al*. Spontaneous and Induced Tumors in Germ-Free Animals: A General Review. Medicina (Kaunas, Lithuania). 2021; 57: 260.
[67] Yoshimoto S, Loo TM, Atarashi K, Kanda H, Sato S, Oyadomari S, *et al*. Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome. Nature. 2013; 499: 97–101.
[68] Khan AA, Shrivastava A. Bacterial infections associated with cancer: possible implication in etiology with special reference to lateral gene transfer. Cancer Metastasis Reviews. 2010; 29: 331–337.
[69] Castellarin M, Warren RL, Freeman JD, Dreolini L, Krzywinski M, Strauss J, *et al*. Fusobacterium nucleatum infection is prevalent in human colorectal carcinoma. Genome Research. 2012; 22: 299–306.
[70] Hoepelman AI, Tuomanen EI. Consequences of microbial attachment: directing host cell functions with adhesins. Infection and Immunity. 1992; 60: 1729–1733.
[71] Lee JH, Choi HJ, Jung J, Lee MG, Lee JB, Lee KH. Receptors for Treponema pallidum attachment to the surface and matrix proteins of cultured human dermal microvascular endothelial cells. Yonsei Medical Journal. 2003; 44: 371–378.
[72] Zhang Q, Young TF, Ross RF. Glycolipid receptors for attachment of Mycoplasma hyopneumoniae to porcine respiratory ciliated cells. Infection and Immunity. 1994; 62: 4367–4373.
[73] Fadnes B, Uhlin-Hansen L, Lindin I, Rekdal Ø. Small lytic pep-

tides escape the inhibitory effect of heparan sulfate on the surface of cancer cells. BMC Cancer. 2011; 11: 116.
[74] Nath S, Mukherjee P. MUC1: a multifaceted oncoprotein with a key role in cancer progression. Trends in Molecular Medicine. 2014; 20: 332–342.
[75] Guang W, Ding H, Czinn SJ, Kim KC, Blanchard TG, Lillehoj EP. Muc1 cell surface mucin attenuates epithelial inflammation in response to a common mucosal pathogen. The Journal of Biological Chemistry. 2010; 285: 20547–20557.
[76] Lindén SK, Sheng YH, Every AL, Miles KM, Skoog EC, Florin THJ, *et al*. MUC1 limits Helicobacter pylori infection both by steric hindrance and by acting as a releasable decoy. PLoS Pathogens. 2009; 5: e1000617.
[77] McGuckin MA, Every AL, Skene CD, Linden SK, Chionh YT, Swierczak A, *et al*. Muc1 mucin limits both Helicobacter pylori colonization of the murine gastric mucosa and associated gastritis. Gastroenterology. 2007; 133: 1210–1218.
[78] Boll EJ, Ayala-Lujan J, Szabady RL, Louissaint C, Smith RZ, Krogfelt KA, *et al*. Enteroaggregative *Escherichia coli* Adherence Fimbriae Drive Inflammatory Cell Recruitment via Interactions with Epithelial MUC1. mBio. 2017; 8: e00717–17.
[79] Genua F, Raghunathan V, Jenab M, Gallagher WM, Hughes DJ. The Role of Gut Barrier Dysfunction and Microbiome Dysbiosis in Colorectal Cancer Development. Frontiers in Oncology. 2021; 11: 626349.
[80] Round JL, Lee SM, Li J, Tran G, Jabri B, Chatila TA, *et al*. The Toll-like receptor 2 pathway establishes colonization by a commensal of the human microbiota. Science (New York, N.Y.). 2011; 332: 974–977.
[81] Zhang YB, He FL, Fang M, Hua TF, Hu BD, Zhang ZH, *et al*. Increased expression of Toll-like receptors 4 and 9 in human lung cancer. Molecular Biology Reports. 2009; 36: 1475–1481.
[82] Clayton PE, Banerjee I, Murray PG, Renehan AG. Growth hormone, the insulin-like growth factor axis, insulin and cancer risk. Nature Reviews. Endocrinology. 2011; 7: 11–24.
[83] Bezirtzoglou E, Voidarou C, Papadaki A, Tsiotsias A, Kotsovolou O, Konstandi M. Hormone therapy alters the composition of the vaginal microflora in ovariectomized rats. Microbial Ecology. 2008; 55: 751–759.
[84] Adlercreutz H, Pulkkinen MO, Hämäläinen EK, Korpela JT. Studies on the role of intestinal bacteria in metabolism of synthetic and natural steroid hormones. Journal of Steroid Biochemistry. 1984; 20: 217–229.
[85] Höckel M, Vaupel P. Tumor hypoxia: definitions and current clinical, biologic, and molecular aspects. Journal of the National Cancer Institute. 2001; 93: 266–276.
[86] Kang Y, Cai Y, Yang Y. The Gut Microbiome and Hepatocellular Carcinoma: Implications for Early Diagnostic Biomarkers and Novel Therapies. Liver Cancer. 2021; 11: 113–125.
[87] Gómez-Hurtado I, Santacruz A, Peiró G, Zapater P, Gutiérrez A, Pérez-Mateo M, *et al*. Gut microbiota dysbiosis is associated with inflammation and bacterial translocation in mice with CCl4-induced fibrosis. PloS One. 2011; 6: e23037.
[88] Carter JK, Bhattacharya D, Borgerding JN, Fiel MI, Faith JJ, Friedman SL. Modeling dysbiosis of human NASH in mice: Loss of gut microbiome diversity and overgrowth of Erysipelotrichales. PloS One. 2021; 16: e0244763.
[89] Mu HN, Zhou Q, Yang RY, Tang WQ, Li HX, Wang SM, *et al*. Caffeic acid prevents non-alcoholic fatty liver disease induced by a high-fat diet through gut microbiota modulation in mice. Food Research International (Ottawa, Ont.). 2021; 143: 110240.
[90] Shi D, Lv L, Fang D, Wu W, Hu C, Xu L, *et al*. Administration of Lactobacillus salivarius LI01 or Pediococcus pentosaceus LI05 prevents CCl_4-induced liver cirrhosis by protecting the intestinal barrier in rats. Scientific Reports. 2017; 7: 6927.
[91] Santiago A, Sanchez E, Clark A, Pozuelo M, Calvo M, Yañez F, *et al*. Sequential Changes in the Mesenteric Lymph Node Microbiome and Immune Response during Cirrhosis Induction in Rats. MSystems. 2019; 4: e00278–18.
[92] Velázquez KT, Enos RT, Bader JE, Sougiannis AT, Carson MS, Chatzistamou I, *et al*. Prolonged high-fat-diet feeding promotes non-alcoholic fatty liver disease and alters gut microbiota in mice. World Journal of Hepatology. 2019; 11: 619–637.
[93] Gauffin Cano P, Santacruz A, Moya Á, Sanz Y. Bacteroides uniformis CECT 7771 ameliorates metabolic and immunological dysfunction in mice with high-fat-diet induced obesity. PloS One. 2012; 7: e41079.
[94] Mei L, Tang Y, Li M, Yang P, Liu Z, Yuan J, *et al*. Co-Administration of Cholesterol-Lowering Probiotics and Anthraquinone from Cassia obtusifolia L. Ameliorate Non-Alcoholic Fatty Liver. PloS One. 2015; 10: e0138078.
[95] Seo DB, Jeong HW, Cho D, Lee BJ, Lee JH, Choi JY, *et al*. Fermented green tea extract alleviates obesity and related complications and alters gut microbiota composition in diet-induced obese mice. Journal of Medicinal Food. 2015; 18: 549–556.
[96] Wang J, Tang H, Zhang C, Zhao Y, Derrien M, Rocher E, *et al*. Modulation of gut microbiota during probiotic-mediated attenuation of metabolic syndrome in high fat diet-fed mice. The ISME Journal. 2015; 9: 1–15.
[97] Monteiro NES, Roquetto AR, de Pace F, Moura CS, Santos AD, Yamada AT, *et al*. Dietary whey proteins shield murine cecal microbiota from extensive disarray caused by a high-fat diet. Food Research International (Ottawa, Ont.). 2016; 85: 121–130.
[98] Tian Y, Wang H, Yuan F, Li N, Huang Q, He L, *et al*. Perilla Oil Has Similar Protective Effects of Fish Oil on High-Fat Diet-Induced Nonalcoholic Fatty Liver Disease and Gut Dysbiosis. BioMed Research International. 2016; 2016: 9462571.
[99] Feng W, Wang H, Zhang P, Gao C, Tao J, Ge Z, *et al*. Modulation of gut microbiota contributes to curcumin-mediated attenuation of hepatic steatosis in rats. Biochimica et Biophysica Acta. General Subjects. 2017; 1861: 1801–1812.
[100] Porras D, Nistal E, Martínez-Flórez S, Pisonero-Vaquero S, Olcoz JL, Jover R, *et al*. Protective effect of quercetin on high-fat diet-induced non-alcoholic fatty liver disease in mice is mediated by modulating intestinal microbiota imbalance and related gut-liver axis activation. Free Radical Biology & Medicine. 2017; 102: 188–202.
[101] Xu P, Hong F, Wang J, Wang J, Zhao X, Wang S, *et al*. DBZ is a putative PPARγ agonist that prevents high fat diet-induced obesity, insulin resistance and gut dysbiosis. Biochimica et Biophysica Acta. General Subjects. 2017; 1861: 2690–2701.
[102] Chen YT, Lin YC, Lin JS, Yang NS, Chen MJ. Sugary Kefir Strain Lactobacillus mali APS1 Ameliorated Hepatic Steatosis by Regulation of SIRT-1/Nrf-2 and Gut Microbiota in Rats. Molecular Nutrition & Food Research. 2018; 62: e1700903.
[103] Ye JZ, Li YT, Wu WR, Shi D, Fang DQ, Yang LY, *et al*. Dynamic alterations in the gut microbiota and metabolome during the development of methionine-choline-deficient diet-induced nonalcoholic steatohepatitis. World Journal of Gastroenterology. 2018; 24: 2468–2481.
[104] Duan M, Sun X, Ma N, Liu Y, Luo T, Song S, *et al*. Polysaccharides from Laminaria japonica alleviated metabolic syndrome in BALB/c mice by normalizing the gut microbiota. International Journal of Biological Macromolecules. 2019; 121: 996–1004.
[105] Ishioka M, Miura K, Minami S, Shimura Y, Ohnishi H. Altered Gut Microbiota Composition and Immune Response in Experimental Steatohepatitis Mouse Models. Digestive Diseases and Sciences. 2017; 62: 396–406.
[106] Natividad JM, Lamas B, Pham HP, Michel ML, Rainteau D, Bridonneau C, *et al*. Bilophila wadsworthia aggravates high fat diet induced metabolic dysfunctions in mice. Nature Communications. 2018; 9: 2802.
[107] Ponziani FR, Bhoori S, Castelli C, Putignani L, Rivoltini L, Del Chierico F, *et al*. Hepatocellular Carcinoma Is Associated With

Gut Microbiota Profile and Inflammation in Nonalcoholic Fatty Liver Disease. Hepatology (Baltimore, Md.). 2019; 69: 107–120.

[108] Ren Z, Li A, Jiang J, Zhou L, Yu Z, Lu H, *et al*. Gut microbiome analysis as a tool towards targeted non-invasive biomarkers for early hepatocellular carcinoma. Gut. 2019; 68: 1014–1023.

[109] Liu Q, Li F, Zhuang Y, Xu J, Wang J, Mao X, *et al*. Alteration in gut microbiota associated with hepatitis B and non-hepatitis virus related hepatocellular carcinoma. Gut Pathogens. 2019; 11: 1.

[110] Zheng R, Wang G, Pang Z, Ran N, Gu Y, Guan X, *et al*. Liver cirrhosis contributes to the disorder of gut microbiota in patients with hepatocellular carcinoma. Cancer Medicine. 2020; 9: 4232–4250.

[111] Zhang N, Gou Y, Liang S, Chen N, Liu Y, He Q, *et al*. Dysbiosis of Gut Microbiota Promotes Hepatocellular Carcinoma Progression by Regulating the Immune Response. Journal of Immunology Research. 2021; 2021: 4973589.

[112] Wiest R, Garcia-Tsao G. Bacterial translocation (BT) in cirrhosis. Hepatology (Baltimore, Md.). 2005; 41: 422–433.

[113] Dapito DH, Mencin A, Gwak GY, Pradere JP, Jang MK, Mederacke I, *et al*. Promotion of hepatocellular carcinoma by the intestinal microbiota and TLR4. Cancer Cell. 2012; 21: 504–516.

[114] Tye H, Kennedy CL, Najdovska M, McLeod L, McCormack W, Hughes N, *et al*. STAT3-driven upregulation of TLR2 promotes gastric tumorigenesis independent of tumor inflammation. Cancer Cell. 2012; 22: 466–478.

[115] Ngo VN, Young RM, Schmitz R, Jhavar S, Xiao W, Lim KH, *et al*. Oncogenically active MYD88 mutations in human lymphoma. Nature. 2011; 470: 115–119.

[116] Vijay-Kumar M, Aitken JD, Carvalho FA, Cullender TC, Mwangi S, Srinivasan S, *et al*. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. Science (New York, N.Y.). 2010; 328: 228–231.

[117] Couturier-Maillard A, Secher T, Rehman A, Normand S, De Arcangelis A, Haesler R, *et al*. NOD2-mediated dysbiosis predisposes mice to transmissible colitis and colorectal cancer. The Journal of Clinical Investigation. 2013; 123: 700–711.

[118] Cuevas-Ramos G, Petit CR, Marcq I, Boury M, Oswald E, Nougayrède JP. Escherichia coli induces DNA damage in vivo and triggers genomic instability in mammalian cells. Proceedings of the National Academy of Sciences of the United States of America. 2010; 107: 11537–11542.

[119] Smith JL, Bayles DO. The contribution of cytolethal distending toxin to bacterial pathogenesis. Critical Reviews in Microbiology. 2006; 32: 227–248.

[120] Elwell CA, Dreyfus LA. DNase I homologous residues in CdtB are critical for cytolethal distending toxin-mediated cell cycle arrest. Molecular Microbiology. 2000; 37: 952–963.

[121] Balish E, Warner T. Enterococcus faecalis induces inflammatory bowel disease in interleukin-10 knockout mice. The American Journal of Pathology. 2002; 160: 2253–2257.

[122] Windey K, De Preter V, Verbeke K. Relevance of protein fermentation to gut health. Molecular Nutrition & Food Research. 2012; 56: 184–196.

[123] Seitz HK, Simanowski UA, Garzon FT, Rideout JM, Peters TJ, Koch A, *et al*. Possible role of acetaldehyde in ethanol-related rectal cocarcinogenesis in the rat. Gastroenterology. 1990; 98: 406–413.

[124] Wu L, Feng J, Li J, Yu Q, Ji J, Wu J, *et al*. The gut microbiome-bile acid axis in hepatocarcinogenesis. Biomedicine & Pharmacotherapy. 2021; 133: 111036.

[125] Galle PR, Theilmann L, Raedsch R, Otto G, Stiehl A. Ursodeoxycholate reduces hepatotoxicity of bile salts in primary human hepatocytes. Hepatology (Baltimore, Md.). 1990; 12: 486–491.

[126] Jia B, Jeon CO. Promotion and induction of liver cancer by gut microbiome-mediated modulation of bile acids. PLoS Pathogens. 2019; 15: e1007954.

[127] Yamada S, Takashina Y, Watanabe M, Nagamine R, Saito Y, Kamada N, *et al*. Bile acid metabolism regulated by the gut microbiota promotes non-alcoholic steatohepatitis-associated hepatocellular carcinoma in mice. Oncotarget. 2018; 9: 9925–9939.

[128] Shen R, Ke L, Li Q, Dang X, Shen S, Shen J, *et al*. Abnormal bile acid-microbiota crosstalk promotes the development of hepatocellular carcinoma. Hepatology International. 2022; 16: 396–411.

[129] Ohtani N, Hara E. Gut-liver axis-mediated mechanism of liver cancer: A special focus on the role of gut microbiota. Cancer Science. 2021; 112: 4433–4443.

[130] Kimura I, Ozawa K, Inoue D, Imamura T, Kimura K, Maeda T, *et al*. The gut microbiota suppresses insulin-mediated fat accumulation via the short-chain fatty acid receptor GPR43. Nature Communications. 2013; 4: 1829.

[131] Kimura I, Inoue D, Maeda T, Hara T, Ichimura A, Miyauchi S, *et al*. Short-chain fatty acids and ketones directly regulate sympathetic nervous system via G protein-coupled receptor 41 (GPR41). Proceedings of the National Academy of Sciences of the United States of America. 2011; 108: 8030–8035.

[132] Xie L, Alam MJ, Marques FZ, Mackay CR. A major mechanism for immunomodulation: Dietary fibres and acid metabolites. Seminars in Immunology. 2023; 66: 101737.

[133] Satapathy SK, Banerjee P, Pierre JF, Higgins D, Dutta S, Heda R, *et al*. Characterization of Gut Microbiome in Liver Transplant Recipients With Nonalcoholic Steatohepatitis. Transplantation Direct. 2020; 6: e625.

[134] Volynets V, Küper MA, Strahl S, Maier IB, Spruss A, Wagnerberger S, *et al*. Nutrition, intestinal permeability, and blood ethanol levels are altered in patients with nonalcoholic fatty liver disease (NAFLD). Digestive Diseases and Sciences. 2012; 57: 1932–1941.

[135] Liu S, Dai J, Lan X, Fan B, Dong T, Zhang Y, *et al*. Intestinal bacteria are potential biomarkers and therapeutic targets for gastric cancer. Microbial Pathogenesis. 2021; 151: 104747.

[136] Laborda-Illanes A, Sanchez-Alcoholado L, Dominguez-Recio ME, Jimenez-Rodriguez B, Lavado R, Comino-Méndez I, *et al*. Breast and Gut Microbiota Action Mechanisms in Breast Cancer Pathogenesis and Treatment. Cancers. 2020; 12: 2465.

[137] Goedert JJ, Jones G, Hua X, Xu X, Yu G, Flores R, *et al*. Investigation of the association between the fecal microbiota and breast cancer in postmenopausal women: a population-based case-control pilot study. Journal of the National Cancer Institute. 2015; 107: djv147.

[138] Zhuang H, Cheng L, Wang Y, Zhang YK, Zhao MF, Liang GD, *et al*. Dysbiosis of the Gut Microbiome in Lung Cancer. Frontiers in Cellular and Infection Microbiology. 2019; 9: 112.

[139] Bhandari MP, Polaka I, Vangravs R, Mezmale L, Veliks V, Kirshners A, *et al*. Volatile Markers for Cancer in Exhaled Breath-Could They Be the Signature of the Gut Microbiota? Molecules (Basel, Switzerland). 2023; 28: 3488.

[140] Komiyama S, Yamada T, Takemura N, Kokudo N, Hase K, Kawamura YI. Profiling of tumour-associated microbiota in human hepatocellular carcinoma. Scientific Reports. 2021; 11: 10589.

[141] Ni J, Huang R, Zhou H, Xu X, Li Y, Cao P, *et al*. Analysis of the Relationship Between the Degree of Dysbiosis in Gut Microbiota and Prognosis at Different Stages of Primary Hepatocellular Carcinoma. Frontiers in Microbiology. 2019; 10: 1458.

[142] Piñero F, Vazquez M, Baré P, Rohr C, Mendizabal M, Sciara M, *et al*. A different gut microbiome linked to inflammation found in cirrhotic patients with and without hepatocellular carcinoma. Annals of Hepatology. 2019; 18: 480–487.

[143] You S, Ma Y, Yan B, Pei W, Wu Q, Ding C, *et al*. The promotion mechanism of prebiotics for probiotics: A review. Frontiers in

Nutrition. 2022; 9: 1000517.
[144] Chrysostomou D, Roberts LA, Marchesi JR, Kinross JM. Gut Microbiota Modulation of Efficacy and Toxicity of Cancer Chemotherapy and Immunotherapy. Gastroenterology. 2023; 164: 198–213.
[145] Singh NK, Beckett JM, Kalpurath K, Ishaq M, Ahmad T, Eri RD. Synbiotics as Supplemental Therapy for the Alleviation of Chemotherapy-Associated Symptoms in Patients with Solid Tumours. Nutrients. 2023; 15: 1759.
[146] Dhiman RK, Rana B, Agrawal S, Garg A, Chopra M, Thumburu KK, *et al*. Probiotic VSL#3 reduces liver disease severity and hospitalization in patients with cirrhosis: a randomized, controlled trial. Gastroenterology. 2014; 147: 1327–37.e3.
[147] Li J, Sung CYJ, Lee N, Ni Y, Pihlajamäki J, Panagiotou G, *et al*. Probiotics modulated gut microbiota suppresses hepatocellular carcinoma growth in mice. Proceedings of the National Academy of Sciences of the United States of America. 2016; 113: E1306–E1315.
[148] Mihailović M, Živković M, Jovanović JA, Tolinački M, Sinadinović M, Rajić J, *et al*. Oral administration of probiotic Lactobacillus paraplantarum BGCG11 attenuates diabetes-induced liver and kidney damage in rats. Journal of Functional Foods. 2017; 38: 427–437.
[149] Zhang HL, Yu LX, Yang W, Tang L, Lin Y, Wu H, *et al*. Profound impact of gut homeostasis on chemically-induced pro-tumorigenic inflammation and hepatocarcinogenesis in rats. Journal of Hepatology. 2012; 57: 803–812.
[150] Elshaer AM, El-Kharashi OA, Hamam GG, Nabih ES, Magdy YM, Abd El Samad AA. Involvement of TLR4/ CXCL9/ PREX-2 pathway in the development of hepatocellular carcinoma (HCC) and the promising role of early administration of lactobacillus plantarum in Wistar rats. Tissue & Cell. 2019; 60: 38–47.
[151] Million M, Angelakis E, Paul M, Armougom F, Leibovici L, Raoult D. Comparative meta-analysis of the effect of Lactobacillus species on weight gain in humans and animals. Microbial Pathogenesis. 2012; 53: 100–108.
[152] Yadav MK, Kumari I, Singh B, Sharma KK, Tiwari SK. Probiotics, prebiotics and synbiotics: Safe options for next-generation therapeutics. Applied Microbiology and Biotechnology. 2022; 106: 505–521.
[153] Etxeberria U, Fernández-Quintela A, Milagro FI, Aguirre L, Martínez JA, Portillo MP. Impact of polyphenols and polyphenol-rich dietary sources on gut microbiota composition. Journal of Agricultural and Food Chemistry. 2013; 61: 9517–9533.
[154] Mandair DS, Rossi RE, Pericleous M, Whyand T, Caplin M. The impact of diet and nutrition in the prevention and progression of hepatocellular carcinoma. Expert Review of Gastroenterology & Hepatology. 2014; 8: 369–382.
[155] Lee HC, Jenner AM, Low CS, Lee YK. Effect of tea phenolics and their aromatic fecal bacterial metabolites on intestinal microbiota. Research in Microbiology. 2006; 157: 876–884.
[156] Darvesh AS, Bishayee A. Chemopreventive and therapeutic potential of tea polyphenols in hepatocellular cancer. Nutrition and Cancer. 2013; 65: 329–344.
[157] Patel S, Goyal A. Functional oligosaccharides: production, properties and applications. World Journal of Microbiology and Biotechnology. 2011; 27: 1119–1128.
[158] Yu J, Zhang W, Zhang R, Ruan X, Ren P, Lu B. Lactulose accelerates liver regeneration in rats by inducing hydrogen. The Journal of Surgical Research. 2015; 195: 128–135.
[159] Zong DW, Guo CY, Cheng HT, Hu HT, Xiao JC, Li HL. Influence of lactulose on interventional therapy for HCC patients with hepatocirrhosis and hypersplenism. Asian Pacific Journal of Tropical Medicine. 2016; 9: 193–196.
[160] Zhao WX, Wang T, Zhang YN, Chen Q, Wang Y, Xing YQ, *et al*. Molecular Mechanism of Polysaccharides Extracted from Chinese Medicine Targeting Gut Microbiota for Promoting Health. Chinese Journal of Integrative Medicine. 2024; 30: 171–180.
[161] Bhat SA, Kaur R, Chauhan A, Pal A. The microbiome and precision oncology: an emerging paradigm in anticancer therapy. Critical Reviews in Microbiology. 2022; 48: 770–783.
[162] Surolia R, Ali S, Singh A. Synbiotics: a promising approach for improving human health. Journal of Pharmaceutical Negative Results. 2022; 766–777.
[163] Arruda HS, Geraldi MV, Cedran MF, Bicas JL, Marostica Junior MR, Pastore GM. Prebiotics and probiotics. Bioactive Food Components Activity in Mechanistic Approach. 2022; 145: 55–118.
[164] Tang G, Zhang L, Huang W, Wei Z. Probiotics or Synbiotics for Preventing Postoperative Infection in Hepatopancreatobiliary Cancer Patients: A Meta-Analysis of Randomized Controlled Trials. Nutrition and Cancer. 2022; 74: 3468–3478.
[165] Kahn J, Pregartner G, Schemmer P. Effects of both Pro- and Synbiotics in Liver Surgery and Transplantation with Special Focus on the Gut-Liver Axis-A Systematic Review and Meta-Analysis. Nutrients. 2020; 12: 2461.
[166] Cook MA, Wright GD. The past, present, and future of antibiotics. Science Translational Medicine. 2022; 14: eabo7793.
[167] Gonugunta AS, Von Itzstein MS, Hsiehchen D, Le T, Rashdan S, Yang H, *et al*. Antibiotic Prescriptions in Lung Cancer and Melanoma Populations: Differences With Potential Clinical Implications in the Immunotherapy Era. Clinical Lung Cancer. 2023; 24: 11–17.
[168] Zhang L, Chen C, Chai D, Li C, Guan Y, Liu L, *et al*. The association between antibiotic use and outcomes of HCC patients treated with immune checkpoint inhibitors. Frontiers in Immunology. 2022; 13: 956533.
[169] Pinato DJ, Li X, Mishra-Kalyani P, D'Alessio A, Fulgenzi CAM, Scheiner B, *et al*. Association between antibiotics and adverse oncological outcomes in patients receiving targeted or immune-based therapy for hepatocellular carcinoma. JHEP Reports: Innovation in Hepatology. 2023; 5: 100747.
[170] Song Q, Zhang X, Liu W, Wei H, Liang W, Zhou Y, *et al*. Bifidobacterium pseudolongum-generated acetate suppresses non-alcoholic fatty liver disease-associated hepatocellular carcinoma. Journal of Hepatology. 2023; 79: 1352–1365.
[171] Santopaolo F, Coppola G, Giuli L, Gasbarrini A, Ponziani FR. Influence of Gut–Liver Axis on Portal Hypertension in Advanced Chronic Liver Disease: The Gut Microbiome as a New Protagonist in Therapeutic Management. Microbiology Research. 2022; 13: 539–555.
[172] Kalathil SG, Thanavala Y. Importance of myeloid derived suppressor cells in cancer from a biomarker perspective. Cellular Immunology. 2021; 361: 104280.
[173] Singh V, Yeoh BS, Abokor AA, Golonka RM, Tian Y, Patterson AD, *et al*. Vancomycin prevents fermentable fiber-induced liver cancer in mice with dysbiotic gut microbiota. Gut Microbes. 2020; 11: 1077–1091.
[174] Ginés P, Rimola A, Planas R, Vargas V, Marco F, Almela M, *et al*. Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: results of a double-blind, placebo-controlled trial. Hepatology (Baltimore, Md.). 1990; 12: 716–724.
[175] Tandon P, Delisle A, Topal JE, Garcia-Tsao G. High prevalence of antibiotic-resistant bacterial infections among patients with cirrhosis at a US liver center. Clinical Gastroenterology and Hepatology: the Official Clinical Practice Journal of the American Gastroenterological Association. 2012; 10: 1291–1298.
[176] Fujinaga Y, Kawaratani H, Kaya D, Tsuji Y, Ozutsumi T, Furukawa M, *et al*. Effective Combination Therapy of Angiotensin-II Receptor Blocker and Rifaximin for Hepatic Fibrosis in Rat Model of Nonalcoholic Steatohepatitis. Interna-

tional Journal of Molecular Sciences. 2020; 21: 5589.
[177] Booser DJ, Hortobagyi GN. Anthracycline antibiotics in cancer therapy. Focus on drug resistance. Drugs. 1994; 47: 223–258.
[178] Sommer F, Anderson JM, Bharti R, Raes J, Rosenstiel P. The resilience of the intestinal microbiota influences health and disease. Nature Reviews. Microbiology. 2017; 15: 630–638.
[179] Cammarota G, Ianiro G, Tilg H, Rajilić-Stojanović M, Kump P, Satokari R, *et al*. European consensus conference on faecal microbiota transplantation in clinical practice. Gut. 2017; 66: 569–580.
[180] Zhang F, Luo W, Shi Y, Fan Z, Ji G. Should we standardize the 1,700-year-old fecal microbiota transplantation? The American Journal of Gastroenterology. 2012; 107: 1755–1756.
[181] Ghouri YA, Richards DM, Rahimi EF, Krill JT, Jelinek KA, DuPont AW. Systematic review of randomized controlled trials of probiotics, prebiotics, and synbiotics in inflammatory bowel disease. Clinical and Experimental Gastroenterology. 2014; 7: 473–487.
[182] Cammarota G, Masucci L, Ianiro G, Bibbò S, Dinoi G, Costamagna G, *et al*. Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent Clostridium difficile infection. Alimentary Pharmacology & Therapeutics. 2015; 41: 835–843.
[183] van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, *et al*. Duodenal infusion of donor feces for recurrent Clostridium difficile. The New England Journal of Medicine. 2013; 368: 407–415.
[184] Chin SM, Sauk J, Mahabamunuge J, Kaplan JL, Hohmann EL, Khalili H. Fecal Microbiota Transplantation for Recurrent Clostridium difficile Infection in Patients With Inflammatory Bowel Disease: A Single-Center Experience. Clinical Gastroenterology and Hepatology: the Official Clinical Practice Journal of the American Gastroenterological Association. 2017; 15: 597–599.
[185] DeFilipp Z, Bloom PP, Torres Soto M, Mansour MK, Sater MRA, Huntley MH, *et al*. Drug-Resistant *E. coli* Bacteremia Transmitted by Fecal Microbiota Transplant. The New England Journal of Medicine. 2019; 381: 2043–2050.
[186] Cho K, Spasova D, Hong SW, O E, Surh CD, Im SH, *et al*. *Listeria monocytogenes* Establishes Commensalism in Germ-Free Mice Through the Reversible Downregulation of Virulence Gene Expression. Frontiers in Immunology. 2021; 12: 666088.
[187] Zhou D, Pan Q, Shen F, Cao HX, Ding WJ, Chen YW, *et al*. Total fecal microbiota transplantation alleviates high-fat diet-induced steatohepatitis in mice via beneficial regulation of gut microbiota. Scientific Reports. 2017; 7: 1529.
[188] Wang WW, Zhang Y, Huang XB, You N, Zheng L, Li J. Fecal microbiota transplantation prevents hepatic encephalopathy in rats with carbon tetrachloride-induced acute hepatic dysfunction. World Journal of Gastroenterology. 2017; 23: 6983–6994.
[189] Kelly CR, Ihunnah C, Fischer M, Khoruts A, Surawicz C, Afzali A, *et al*. Fecal microbiota transplant for treatment of Clostridium difficile infection in immunocompromised patients. The American Journal of Gastroenterology. 2014; 109: 1065–1071.
[190] Yu Q, Wu L, Ji J, Feng J, Dai W, Li J, *et al*. Gut Microbiota, Peroxisome Proliferator-Activated Receptors, and Hepatocellular Carcinoma. Journal of Hepatocellular Carcinoma. 2020; 7: 271–288.
[191] Wang Y, Wiesnoski DH, Helmink BA, Gopalakrishnan V, Choi K, DuPont HL, *et al*. Fecal microbiota transplantation for refractory immune checkpoint inhibitor-associated colitis. Nature Medicine. 2018; 24: 1804–1808.
[192] Brigger I, Dubernet C, Couvreur P. Nanoparticles in cancer therapy and diagnosis. Advanced Drug Delivery Reviews. 2002; 54: 631–651.
[193] Ma J, Chen QL, O'Connor P, Sheng GD. Does soil CuO nanoparticles pollution alter the gut microbiota and resistome of Enchytraeus crypticus? Environmental Pollution (Barking, Essex: 1987). 2020; 256: 113463.
[194] Tong T, Shereef A, Wu J, Binh CTT, Kelly JJ, Gaillard JF, *et al*. Effects of material morphology on the phototoxicity of nano-TiO2 to bacteria. Environmental Science & Technology. 2013; 47: 12486–12495.
[195] Foster HA, Ditta IB, Varghese S, Steele A. Photocatalytic disinfection using titanium dioxide: spectrum and mechanism of antimicrobial activity. Applied Microbiology and Biotechnology. 2011; 90: 1847–1868.
[196] Fares MM, Salem MS. Dissolution enhancement of curcumin via curcumin-prebiotic inulin nanoparticles. Drug Development and Industrial Pharmacy. 2015; 41: 1785–1792.
[197] Gao W, Thamphiwatana S, Angsantikul P, Zhang L. Nanoparticle approaches against bacterial infections. Wiley Interdisciplinary Reviews. Nanomedicine and Nanobiotechnology. 2014; 6: 532–547.
[198] Song R, Yao J, Shi Q, Wei R. Nanocomposite of Half-Fin Anchovy Hydrolysates/Zinc Oxide Nanoparticles Exhibits Actual Non-Toxicity and Regulates Intestinal Microbiota, Short-Chain Fatty Acids Production and Oxidative Status in Mice. Marine Drugs. 2018; 16: 23.
[199] Song W, Tiruthani K, Wang Y, Shen L, Hu M, Dorosheva O, *et al*. Trapping of Lipopolysaccharide to Promote Immunotherapy against Colorectal Cancer and Attenuate Liver Metastasis. Advanced Materials (Deerfield Beach, Fla.). 2018; 30: e1805007.
[200] Ren Z, Chen X, Hong L, Zhao X, Cui G, Li A, *et al*. Nanoparticle Conjugation of Ginsenoside Rg3 Inhibits Hepatocellular Carcinoma Development and Metastasis. Small (Weinheim an Der Bergstrasse, Germany). 2020; 16: e1905233.
[201] Watahiki T, Okada K, Miura I, To K, Tanaka S, Warabi E, *et al*. Antioxidative Self-Assembling Nanoparticles Attenuate the Development of Steatohepatitis and Inhibit Hepatocarcinogenesis in Mice. Antioxidants (Basel, Switzerland). 2022; 11: 1939.
[202] Sharp R. Bacteriophages: biology and history. Journal of Chemical Technology & Biotechnology. 2001; 76: 667–672.
[203] Bar H, Yacoby I, Benhar I. Killing cancer cells by targeted drug-carrying phage nanomedicines. BMC Biotechnology. 2008; 8: 37.
[204] Handley SA, Devkota S. Going Viral: a Novel Role for Bacteriophage in Colorectal Cancer. mBio. 2019; 10: e02626–18.
[205] Duan Y, Young R, Schnabl B. Bacteriophages and their potential for treatment of gastrointestinal diseases. Nature Reviews. Gastroenterology & Hepatology. 2022; 19: 135–144.
[206] Galtier M, De Sordi L, Sivignon A, de Vallée A, Maura D, Neut C, *et al*. Bacteriophages Targeting Adherent Invasive Escherichia coli Strains as a Promising New Treatment for Crohn's Disease. Journal of Crohn's & Colitis. 2017; 11: 840–847.
[207] Duan Y, Llorente C, Lang S, Brandl K, Chu H, Jiang L, *et al*. Bacteriophage targeting of gut bacterium attenuates alcoholic liver disease. Nature. 2019; 575: 505–511.
[208] Wang Y, Gao S, Lv J, Lin Y, Zhou L, Han L. Phage Display Technology and its Applications in Cancer Immunotherapy. Anti-cancer Agents in Medicinal Chemistry. 2019; 19: 229–235.