**The Place And Importance of the Gut-Liver Axis in Liver Diseases**

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**Abstract**

Liver diseases are considered global health problems that cause more than 1 million deaths each year. As a result of the increase in the prevalence of liver diseases worldwide, studies on different treatment methods have increased. One of these methods is diagnostic and therapeutic applications based on the examination of the intestinal and intestinal microbiota called where the intestine is called "second brain". In this study, the publications in the literature were examined in order to determine gut-liver axis relationship and treatment methods for liver diseases with gut modulation methods. Studies related to the subject have been searched in Google Scholar and Pubmed databases. The keywords "liver disease" and "gut-liver axis" and "microbiota" and "gut modulation methods" or "probiotic" or "prebiotic" or "symbiotic" or “antibiotic” or “bile acid regulation” or “adsorbent” or “fecal microbiota transplantation” were used in the searches. Research articles, systematic review and review examining the relationship between gut-liver axis and gut modulation methods are included in the review. Improvements have been achieved in biomarkers of liver diseases by providing intestinal modulation with probiotic, prebiotic, symbiotic, antibiotic and adsorbents applications, bile acid regulation and fecal microbiota transplantation. In the results of experimental and clinical studies, it was seen that the therapeutic potential of the treatments performed by applying probiotics, prebiotics and symbiotics was higher. The gut-liver axis is also an important way with positive results to develop strategies for preventing and treating liver diseases.

**Keywords:** Gut-liver axis, Gut modulation methods, Microbiota, Liver disease

**Introduction**

The gut-liver axis refers to the interaction between the gut and the liver, including the microbiota, and emerges as a result of the signals generated by environmental, genetic and dietary factors (Albillos et al., 2020). There is a strong relationship between immune response, intestinal barrier function, and microbiota dysbiosis (Porras et al., 2017). As more information became known about the role of bile in the gut-liver interaction, gut barrier homeostasis, and gut microbiome function and composition, it has begun to be recognized that many liver diseases are based on this axis (Albillos et al., 2020).

Intestinal microbiota dysbiosis has been associated with liver disorders such as non-alcoholic steatohepatitis (NASH), hepatic encephalopathy (HE), cirrhosis, alcoholic liver disease (ALD), and non-alcoholic fatty liver disease (NAFLD) (Mancini et al., 2018). The liver is affected by a change in the microbiome and mucosal immune response. Mucosal immunity also plays a role in steatohepatitis and autoimmune liver diseases, in which bacteria perception changes and enteric barrier function is impaired (Trivedi and Adams, 2016). The liver is important in the modulation of the gut microbiota through response to nutrients and bacterial end products taken through the portal vein and for its functions in enterohepatic circulation and bile acid production (Bajaj, 2019). Methods such as prebiotics, probiotics, symbiotics, antibiotics and fecal microbiota transplantation (FMT) are perceived as potential future treatments because of their ability to affect and correct markers that cause liver diseases by modulating the gut (Tilg et al., 2016).

Liver diseases are considered as global health problems that cause more than 1 million deaths each year (Qamar et al., 2018). Nonalcoholic fatty liver disease (NAFLD), one of the liver diseases, is the most common liver disease, affecting more than 65 million people in the United States and causing a financial burden of 103 billion dollars. In order to reduce the social and economic burden of liver diseases, molecular events should be elucidated and new therapeutic methods should be developed (Tripathi et al., 2018).

**Microbiota**

The human intestine is a complex ecosystem with a mass of about 1-2 kg (Suk and Kim, 2019). Microbiota contains to a live microbial community and includes viruses, bacteria, and Archaea and Eukarya habitat members (Vaughn et al., 2018). The microbiota composition varies significantly from birth to old age (Bajaj, 2019).

Intestinal microbiota has important roles in bacterial translocation, mucosal immune system and vitamin production (Suk and Kim, 2019). It indirectly regulates the functions of extraintestinal organs such as kidney, brain and liver and directly regulates intestinal functions (Konturek et al., 2018). The intestinal microbiota is involved in the production of short chain fatty acids (SCFA) and polysaccharide fermentation, which can be used for de novo synthesis of lipids, glucose or bile acids, or can be metabolized. In addition, it protects the intestinal barrier function against endotoxemia by ensuring the transport of lipopolysaccharides (Wolters et al., 2019).

Metabolites produced in microbiota have a good or bad role in metabolic diseases. It is known that *Bifidobacterium* and *Akkermansia* produce SCFAs in the intestinal lumen. SCFA’ların diyet lifleri ve prebiyotiklerle üretimi artmakta olup, artan tuz tüketimi ile üretimi azalmaktadır. The production of SCFAs with dietary fibers and prebiotics is increasing, and their production decreases with increasing salt consumption. SCFAs increase intestinal barrier function and reduce fat mass (Cani, 2019). As a matter of fact, Akkermansia muciniphila supplement has been reported to be well tolerated and safe when administered to humans, increases insulin sensitivity and lowers blood markers related to liver dysfunction (Depommier et al., 2019). It has been found that indole, a bacterial metabolite produced from tryptophan, one of the aromatic amino acids, reduces the damages of lipopolysaccharid (LPS) and hepatic inflammation (Beaumont et al., 2018). Imidazole propionate, another metabolite produced in the microbiota, contributes to the initiation of insulin resistance by blocking the insulin receptor signaling pathway and impairs glucose tolerance (Koh et al., 2018). Trimethylamine N-oxide (TMAO) produced in the intestinal microbiota is reported to increase vascular inflammation and promote the progression of cardiovascular diseases (Matsuzawa et al., 2019).

Dietary fibers such as inulin, oligofructose, galactooligosaccharides and arabinoxylanes suppress harmful species in the microbiota and increase the rate of beneficial bacteria. Polyphenols in fruit / wine and tea, a high-fiber diet, and a diet with a fat ratio of around 28-35% reduce the ratio of firmicutes / bacteroides, which are associated with modulating energy balance, while saturated fats and a fat diet (44-72%) increase this ratio (Yang et al., 2020). It is also stated that the Mediterranean diet is an effective method in the treatment of visceral obesity, overweight and serum transaminase in NAFLD patients (Biolato et al., 2019). As dietary fiber intake increases, there is a decrease in zonulin level, which is a marker of intestinal permeability, an improvement in hepatic steatosis, and a decrease in liver enzymes (Krawczyk et al., 2018). Vitamin D also has immunomodulatory properties and increases the rate of beneficial bacteria (Yang et al., 2020).

**Gut – Liver Axis**

The gut-liver axis theory was first proposed by Marshall in 1998 (Marshall, 1998). There is an anatomical connection between the intestine and the liver via the hepatic portal system. Through this connection, intestinal microbiota and formed metabolic products can affect liver pathology (Zhou et al., 2018). Approximately 70% of the liver blood is supplied through the portal vein, which contains intestinal microbial antigens and metabolites and most metabolites in the digestive system (Jiang et al., 2019).

Tight junctions, antimicrobial molecules (eg Reg3b) and a thick mucus layer (eg Muc-2) in the intestinal epithelium form a natural barrier against metabolic products and bacteria. These protective mechanisms can be damaged by endogenous factors (e.g. endocannabinoids, TNF), harmful agents (e.g. dextran suphate sodium (DSS)) and dietary factors (e.g. high fat intake) (Brandl et al., 2017). As a result of increased permeability in the intestine and intestinal dysbiosis, the translocation of microbial products and microorganisms containing DNA and cell wall components (β-glucan and endotoxins) associated with PAMPs (pathogen-associated molecular patterns; which also activate the stellate cells that enable the development of fibrosis) and MAMPs (microbial-associated molecular patterns) occurs (Tripathi et al., 2018).

Antigens pass through tight junctions and either modulate the T cell response activating the adaptive immune system or are recognized by dendritic cells. Minimum concentrations of PAMPs (flagelin, peptidoglycans and lipopolysaccharides (LPS)) activate nuclear factor kappa B (NF-Kβ) through toll-like receptors (TLRs) and nod-like receptors (NLRs). NF-Kβ causes the production of chemokines and inflammatory cytokines that enter the portal circulation (Milosevic et al., 2019). The immune response in the liver against dysbiosis in the intestine is shown in Figure 1.

The liver receives most of its food and blood supply from the intestine through the portal vein. Therefore, the liver is the first organ to be exposed to intestinal toxic factors (bacteria, bacterial products or damaged metabolites) (Suk and Kim, 2019). Since the ingested xenobiotic interacts with the intestinal microbiota before being transported to the liver via the portal circulation, the microbiota plays an important role in regulating drug metabolism (Ojeda et al., 2016). The decrease in the bioavailability of Levi-dopa (L-dopa) used for the treatment of Parkinson's disease in patients with *Helicobacter pylori* colonization in the stomach is an example (Niehus and Hensel, 2009).

“Figure 1 is here”

A change in the enzymatic activity of the liver has been associated with the intestinal microbiota (Ojeda et al., 2016). In case of liver injury or disease, microbial dysbiosis in the intestine may increase. Inflammatory factors produced in the liver increase the permeability of the intestinal mucosa. On the other hand, when the intestinal barrier function is damaged, bacteria and their products in the intestine are transported to the liver via the portal vein and begin to further damage the immune system in the liver (Jiang et al., 2019).

**Liver Diseases**

Liver diseases are an important cause of mortality and morbidity worldwide. The most common etiologies of chronic liver disease include chronic hepatitis C virus (HCV) infection, chronic hepatitis B virus (HBV) infection, alcohol abuse, and nonalcoholic fatty liver disease (NAFLD). Chronic liver damage can lead to liver fibrosis. In the last stage of fibrosis, liver failure, portal hypertension and cirrhosis can be seen (Kennedy et al., 2018).

Bacterial translocation is the migration of bacterial endotoxins (e.g. lipopeptide, peptidoglycan, LPS) or living microorganisms from the intestinal lumen to the extraintestinal areas and mesenteric lymph nodes. Bacterial translocation is associated with liver failure and is evident in advanced liver disease (Alexandra et al., 2017).

There are non-parenchymal Kupffer cells and monocyte-derived macrophages in the liver. Kuppfer cells, a community of macrophages located in the liver, have phagocytic properties, provide intercellular interaction, initiate inflammation, and assist in the recruitment of blood-borne monocytes (Kazankov et al., 2019). It responds more to lipopolysaccharides than hepatocytes (Milosevic et al., 2019). Monocyte-derived macrophages are a key component of the immune system (Kazankov et al., 2019). Toll-like receptor (TLR) can transform exaggerated inflammatory responses to systemic inflammation (Wilde and Katsounas, 2019).

**Nonalcoholic steatohepatitis (NASH)**

Nonalcoholic steatohepatitis is an inflammatory and often progressive subtype of nonalcoholic fatty liver disease (NAFLD). As the disease progresses, cirrhosis may develop and liver transplantation may be needed (Sheka et al., 2020). Its proportion in the general population is estimated to be 1.5% and 6.45% (Younossi et al., 2019).

Disruption of the intestinal vascular barrier and intestinal epithelial barrier are among the events that lead to the formation of NASH (Mouries et al., 2019). Mouzaki et al. measured the total bacterial content in the stool samples they collected. They revealed that there is a significant relationship between the low percentage of *Bacteroidetes* and the presence of NASH regardless of diet and BMI (Mouzaki, 2013). Pathophysiological events leading to hepatic steatohepatitis as a result of intestinal dysbiosis;

1. Increase in hepatic inflammation due to TLR-mediated cytokine production and metabolic endotoxemia,
2. Hepatic steatosis (*de novo* lipogenesis),
3. Increase in insulin resistance,
4. Inflammation and oxidative stress induction by endogenous ethanol and change in intestinal barrier permeability (leaky gut),
5. Change in farnesoid X receptor (FXR) signaling and bile acid metabolism,
6. The change in choline metabolism as a result of dysbiosis in the intestine and a decrease in VLDL (very-low density lipoprotein) secretion and its combination (Konturek et al., 2018).

**Nonalcoholic fatty liver disease (NAFLD)**

NAFLD is associated with increased plasma endotoxin levels as a result of bacterial proliferation in the small intestine, changes in intestinal microbiota, and intestinal permeability. Endotoxins produced in the gut, molecules associated with hepatocellular damage, and lipid and lipid metabolites contribute to macrophage activation (Kazankov et al., 2019). When the intestinal flora balance is disturbed, it can cause intestinal endotoxemia and can lead to the progression of NAFLD (Zhou et al., 2018). Its ratio in worldwide is estimated to be 25.2% (Younossi et al., 2016).

**Alcoholic steatohepatitis (ASH)**

The main reason for the progression and development of alcoholic steatohepatitis is inflammatory processes. Inflammatory processes develop in response to loss of intestinal barrier integrity, microbial dysbiosis (unstable or abnormal intestinal microbial composition), hepatocellular stress / death, and impaired communication between organs (Gao et al., 2019). Apoptotic hepatocytes and hepatocyte ballooning are observed in these patients (Choi et al., 2018). Infiltration of neutrophils is also seen in severe ASH (Gao et al., 2019).

**Alcoholic liver disease (ALD)**

Alcoholic liver disease is one of the most common liver diseases seen in the US and Europe. The amount of heavy chronic alcohol consumption that causes the disease occurs when there is >40 g of pure alcohol (equating to> 1 liter of 5 vol% beer or 375 ml of 13 vol% wine) every day (Seitz et al., 2018).

One of the consequences of acute alcohol damage and one of the factors that lead to the progression of liver damage is hepatocyte apoptosis caused by oxidative stress. The immune cell activation cycle also allows the liver damage to progress. Excessive hepatocyte stimulates apoptosis, which stimulates the production of reactive oxidative species and proinflammatory cytokines (Choi et al., 2018).

**Hepatic encephalopathy (HE) ve spontaneous bacterial peritonitis (SBP)**

Hepatic encephalopathy is a complication of chronic or severe acute liver failure and is characterized by changes in cognitive, personality, motor function and consciousness. Conditions that also affect the intestine such as digestive system bleeding, infection, electrolyte disturbance, dehydration, constipation, overdose of diuretics are the leading factors of HE episodes (Weissenborn, 2019).

Spontaneous bacterial peritonitis is the most common type of bacterial infection in patients with cirrhosis, and HE is a serious complication that causes high mortality (10% -50%) and acute kidney injury in cirrhotic patients. Decreasing intestinal motility and causing excessive bacterial growth in the intestine, deficiency in the local immune response system, bacterial translocation and changes in the function and structure of the intestinal mucosal defense barrier are among the mechanisms that lead to SBP (Pericleous et al., 2016; Tergast et al., 2018).

**Hepatocellular carcinoma (HCC)**

Hepatocellular carcinoma is responsible for most primary liver cancers. Hepatocellular carcinoma formation is mainly due to Hepatitis C virus (HCV) and Hepatitis B virus (HBV) infections and sometimes NAFLD and/or alcohol abuse. The contribution of being alcoholic (low dose of risk initiation: 10 g/1 unit/day) to HCC cases was found to be approximately 30% in 2015 (Ganne-Carrié and Nahon, 2019).

In the intestine, pathogenic bacteria overgrow and liver DNA and carcinogens bind. Later, intestinal barrier function is impaired. Endotoxemia is observed (LPS increases, TLR4 signal activation occurs etc.) and bacterial translocation occurs. Proinflammatory cytokines are released and Kupffer cells are activated (Wan and El-Nezami, 2018).

**Hepatitis B virus (HBV) infection**

Hepatitis B virus is a hepatotropic DNA virus belonging to the Hepadnaviridae family, which can cause a chronic infection in humans through immune anergy (absence of a normal immune response to a specific allergen or antigen), which is infected and multiplies largely in hepatocytes (Yuen et al., 2018). It is thought to infect approximately 350-400 million people worldwide. Approximately 1 million people die each year from diseases associated with HBV (Kasap et al., 2020). Hepatitis B virüs replicates itself in liver cells and induces an antagonistic immune response that includes T helper 1, T helper 2, T helper 17 and T cell (promotes an appropriate immune response against infection) simultaneously with antigen release (Tuyji Tok et al., 2020) .

**Hepatitis C virus (HCV) infection**

Hepatitis C is an infectious disease caused by HCV, a hepatotropic RNA virus belonging to the *Flaviviridae* family, that can cause acute and then chronic HCV development, resulting in liver damage (Manns et al., 2017). It is estimated to infect more than 170 million people worldwide and 3-4 million people are infected each year (Cacoub and Comarmond, 2019; Kuna et al., 2019). Chronic HCV infection can trigger a chronic inflammatory process, leading to cirrhosis, death, liver fibrosis, and hepatocellular carcinoma (Manns et al., 2017). As a result, the liver-related mortality rate caused by HCV is on average 350,000 people annually (Cacoub and Comarmond, 2019).

**Liver cirrhosis**

Liver cirrhosis is a recent organic disease that develops as a result of immune dysfunction and disruption of antimicrobial elimination and recognition mechanisms in macrophages (Wilde and Katsounas, 2019). It is one of the most common causes of mortality and morbidity worldwide and has a death rate of 26.4% in 2 years even in the USA (Acharya et al., 2017).

Bacterial translocation is triggered by loss of Toll-like receptor (TOR) tolerance and / or uncontrolled activation of the immune cell response. When TLR-2 and TLR-4 dependent pathways are activated, systemic inflammatory activity increases with endotoxin or lipopolysaccharide (LPS) and cytokine production is facilitated. The secretion of reactive oxygen species (ROS) increases and leaky gut occurs as a result of increased permeability in the intestine (Wilde and Katsounas, 2019). The most common infections in patients with cirrhosis are urinary tract infection, soft tissue infections, pneumonia, spontaneous bacterial peritonitis (SBP) and spontaneous bacteremia (Alexopoulou et al., 2017).

**Intestinal Modulation Methods to Treat Liver Diseases: Examples from Animal and Human Studies**

Studies on probiotic, prebiotic, symbiotic, antibiotic and adsorbents applications, bile acid regulation and fecal microbiota transplantation methods for intestinal modulation have been conducted. The results of some of the studies are shown in Table 1.

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**Probiotics**

Probiotics are defined by the International Scientific Association of Probiotics and Prebiotics as "living microorganisms that, when administered in sufficient amounts, provide health benefits to the host." Probiotics are named according to the strain, genus and species (Sanders et al., 2018). The most common types are *Lactobacillus johnsonii, Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus gasseri, Lactobacillus plantarum, Lactobacillus rhamnosus, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis ve Bifidobacterium bifidum* (Zawistowska-Rojek and Tyski, 2018). Lactobacilli, Bifidobacterium, lactococci and some yeasts are accepted as “generally regarded as safe (GRAS)”. Bacillus, Enterococcus, streptococci and other spore-forming bacteria are groups of organisms that are used as probiotics but are not considered safe (Snydman, 2008).

According to the report published by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) in 2002 (FAO and WHO, 2002); “Probiotics may theoretically be responsible for four types of side-effects:

1. Systemic infections
2. Deterious metabolic activities
3. Excessive immune stimulation in susceptible individuals
4. Transfer again "

Especially in some clinical conditions such as leakly gout, post-organ transplant, malignancies and diabetes mellitus, and in neonatal individuals, they are likely not to benefit from the beneficial effects of probiotics. Some probiotic strains to be administered in these groups may worsen the conditions due to weak immunity and may turn into pathogens causing sepsis, endocarditis and pneumonia (Kothari et al., 2019).

After oral administration, probiotic bacteria interact with lamina propria or intestinal epithelial cells via Toll-like receptors and induce the production of different chemokines and cytokines. Probiotics activate T cells that release IL-10. It also strengthens the intestinal barrier by increasing tight junction proteins, mucins, and Paneth and Goblet cells (Galdeano et al., 2019). Probiotics chelate the metal ion, produce antioxidant metabolites (Folate, GSH) and increase the host's antioxidant activity (SOD, CAT) and antioxidant metabolites. It also reduces the activities of ROS-producing enzymes and regulates the intestinal microbiota (Wang et al., 2017).

**Prebiotics**

Prebiotics are food components that can be selectively digested and stimulate the activity and/or growth of probiotics in the colon after fermentation and benefit the host (Tsai et al., 2019). Prebiotic dietary fiber sources are beta-glucan, inulin, oligofructose, FOSs, GOSs, isomaltooligosaccharides, guar gum, lactulose, resistant starches (RSs) and maltodextrin, xylooligosaccharides and arabinooligosaccharides (Carlson et al., 2018).

Criteria that a compound must meet for classification as a prebiotic;

1. The activity and / or growth of intestinal bacteria should be selectively stimulated with this compound and this should benefit the health of the host.
2. It must be able to be fermented by the intestinal microbiota
3. It should not be hydrolyzed by mammalian enzymes, should be resistant to the acidic pH of the stomach and should not be absorbed in the GIS (Davani-Davari et al., 2019).

Prebiotic dietary fibers provides increase in Lactobacilli and Bifidobacteria and calcium absorption and decrease in protein fermentation, allergy risk and pathogenic bacteria population. It produces beneficial metabolites, improves immune defense, and is effective on gut barrier permeability (Carlson et al., 2018). Fiber and prebiotic consumption affects the gastrointestinal microbiota, but individual responses are different. These phenotypic responses depend on the dosage of the respective dietary polysaccharide, the individual's microbiota composition, whole dietary fiber intake, and host genetics (Holscher, 2017).

After the prebiotics are fermented in the gut, short-chain fatty acids increase in the portal vein blood (propionate and acetate doubles) and in the cecum. While acetate acts as the lipogenic substrate, propionate helps reduce hepatic lipogenesis. Prebiotics reduce triglyceride through inhibition of lipogenic enzymes fatty acid synthase, ATP citrate lyase, coenzyme A carboxylase, malic enzyme and glucose-6-phosphate dehydrogenase (Tilg et al., 2016).

**Symbiotics**

Symbiotics are a combination of probiotics and prebiotics (Hadi et al., 2020; Sangoni and Ghavamzadeh, 2019). It creates a synergistic effect to increase both the durability of bacteria as they pass through the upper part of the gastrointestinal tract and their effectiveness in the large intestine (Hadi et al., 2020). Probiotics used as symbiotics are generally strains belonging to Bifidobacterium, Streptococcus, Lactobacillus and Enterococcus genera. Prebiotics are generally GOS, FOS, inulin, xylose olgosaccharide, lactulose, lactosucrose, lactitol and transgalactooligosaccharides (Bustamante et al., 2020).

It has beneficial effects on dyslipidemia, obesity, insulin resistance, oxidative stress and inflammation (Sangoni and Ghavamzadeh, 2019). Probiotics, prebiotics and symbiotics can play a role in the improvement of NAFLD by delaying the absorption of macronutrients, by metabolism of bile acids, by reducing the absorption of toxic elements with improved barrier function (lipopolysaccharide, trimethylamine, etc.) and by the production of short-chain fatty acids (Loman et al., 2018) . The benefits of symbiotic consumption by humans: 1) It reduces nosocomial infections and prevents bacterial translocation in surgical patients, 2) Improves immunomodulation power, 3) Improves liver function in cirrhosis patients 4) Balances the gut microbiota and increases the level of bifidobacteria and lactobacilli, etc. (Pandey et al., 2015).

**Antibiotics**

Antibiotics are used in clinical practice in the prophylaxis and treatment of infections to prevent the activity of pathogens. It reaches therapeutic serum concentrations by effectively crossing the intestinal barrier (Becattini et al., 2016; Wiest et al., 2017).

Rifaximin is a nonabsorbable antibiotic that lowers inflammation by reducing bacterial translocation and modulating gut microbiota function and composition. It improves hemodynamics and reduces endotoxemia in patients with cirrhosis. It is a safer option in advanced liver diseases as the amount of drug in circulation is low (Ponziani et al., 2015). Statins reduce portal hypertension and have beneficial effects on intrahepatic circulation (Pose et al., 2020). Vancomycin is an agent used in the treatment of Gram-positive beta-lactam-resistant bacteria and methicillin-resistant Staphylococcus aureus and its dose is adjusted according to the plasma trough level and body weight of the drug (Álvarez, 2016). Amoxicillin, on the other hand, is an antibiotic agent with a widespread antibacterial spectrum used against gram-negative organisms in a limited amount and widely used against gram-positive organisms (Türkan and Atalar, 2018).

With antibiotic treatment, the expression of antimicrobial peptides (AMPs) and the thickness of the mucus layer decrease, commensal communities in the intestine are exhausted and the susceptibility to infections increases (Becattini et al., 2016). Thus, dysbiosis occurs as a result of a decrease in microbial diversity and loss of beneficial microorganisms (Ponziani et al., 2016). It should be kept in mind that exposure to antibiotics, even for short periods, especially in infancy, causes long-term effects on the microbiota and makes individuals susceptible to different diseases (Becattini et al., 2016).

**Bile acid regulation**

In the liver, bile acids are produced from cholesterol and metabolized in the gut by the microbiota. Bile acids can modulate the gut microbial composition by activating innate immune genes found in the small intestine. Therefore, microbial modulation of bile acids can affect host metabolism by causing an altered signal via the bile acid receptors FXR (farnesoid x receptor) and / or TGR5 (G protein-coupled membrane receptor 5) (Wahlström et al., 2016).

Farnesoid X receptor (FXR) is a bile acid nuclear receptor and is produced in excess in kidneys, small intestine mucosa and liver. The mechanism of action of FXR on steatosis; It is FXR-dependent induction of PPARα and several genes associated with VLDL and TG metabolism and inhibition of SREBP-1c with small heterodimer partners (Arab et al., 2018). The TGR5 (aka GPBAR1) receptor, on the other hand, functions in the regulation of glucose metabolism and energy homeostasis. TGR5 ligands play a role in anti-inflammation and negatively regulate hepatic inflammation through NF-kB (Wang et al., 2011). Obeticholic acid (INT-747), Px-104, Tropifexor (LJN452), Nidufexor (LMB763), Cilofexor (GS-9674), EYP001 and MET409 are nonsteroidal FXR agonists used in clinical studies in NASH. INT-767 is a FXR / TGR5 agonist and INT-777 is a TGR5 agonist and is used in clinical studies on some liver diseases (Gege et al., 2019).

**Adsorbents**

Adsorbents allow bacterial products and toxins produced in the intestine to bind to an adsorptive material, reducing its absorption and then excreting it with feces reducing its absorption and then excreting it with feces to prevent systemic circulation and liver flow (Wiest et al., 2017).

Lactulose (a nonabsorbable disaccharide), one of the adsorbents, is used in the treatment of hepatic encephalopathy and reduces ammonia absorption in the intestine. Cholestramine is used in the treatment of itching and allows bile acids to bind in the intestinal lumen (Wiest et al., 2017). Oral activated adsorbent AST-120 is used in chronic kidney disease, modulates immune cells in the intestinal mucosa and inhibits the acceleration of atherosclerosis (Tsuchida et al., 2016). A new synthetic activated carbon named Yaq-001 developed by Yaqrit Ltd. is used in studies to treat intestinal microbiota and regulate metabolites in NAFLD (Pan et al., 2020).

**Fecal microbiota transplantation (FMT)**

Fecal microbiota transplantation aims to optimize microbiota function and composition (Vaughn et al., 2018). Failure of treatment of antibiotic-resistant *Clostridium difficile* infection is the basis of FMT. Freeze-thawed donor microbiota can be introduced into fecal microbiota by nasoduodinal or nasogastric route, enema or endoscopic route. Recently, encapsulated freeze-dried preparations have been made by providing the capsule to be administered orally, without the need for colon cleansing beforehand (Vaughn et al., 2018). With FMT, AMP secretion, mucus production, and a healthy microbiota can be restored and colonization resistance against pathogens can be achieved (Becattini et al., 2016).

**Conclusion**

As a result, the relationship of intestinal microbiota with liver as well as with many organs has been proven by studies. Intestinal microbiota is associated with chronic liver diseases such as NAFLD, HCV, HBV, liver cirrhosis, HCC, ALD, ASH, HE, NASH. However, the mechanisms on which this relationship is based remain unclear. Considering the experimental and clinical studies, it was seen that the therapeutic potential of the treatments performed by applying probiotics, prebiotics and symbiotics was higher. There is a need for large controlled prospective and patient follow-up studies regarding the relationship between host-microbiota, which product to choose and safe usage amounts.

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**Figure 1. The immune response in the liver against dysbiosis in the intestine.** Intestinal dysbiosis occurs in the intestinal lumen as a result of genetic factors, infection, specific xenobiotics, alcohol, injury and HFD and lower fiber nutrition, and intestinal permeability increases. With bacterial translocation, products such as PAMPs (pathogen-associated molecular patterns), MAMPs (microbial-associated molecular patterns), bacteria, VOCs (volatile organic compound), DAMPs (damage-associated molecular patterns), pathogens etc pass through tight junctions and reach hepatosites via the portal vein and may cause damage resulting in hepatocellular carcinoma. Lipopolysaccharides that pass into intestinal epithelial cells cause metabolic endotoxemia and cause inflammation and insulin resistance in muscle and adipose tissue. EtOH passing through the lumen can increase ROS production and cause steatosis in the liver. SCFA; GPR41 and GPR43 activate dependent mechanisms, acting as substrates for *de novo* lipogenesis and gluconeogenesis in the liver. With the decrease of ANGPL4 in the lumen, fat storage increases in adipose tissue and liver. TLR, tool-like receptor; NLR, nod-like receptors; TJ, tight-junction; ANGPTL4, lipoprotein lipaz inhibitörü; LPS, lipopolysaccharide; SCFA, short chain fatty acids; TNF-α, tumor necrosis factor-α; Nfkβ, nuclear factor kappa-β.

Table 1. Gut modulation methods applied to treat different liver diseases

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Medication** | **Mechanism** | **Target population** | **İmportant results** | **Reference** |
| *B.bifidum W23, B. Lactis W52, L. Acidophilus W37, L. Brevis W63, L. Casei W56, L. Salivarius W24, L. Lactis W19, L. Lactis W58* | Probiotic | 80 patients with cirrhosis | Serum neopterin level and ROS production increased significantly.Some increase in liver function has been observed | Horvath et al., 2016 |
| *L.acidophilus* ATCC B3208, *B.lactis* DSMZ 32269, *B.bifidum* ATCC SD6576, *L.rhamnosus* DSMZ 21690 | Probiotic | 64 obese children with NAFLD | Improved lipid profile | Famouri et al., 2017 |
| Multi-probiotic “Symbiter” (concentrated biomass of 14 probiotic bacteria genera *Lactobacillus, Propionibacterium, Bifidobacterium, Lactococcus*) | Probiotic | 58 NAFLD patients | Decreased liver fat, TNF-α and IL-6 levels and aminotransferase levels were observed. | Kobyliak et al., 2018a |

Table 1. (continued) Gut modulation methods applied to treat different liver diseases

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Medication** | **Mechanism** | **Target population** | **İmportant results** | **Reference** |
| Omega-3 + probiotic | Probiotic | Type 2 DM patients with 48 NAFLD | Reduction in serum gamma-glutamyl transpeptidase, total cholesterol and triglycerides | Kobyliak et al., 2018b |
| VSL#3 | Probiotic | 19 obese adolescents | No significant changes in liver fat / fibrosis were observed | Jones et al., 2018 |
| Chicory enriched with inulin | Prebiotic | Type2 DM | Significant decrease in liver function tests (AST, ALT) | Farhangi et al., 2016 |
| Quercetin | Prebiotic | Obesity-associated NAFLD animal model | Decrease in intrahepatic lipid accumulation and insulin resistance | Porras et al., 2017 |
| Oligofructose | Prebiotic | Individuals with NASH | Improvement in liver steatosis,Increase in *Bifidobacterium* | Bomhof et al., 2019 |

Table 1. (continued) Gut modulation methods applied to treat different liver diseases

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| --- | --- | --- | --- | --- |
| **Medication** | **Mechanism** | **Target population** | **İmportant results** | **Reference** |
| Probiotic (*L.* *Reuteri*) + Prebiotic (guar gum and inulin) | Synbiotic | Individuals with NASH | Reduction in BMI, waist circumference and steatosis,Lost weight | Ferolla et al., 2016 |
| Probiotic (*L.rhamnosus, L.casei, L.acidophilus, L.bulgaricus, S.thermophilus, B.breve, B.bulgaricus*) + prebiotic (fructooligosaccharide) + Vitamin E | Synbiotic | NAFLD | Decrease in serum malondialdehyde, liver enzymes and TNFα  | Ekhlasi et al., 2017 |
| Bifidobacterium animalis and inulin or conventional yoghurt daily | Synbiotic | 102 NAFLD patients | Improved liver enzyme concentrations and hepatic steatosis | Bakhshimoghaddam et al., 2018 |
| Grape seed powder + LAB (*Leuconostoc mesenteroides*, *Lactobacillus* *kefiri* DH5) | Synbiotic | Mice fed a high-fat diet | Changes intestinal permeability and cecum propionate | Kwon et al., 2019 |

Table 1. (continued) Gut modulation methods applied to treat different liver diseases

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| --- | --- | --- | --- | --- |
| **Medication** | **Mechanism** | **Target population** | **İmportant results** | **Reference** |
| Probiotic (L. paracasei ssp paracasei, L.plantarum, Leuconostoc mesenteroides, Pediococcus pentosaceus) + Prebiotic (oat bran, peçtin, resistant starch, inulin) + Branched chain amino acids | Synbiotic | 49 patients with Hepatic Encephalopathy | It caused cognitive improvement without any significant change in ammonia levels. | Vidot et al., 2019 |
| Amoxicillin / vancomycin | Antibiotic | 57 obese, prediabetic men | 7 days of antibiotic therapy altered the microbial composition but did not affect adipocyte size, intestinal permeability, systemic inflammation, energy / substrate metabolism, and tissue specific insulin sensitivity. | Reijnders et al., 2016 |

Table 1. (continued) Gut modulation methods applied to treat different liver diseases

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| **Medication** | **Mechanism** | **Target population** | **İmportant results** | **Reference** |
| Rifaximin | Antibiotic | 50 individuals with NASH | Serum endotoxins are decreased. Proinflammatory cytokines, NAFLD-liver fat score, insulin resistance, and cytokeratin-18 are improved. | Abdel-Razik et al., 2018 |
| Rifaximin | Antibiotic | Obese mice | Prevents chronic excess ethanol-induced steatohepatitis | Kitagawa et al., 2019 |
| Rifaximin + different doses of Simvastatin | Antibiotic | Patients with decompensated cirrhosis in six European countries | Administration of rifaximin and simvastatin 40 mg / day caused a significant increase in rhabdomyolysis. The use of rifaximin and simvastatin 20 mg/day was found appropriate. | Pose et al., 2020 |

Table 1. (continued) Gut modulation methods applied to treat different liver diseases

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| **Medication** | **Mechanism** | **Target population** | **İmportant results** | **Reference** |
| INT-777 (TGR5) and INT747/obeticholic acid (FXR) | Bile acid regulation | Ovariectomized and high-fat diet-induced NAFLD mice | BA receptor agonists correct metabolic changesEnergy expenditure increasesExpression patterns of key metabolic genes change. | de Oliveira et al., 2016 |
| Obeticholic acid | Bile acid regulation | Dietary and metabolically obese NAFLD mice | Improves NAFLD and glucose tolerance in dietary obesity | Haczeyni et al., 2017 |
| INT-767 (FXR/TGR5 agonisti)  | Bile acid regulation | Rats with NASH induced by high fat diet | Reduces hepatic infiltration and lipid accumulation of immune cellsSuppresses TNF-α and NF-κB signaling pathway, attenuating proinflammatory responseRepairs glucose and lipid metabolism | Hu et al., 2018 |

Table 1. (continued) Gut modulation methods applied to treat different liver diseases

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| --- | --- | --- | --- | --- |
| **Medication** | **Mechanism** | **Target population** | **İmportant results** | **Reference** |
| Adsorbent (Yaq001) | Adsorption | Cirrhosis | It modulates monocyte function related to inflammasome activation and ROS production. | Macnaughtan et al., 2015 |
| Fecal microbiota transplantation + prebiotic (pectin) | FMT | ALD | Repair intestinal homeostasis and prevent liver inflammation and steatosis | Ferrere et al., 2017 |