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FROM THE GUT TO THE LIVER: EXPLORING THE GUT MICROBIOME'S IMPACT ON ALCOHOL-ASSOCIATED LIVER DISEASE

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Abstract:

Background: Excessive alcohol use disrupts gut bacteria, leading to liver disorders such as alcohol-associated liver disease (ALD) and cirrhosis. Advances in sequencing reveal changes in the gut microbiota related to alcohol intake, suggesting potential treatments. This review examines the complex link between gut microbiota, liver health, and alcohol consumption. It also highlights the importance of microbial-based therapies such as prebiotics, probiotics, postbiotics, and synbiotics.

Methods: We conducted a comprehensive literature review from October to November 2023. using PubMed, Google Scholar, and Google. Studies of any biological sex, ethnicity, and age were included. The studies reviewed spanned a period of 11 years from 2013 to 2024.

Conclusion: Therapeutic approaches based on microbes, such as probiotics, postbiotics, prebiotics, and synbiotics present promising treatment alternatives that could improve the management of ALD.

Keywords: *Alcohol-associated liver disease, gut microbiome, prebiotics, probiotics, postbiotics, synbiotics*

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INTRODUCTION:

The gut, often called the body's “second brain”, is crucial to overall health as it hosts a dynamic and diverse microbial community. Chronic and excessive alcohol intake can significantly alter the gut microbiota, leading to a range of liver disorders such as alcoholic liver disease (ALD), hepatitis, cirrhosis, and hepatocellular carcinoma. [1] Alcohol use has been linked to gut microbiota (GM) alterations even before the onset of ALD.

Prebiotics are nondigestible short-chain fatty acids, that act as a food source for beneficial gut bacteria.[2] Probiotics are living microbes that, when taken in sufficient quantities, provide health advantages to the host.[3]. A postbiotic is defined as "a preparation of inanimate microorganisms and their components that confers a health benefit on the host".[4] Lastly, a synbiotic is a combination of probiotics and prebiotics. This review explores the changes in the composition, function, and metabolic activities of gut microbiota in relation to ALD by utilizing advancements in high-throughput sequencing. [1] Furthermore, this review aims to explain how altered gut microbiota influences ALD's progression and assess the efficacy of gut microbiota modulation, specifically through prebiotic, probiotic, postbiotic, synbiotic interventions.

METHODS

A comprehensive search was conducted from October to November 2023 using PubMed, Google Scholar, and Google search engine. Studies of any biological sex, ethnicity, and age were included. The studies reviewed spanned a period of 11 years from 2013 to 2024. The general search strategy involved the keywords: gut microbiome, gut microbiota, intestinal microbiota, alcohol liver disease, and alcohol-associated liver disease.

DISCUSSION

ALD is a significant contributor to liver-associated deaths and is the predominant reason for liver transplants. It accounts for approximately 40% to 50% of all liver transplant cases in affluent countries. [5] The reciprocal interaction between the gut and its microbiota and the liver is known as the “gut-liver axis”.[6] Seventy percent of components generated from gut microbes reach the liver from the human gut. The gut-liver axis preserves the immune system's homeostasis, which is essential in defending the body against potentially dangerous and harmful materials from the gut.[7] The gut's epithelial lining normally acts as a barrier between the gut and the liver, but when this lining is destroyed or the gut microbiota is disturbed, microbes and microbial products can more easily infiltrate into the portal vein and trigger inflammation of the liver. Changes in the gut-liver axis have been linked to cirrhosis, hepatocellular carcinoma, non-alcoholic liver disease, and alcoholic liver disease.[8]

Gut microbiota impact on liver health

The intestinal microbiota and bacterial products may contribute to developing liver diseases via various mechanisms such as increased intestinal permeability, chronic systemic inflammation, short-chain fatty acid production, and metabolic changes. [3] The intestinal microbiota is required for the breakdown of food, vitamin synthesis, metabolism, immune system function, inflammation, and cell proliferation. [9] Recent studies have highlighted the reciprocal interaction between the gut and the liver. This interaction is primarily due to the liver obtaining 75% of its blood flow from the intestines through the portal vein, and in turn, the liver secretes bile acids into the biliary tract. [9] [10] Bile acids, produced in the liver, play an essential role in fat digestion and metabolism regulation. Their interaction with the gut microbiota can influence gut health and metabolic processes, thereby influencing the onset and advancement of alcohol-related liver disease. [11] The gut microbiome can alter the structure of the intestinal barrier, such as tight junctions and mucus production, resulting in increased permeability. This allows more bacterial fragments and endotoxins to enter the liver and possibly lead to inflammation thereby contributing to the progression of liver disease. [12]

Impact of alcohol on gut microbiota

ALD develops in individuals who chronically misuse alcohol. Both animal and human studies indicate that alcohol consumption alters the gut microbiota, leading to dysbiosis. Drinking alcohol causes enteric dysbiosis and small intestinal bacterial overgrowth by increasing gut permeability.[13] Fatty liver can progress to fibrosis and cirrhosis with continued alcohol consumption, which can lead to portal hypertension or liver failure. Bacterial products cause an inflammatory response in the liver, leading to hepatic inflammation. [14] Yan et al.'s study provided additional evidence that mice given alcohol for three weeks experienced dysbiosis and bacterial overgrowth in the proximal small intestine. The mucin breakdown is thought to be caused by an overgrowth of Akkermansia muciniphila, which was interestingly shown in mice given alcohol. Furthermore, mice given alcohol had a decreased Lactobacilli population.[3][15] The impact of alcohol on the Gut Microbiome is summarized in (**Table 1**).

Table 1: Impact of alcohol on gut microbiome.

Impact of Alcohol on Gut Microbiome	Effects and Consequences
Changes the Flora Composition	Disrupts balance of gut bacteria, decreasing good bacteria and increasing harmful ones. [10]
Increased Gut Permeability	Weakens the intestinal barrier, allows harmful substances into bloodstream. [10]
Promotes Inflammation	Gut inflammation, progress to additional damage and disease. [16]
Disrupts Mucosal Integrity	Overgrowth of harmful bacteria, disrupting balance. [12]
Affects Metabolic Functions	Alters carbohydrate, protein, and fat metabolism in the gut, impacting overall energy balance. May influence the synthesis of vitamins and neurotransmitters, affecting both gut and brain health. [12][17]
Induces Dysbiosis	Increases the likelihood of gastrointestinal disorders and impairs nutrient absorption. [12]

Clinical manifestations of alcohol-associated liver disease

The cellular and molecular mechanisms underlying the evolution of ALD remain poorly understood despite years of intensive investigations.[3] Alcoholic steatohepatitis, a condition that causes inflammation of the liver and can proceed to alcoholic liver disease (ALD), is arguably the most well-known consequence of long-term alcohol consumption.[18][19][20] Research on patients with alcoholism and animal models strongly suggests that microbial factors derived from the gut, particularly bacterial endotoxins like lipopolysaccharide, are essential for starting the inflammatory cascades in the liver that lead to alcohol-induced liver damage.[21][22][23] There are different progressive stages of ALD and impact of alcohol at these stages differs (**Table 2**).

Table 2: Stages of alcohol-associated liver disease and alcohol impact.

Stages of ALD	Impact of Alcohol
Steatosis	Earliest and most common stage of ALD. accumulation of fat in hepatocytes. [9]
Alcoholic Hepatitis	Acute hepatic inflammation due to steatosis and alcohol consumption. [23]
Fibrosis	Alcoholism and pro-inflammatory cytokines stimulate stellate cells, resulting in progressive fibrosis. [24]
Cirrhosis	Persistent alcohol abuse in the presence of fibrosis leads to cirrhosis, characterized by extensive scarring. [25]
Hepatocellular Carcinoma	Liver cirrhosis, DNA damage, oxidative stress in liver cells, and alcohol-induces chronic inflammation increase the risk of HCC [26]

Abbreviations: ALD- alcohol-associated liver disease, HCC- Hepatocellular Carcinoma.

Approaches to treating alcohol-associated liver disease

Unfortunately, there are no Food and Drug Administration approved treatments for ALD at the time of this review. Depending on the severity of the disease and other comorbidities, the standard treatment for ALD consists of corticosteroids, nutritional support, phosphodiesterase, and tumour necrosis factor alpha.[27] For those in the early stages of ALD, abstaining from alcohol completely is often regarded as the best way to manage the disease. [28] In addition to alcohol cessation, an additional approach to treating ALD that aims to prevent or delay hepatic damage could include therapeutic modification of the gut microbiota.[3] Interventions such as probiotics, prebiotics, and symbiotics hold the potential to manage and mitigate liver damage associated with alcohol abuse.[29] Giving probiotics reduced the amount of circulating endotoxins and reduced liver injury. [29] Prebiotics (oats) can reduce rat liver damage by decreasing gut leakiness. [30] Short-term synbiotic treatment dramatically alter gut flora and improve liver function in cirrhosis patients. This improvement happens despite decreased endotoxemia and could be partly attributed to the treatment-induced

production of interluekin-6 in response to tumour necrosis factor alpha.[31]

Future directions

Even with the advances mentioned, more studies are necessary to comprehend the complexity of the gut-liver axis completely. In-depth research and longitudinal studies are required to create successful microbiome-based treatments for ALD.

CONCLUSION:

This literature review has broad implications, especially for clinicians and patients looking to gain a deeper understanding of alcohol-related liver disease. It provides insights into the early effects of alcohol consumption on gut flora, even before the clinical onset of liver disease by reflecting on the complex connections between the gut microbiota and liver health. It raises the possibility of microbial-based therapies, including probiotics, postbiotics, prebiotics, and synbiotics as viable treatment options that could enhance liver disease treatment. We hope this review can improve public health initiatives, clinical practices, and individual well-being.

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