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Untangling the gut-brain axis: the relevance of gut microbiota in alcohol use disorder

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ABSTRACT

Alcohol Use Disorder (AUD) is a chronic health problem marked by an inability to cease or control alcohol use. This disorder significantly disrupts physiological functions, negatively impacting various body systems and posing significant detriment to both individual and societal health. Recent studies have shown that AUD has a significant impact on the Gut-Brain Axis (GBA), which involves a complex interplay of neuroimmuno-endocrine and metabolic pathways.

There is strong evidence to suggest that alcohol-induced gut dysbiosis is closely linked to the development of various physiological and behavioral symptoms seen in individuals with AUD. Gut dysbiosis can influence brain functions, potentially modulating drinking motivation, reward mechanisms, and the development of alcohol dependence. These observations underscore the potential of the gut microbiota as a therapeutic target for AUD.

New approaches like Fecal Microbiota Transplantation (FMT), where healthy gut bacteria are transferred from a healthy donor to a patient, as well as the use of probiotics and prebiotics, show promise as potential treatments for AUD. The role of postbiotics – byproducts of gut bacteria metabolism – in modulating the microbiota-GBA also holds substantial promise in AUD treatment, indicating that a more detailed understanding of the microbiota-gut-brain axis could lead to novel and effective interventions for this complex disorder.

This review highlights the need for more research to better understand how the different components of the gut-brain axis interact and how they contribute to the development and progression of AUD.

KEYWORDS

ALCOHOL USE DISORDER
ALCOHOL
GUT-BRAIN AXIS
MICROBIOTA
DYSBIOSIS

INTRODUCTION

Alcohol Use Disorder (AUD) is a chronic, recurring condition characterized by the excessive and compulsive consumption of alcohol, leading to detrimental effects for individuals and society. According to the World Health Organization, AUD involves millions of people worldwide and has resulted in an alarming 3.3 million deaths every year. This shows the seriousness of the epidemic and the urgent need to investigate its contributing factors[1].

For effective prevention and treatment of various organ systems, it is crucial to comprehend the complexity of AUD, which is a result of biological, social, and physical factors.
The Gut-Brain Axis (GBA) is a bidirectional network that incorporates the multifaceted interaction of neuroimmunoendocrine and metabolic processes.
These pathway abnormalities could induce a variety of diseases, including AUD[2-5].
The gut microbiota is pivotal to the dynamics of the GBA. According to research, gut microbiota modulates brain function and behavior, particularly about AUD[6], emphasizing the need to understand these interactions in order to provide tailored therapies.
The human microbiome, containing 10^13 to 10^14 bacteria, is significantly more diverse than human genes, with *Bacteroidetes* and *Firmicutes* forming the core gut microbiota.
Alcohol interferes with gut bacteria and alters residents' communities. This condition, called dysbiosis, can be caused by changes in gut bacterial population distribution, metabolic activity, or bacterial species abundance. Alcohol-induced dysbiosis can have wide-ranging effects on both physical and mental health. This results in changes to metabolism, immune system function, and the integrity of the intestinal barrier and has an impact on brain activities, including GBA functions[6].
Current scientific research focuses on the relationships between alcohol addiction, gut dysbiosis, increased intestinal permeability, and brain reward pathways[7].
Gut microbiota plays a role in the production of essential metabolites, neurotransmitters, and appetite-modulating peptides, which are linked to alcohol misuse and alcohol-related diseases like alcoholic liver disease (ALD)[8].
Alcohol consumption leads to gut barrier deterioration, disrupting gut microbiota and allowing bacterial translocation[9,10]. This triggers a stronger inflammatory response in the brain, increasing alcohol dependency[8] and affecting gut microbiota[11-12].
Gut microbiome changes can increase alcohol dependence risk, potentially affecting motivation and craving, and potentially affecting brain reward pathways and AUD progression[13].
The evidence underscores the necessity of comprehensive research on microbial communities, host-microbiota interactions, and the potential effects of AUD. These findings could improve therapeutic interventions and prevent alcohol-induced dysbiosis. Emerging therapeutic strategies for treating AUD include Fecal Microbiota Transplantation (FMT), probiotics, and prebiotics. When combined with conventional treatments, these approaches have shown promising results[14]. Moreover, postbiotics may be useful in the management AUD. These small molecules, participating in microbiota homeostasis, hold the capacity to modulate gut microbiota and metabolite production, manipulate appetite-regulatory peptides, and restore emotional stability in AUD[15,16].
This narrative review will explore the complex relationship between gut microbiota and AUD, highlighting the contribution of the GBA and possible treatment implications.

THE GUT-BRAIN AXIS

AUD is caused by various physiological changes that are influenced by multiple factors, with the GBA playing a significant role in this process[10]. In recent studies that examined the effects of chronic alcohol consumption on the gut microbiota, it was found that alcohol consumption led to gut dysbiosis. The impairment of GBA caused by dysbiosis has a major effect on AUD, emphasizing the role of gut microbiota in its pathogenesis, development, and manifestation[17,18]. Particularly, the composition of the gut microbiota varies remarkably under the influence of chronic alcohol consumption[19]. Alcohol directly affects the microbiota composition. In addition, it affects both the diet and the activity of the autonomous nervous system that regulates gut motility. These processes can affect the diversity, richness, and composition of the microbiome by promoting the growth of potentially harmful bacteria[20]. The GBA provides bidirectional homeostatic communication between the brain and the gastrointestinal tract. The interplay occurs through four distinct routes: neural pathways, particularly the vagus nerve; immune pathways; neuroendocrine pathways also involving the hypothalamic-pituitary-adrenal axis, and metabolic pathways. Inflammatory pathways also play a role, being triggered by molecules like interleukin (IL)-1β and tumor necrosis factor-α (TNF-α)[10].

The Small Molecules in GBA and AUD

The gut microbiota has multiple functions, including the production of metabolites like short-chain fatty acids (SCFAs)[21]. Metabolites play a crucial role in facilitating communication between the gut and the brain, exerting both direct and indirect effects[22]. SCFAs, including butyrate, propionate, and acetate, are produced during the fermentation process when the gut bacteria break down dietary fibers[23]. These fatty acids can pass through the blood-brain barrier, acting as a communication pathway between the gut and the brain[24,25].
In addition, SCFAs have been found to influence circulating immune cells and infiltrating immune cell pop-

ulations in the brain[24]. The influence of SCFAs on the brain impacts neurological activity and mood[26].
SCFAs have the ability to interact with specific receptors on the cells lining the gut. This interaction can induce a wide array of effects that have the potential to modify the movement of the gut and the release of hormones within the gut. Both processes can affect gut-brain interactions, which may affect alcohol use[24].
Releasing gut hormones that affect the vagus nerve is a peripheral action. These nerves are the main way the gut communicates with the brain about organ health. SCFAs influence vagus nerve signaling, changing brain input and visceral processing. The behavior of substance use disorders may also be affected[27].
In addition, gut microbiota and its metabolites, especially SCFAs, affect immune system development and function. They regulate immune cells and produce anti-inflammatory chemicals. They can also affect gut and distant organ immune responses via circulation, linking brain function to immunological responses[28].
Indeed, SCFAs are critical to microglial function, the basic immune cells of the central nervous system (CNS). Microglia maintain homeostasis and respond to pathology, ensuring brain health[29]. SCFAs influence microglial maturation and function, affecting immunological responses and the pathophysiology of many neurological illnesses, including addiction disorders[11].

Peptides, Neurotransmitters, and Hormones in GBA and AUD

The intricate association between neurotransmitters and hormones produced by gut bacteria offers a novel perspective on the pathology of AUD. These neurotransmitters and hormones are documented to influence the body's reactions and attitudes towards alcohol[30]. As such, their roles in AUD pathology extend beyond effecting systemic responses and interactions with the enteric nervous system but also involve potential impacts on neuroendocrine pathways[31].
Gut bacteria release γ-Aminobutyric acid (GABA), a CNS inhibitor. Research indicates that ethanol exposure increases GABA release, affecting GABA receptor plasticity, alcohol reliance, and withdrawal symptoms[32]. While GABA cannot breach the blood-brain barrier due to its polarity, changes in gut GABA levels can provoke physiological reactions, primarily through the host's immunological response and mediated neurogenic signals, thereby influencing AUD-related brain functions and behaviors[33].
Also, gut bacteria significantly influence dopamine synthesis, a neurotransmitter implicated in motivation and reward[34]. Disruptions in gut dopamine could indirectly affect brain functionality, with systemic impacts including changes in immune responses potentially indirectly affecting the brain through gut-derived dopamine[35,36].
Gut bacteria generate and modulate serotonin levels, a neurotransmitter controlling intestinal movements. Gut-produced serotonin may trigger gut lumen receptors that relay brain neuronal impulses[37]. It may also regulate platelet, osteogenic, and cardiovascular functions[38,39].
The gut microbiota synthesizes peptide hormones that directly affect brain function and behavior[40]. For AUD, peptide hormones as cholecystokinin (CCK), leptin, ghrelin, and peptide YY (PYY) may affect alcohol-related physiological responses[41,42]. Leptin, which regulates energy metabolism and appetite, is also altered by chronic ethanol consumption[43]. Ghrelin-commonly referred to as the 'hunger hormone'-has been positively correlated with alcohol consumption. Studies have observed elevated levels of ghrelin in plasma of individuals diagnosed with AUD who have abstained from alcohol, indicating a potential link between plasma ghrelin levels and the duration of alcohol abstinence[44].
The hypothalamic-pituitary-adrenal (HPA) axis is a key neuroendocrine system in AUD[45]. Chronic alcohol use disrupts the HPA axis, affecting stress response[46,47]. An inverse relation has been shown between the ability to manage stress and craving and relapse AUD patients[48,49].

Entero-Biliary Circulation in GBA and AUD

Biliary acids (BAs), produced from cholesterol in hepatocytes, control gut microbiota composition and metabolic as well as immunological processes[50]. Moreover, BAs affect brain physiology, behavior, and cognition[50-52].
Alcohol-related liver impairment affects BAs production, secretion, and transport[53].
Alcohol-induced liver impairment can alter BAs composition and metabolism, affecting enterohepatic circulation, gut flora, and systemic inflammation, leading to intestinal barrier failure and systemic inflammation[54,55].
BAs play a crucial role in the gut-brain axis in AUD, influencing reward and satiety processes[56]. Modulation of gut hormones, particularly glucagon-like peptide-1 (GLP-1), may have profound effects on reward pathways, influencing alcohol seeking and consumption behaviors[57].
BAs also affect neurotransmitter production, linking peripheral biliary function to central nervous regulation. Dysregulated BAs profiles can suggest hepatic dysfunction and have direct neuropsychiatric implications[58].
Therapeutic modulation of these pathways is necessary to improve AUD treatment and reduce biliary disorders[59]. BAs sequestrants and FXR agonists can restore gut-brain balance and reduce some symptoms of AUD[60].
This therapeutic method may modulate gut microbiota and provide neuroprotection[61]. The gut microbiota and brain communicate via entero-hepatic metabolites like

SCFAs, secondary bile acids, amino acid-derived metabolites, and subcellular bacterial components[62]. Food intake and energy balance are affected[62].

The Vagus Nerve in GBA and AUD

The vagus nerve innervates the gut, controlling many gastrointestinal functions from the esophagus to the transverse colon[63]. Its function extends beyond activities related to basic digestion and motility, establishing a linchpin role linking peripheral organs to the CNS[64]. This connection facilitates the transfer of information on visceral organ conditions to the brain, emphasizing the importance of an intact vagus nerve in the GBA communications[65].

Moreover, the brain-gut connection creates an essential pathway for various signal transmissions[66]. Evidence suggests that these pathways allow the gut microbiota to influence an individual's vulnerability to alcohol-related behaviors and AUD[67], substantiating the growing research emphasizing gut microbiota alterations in relation to AUD[68].

These changes in the microbiome profile and metabolite production may affect vagus nerve signal transmission[69]. Thus, the vagal afferent communication pathway between the gut and brain may notably impact neurotransmission and inflammatory responses, potentially providing various strategies to mitigate neuroinflammatory conditions and adjust alcohol-seeking behavior through its influence on the brain's reward systems[70].

A recent study has highlighted a neural circuit connecting the gut and brain, specifically emphasizing the role of vagal neurons in the reward pathway[71]. This investigation suggests that alcohol-induced disturbances in the gut microbiota may impact striatal dopamine levels, contributing to neuroinflammation and impairments in reward responding[72].

Previous studies on rodents have suggested that microbiome-depleted animals exhibit heightened reward sensitivity and withdrawal response alterations, confirming the crucial influence of gut microbiota on reward-seeking behaviors[73].

The vagus nerve's influence extends to the brain's reward system, encompassing the nucleus accumbens, the limbic system, and other areas involved in reward processing, motivation, and emotional regulation, which are essential in addiction[74]. These areas are targeted by multi-synaptic pathways, with the vagal afferents transmitting gut signals to the nucleus tractus solitarius (NTS) in the brainstem, which then projects the signals to these brain locations[75].

Lastly, it is worthy to note that while gut-produced metabolites and immune signaling molecules can impact vagal nerve signaling, the vagus nerve itself also has the capacity to modulate the gut. For instance, stress can trigger increased vagus nerve activity, leading to changes in intestinal cell motility and secretion[76]. This could, in turn, affect the composition and function of the gut microbiota and, hence, its effects on the entire body[77].

The Neuroinflammation in GBA and AUD

Neuroinflammation is a key feature in the intricate landscape of AUD[78]. It is a protective mechanism that the body initiates to guard neural cells against diseases and damaging agents. However, when not properly modulated, as seen in AUD cases, it becomes harmful and can lead to neurological diseases[79].

The gut microbiota has a fundamental role in regulating the immune system; hence, any disruption, notably from AUD, could trigger a host of immunological responses, culminating in neuroinflammation[78]. When AUD prompts alcoholic dysbiosis, gut permeability changes ensue, allowing bacterial toxins like lipopolysaccharides to enter the bloodstream. This escalates immune responses markedly, triggering the production of pro-inflammatory cytokines that affect not only peripheral regions but also the CNS[79,80]. The chronic inflammation of neurons is known to contribute significantly to the detrimental effects of AUD, including cognitive impairments and mood disorders[70].

Moreover, AUD patients with neuroinflammation have altered alcohol responses[78]. However, many unanswered questions linger, necessitating ongoing research into how neuroinflammation influences drug-seeking behaviors, or hinders the cessation of alcohol use[79]. Initial findings suggest that neuroinflammation could impact the dopaminergic reward system, often linked to the motivation for alcohol consumption[79].

The relationships between microbiota alterations, neuroinflammation, and alcohol abuse are complex. The challenge lies in discerning whether microbiome changes prompting neuroinflammation are a consequence of AUD or if there's inherent microbiome variance contributing to AUD developments[79]. The present research notes that both scenarios could exist[70]. There is an observed interplay between alcohol-induced gut dysbiosis and intensified alcohol craving and consumption, creating a harmful cycle[80]. Alternatively, gut microbiota variations could stem from genetic, environmental, or nutritional factors, potentially making certain individuals more susceptible to AUD development or harsher disease progression[79].

In conclusion, the interplay of gut-brain neuroinflammation in AUD ties into the disorder's development, manifestation, and treatment[78].

Gene Expression in GBA and AUD

Enduring changes in activity-dependent transcription and epigenetic modifications to chromatin structure associated with substance use disorders have been illustrated in research[81].

One prime example is evident in germ-free mice. These mice exhibit altered gene expression in integral areas of the brain, such as the prefrontal cortex and amygdala[82]. Both germ-free mice and those subjected to antibiotics to rid their gut microbiome show changes in chromatin structure and gene expression in CNS microglia[83]. Moreover, these mice with a depleted microbiome illustrate abnormal regulation of dopamine receptors and neurotrophic factors when exposed to alcohol[84].

Interestingly, the microbiome's influence on brain transcriptomics and epigenetics is of comparable magnitude in both germ-free mice and those that receive antibiotic treatments later in life. This suggests a significant dynamic role of the microbiome in gene regulation that carries on throughout the organism's lifetime[85].

It appears that neuroactive molecules originating from bacteria are instrumental in triggering changes in gene expression and epigenetics influenced by the microbiome. Short-chain fatty acids (SCFAs), products of bacterial fermentation, have extensive regulatory impacts and can inhibit histone deacetylase. Butyrate and acetate are especially efficient among these SCFAs[26]. Specifically, gut-derived acetate has been found to considerably affect the brain, modifying histone acetylation patterns, and thereby inducing changes in memory consolidation and individual's response to alcohol[86].

PHYSIOLOGICAL IMPLICATIONS OF AUD ON GBA

The Influence of AUD on Neurological Functions: The Involvement of GBA

AUD extensively impacts brain function. Research reveals that AUD inherently modifies various brain areas, including the hippocampus-amygdala-frontal limb circuit, consequently affecting emotional processing and cognitive function[87-89].

Persistent alcohol consumption modifies the gut's microbial flora, which in turn influences the brain's response to AUD. Tests on mice indicated that those with reduced gut microbiota displayed abnormal cognitive and affective processing[90-92], highlighting the correlation between gut microbiota and brain health.

AUD affects the hippocampus, a brain area involved in the brain-gut axis, influencing glycerophospholipid metabolism and, as a result, neurogenesis and neuroplasticity[93]. Studies also indicate that alterations to the gut microbiota can trigger an inflammatory response, leading to a significant decrease in hippocampal Brain-Derived Neurotrophic Factor (BDNF) and monoamine neuromodulation, resulting in mood shift and impaired cognition[33].

Moreover, AUD severely impacts the brain's structure and function, especially in the hippocampus and medial prefrontal cortex. Beck et al. found enduring effects of long-term alcohol consumption on memory and learning capabilities[94].

The hippocampus, crucial for emotional regulation, relies on microbiome input for development[95]. Early gut microbiota disruption leads to reduced BDNF and altered monoamine neuromodulation function[96].

AUD can lead to dysregulation of the amygdala, a brain region essential for regulating negative emotions. Studies found a correlation between heightened amygdala activation and the presence of mood disorders and cognitive dysfunction[97,98].

Significant alterations in behavior and cognition can also arise from gut microbial interference with the fronto-limbic system, specifically the amygdala and hippocampus[99,100]. Behavioral disturbances imply increased risk-taking behavior as a result of microbiome changes.

Furthermore, it is important to note that AUD has a detrimental effect on the prefrontal cortex, which is important for emotional regulation. This serves as a risk factor for the development of various mental disorders[101]. This alteration contributes to the modification of the gut-brain axis through a top-down mechanism[102]. It suggests therapeutic targeting of the gut microbiota could potentially remediate mental disorders.

The gut microbiota also plays a role in prefrontal cortex (PFC) development, essential for inhibitory control, cognitive flexibility, and emotion regulation[103]. Disruptions in PFC-related behaviors were observed with gut microbiota disruptions[104,105].

The physiological effects of AUD are further complicated by its detrimental impact on the Blood-Brain Barrier (BBB). Excessive alcohol consumption can negatively impact the BBB's structure and function[106]. This occurs due to an increase in oxidative stress. Toxic byproducts can pass through the BBB, causing neural depletion and dysfunction in glial cells, ultimately resulting in brain damage[107]. BBB damage can enable bacterial metabolites, such as LPS, to reach the CNS, leading to an increased pro-inflammatory response[108].

The Influence of AUD on Gut Microbiota Composition

Alcohol and its metabolites have a significant influence on the gut microbiota[109]. Alcohol has direct effects on bacterial proliferation and indirect effects on the intestinal milieu, causing acidity and inflammation that affect gut microbiota[109].

Among phylum-level changes, studies have shown that alcohol consumption promotes a rise in the relative abundance of *Proteobacteria* and *Verrucomicrobia*, contrasted with a decrease in *Actinobacteria, Firmicutes*, and *Bacteroidetes*[110,111]. Concurrently, alcohol leads to an increase in the abundance of classes like *Gammaproteobacteria, Bacilli*, and *Fusobacteria*, while decreasing the relative abundance of *Bacteroidetes, Clostridia*, and *Actinobacteria*[111,112].
Family-level alterations as a result of alcohol exposure include an increased abundance of *Enterobactericaea, Desulfovibrionaceae, Erysipelotrichaceae, Ruminococcaceae*, and *Lachnospiraceae*. A decrease is observed for *Porphyromonadaceae, Veillonellaceae, Bacteroidaceae, Paraprevotellaceae, Lachnospiraceae*, and *Clostridiaceae*[111,113].
In regard to genera, entities such as *Klebsiella* and *Lactococcus* see a noticeable increase because of alcohol exposure. On the other hand, *Clostridium, Akkermansia, Clostridiales*, and *Coprococcus* display reduced levels upon alcohol consumption[114].
The gut hosts a combination of both beneficial and harmful bacteria[115-120]. Beneficial bacteria such as *Lactobacillus, Bifidobacterium, Muribaculum intestinale, Ruminococcus, Faecalibacterium prausnitzii*, and *Akkermansia* play essential roles in maintaining gut function, immune regulation, and managing inflammatory responses, while counteracting alcohol-induced perturbations[115-120].
Conversely, harmful bacteria like E*nterobacteriaceae, Klebsiella, Lactococcus*, and the *Clostridium* cluster XIVa create inflammation, liver damage, and chronic neuroinflammation while spurring the onset and spread of diseases[121-124].
Studies using 16S rRNA sequencing reveal that alcohol alters the composition of the gut microbiota[125]. Key findings include a re- duction of beneficial bacteria like *Lactobacillus* (or *Sporolactobacillus*) and a parallel increase of entities such as *Allobaculum* following alcohol exposure.. These changes occur without altering the overall number of gut microbiota species, as confirmed through Shannon analysis[125].
The pattern and dosage of alcohol consumption induce distinct modifications in gut microbiota composition. Acute, or episodic, drinking commonly induces reversible, temporary changes[20]. In contrast, sustained exposure to alcohol prompts more intense and long-lasting transformations, usually calling for complex and comprehensive intervention strategies for reversa[120,126].
The variability in drinking dosages leads to disparate timelines for the restoration of normal gut microbiota. Specifically, changes induced by lower alcohol doses can be modified using suitable interventions[127]. However, the reestablishment of extreme alcohol dose-induced gut dysbiosis requires a substantially extended duration[3].
Patients with AUD manifest a decrease in *Akkermansia* and an escalation in *Bacteroides*, possibly representing a distinct gut microbial fingerprint[128].

Microbiota: Implications for Alcohol Dependence and Cravings

Preclinical studies suggest the role of the gut microbiota in the pathophysiology of alcohol addiction. Mice exposed to ethanol over four weeks exhibited significant changes in bacterial taxa, especially substantial reductions in the genus *Clostridium*[129]. Furthermore, correlations have been reported between this specific genus of bacteria and several addiction-related behaviors, predominantly increased impulsivity, inattention deficits, and reward learning[130].
Preliminary human investigations have greatly emphasized the relationship between AUD-induced gut dysbiosis and alcohol withdrawal and craving responses. Bajaj et al[131] propose that the gut microbiota composition remained affected despite the restoration of intestinal permeability following a three-week detoxification period. These alterations and their physiological effects may significantly contribute to the negative reinforcement process linked to alcohol consumption[132].
Experiments involving the FMT from alcohol-consuming mice to healthy mice resulted in the recipient mice displaying symptoms of withdrawal-anxiety[131]. According to a phase 1 clinical trial, individuals who underwent FMT therapy experienced short-term enhancements in their impulse control and reduced cravings. These improvements were found to have a negative association with the *Ruminococcaceae genera*[131].

THE GUT-BRAIN AXIS: A POSSIBLE THERAPEUTIC TARGET

Gut microbiota could be an important target for GBA therapy due to its ease of manipulation[81].
Probiotics, living microorganisms conferring health benefit, have been extensively studied for their therapeutic effects and potential to regulate gut microbiota imbalances caused by AUD[133]. They influence neurotransmitter systems, immune responses, and gut barrier function[134]. *Lactobacillus* and *Bifidobacterium* strains produce neurotransmitters such as GABA[135].
Clinical research and systematic reviews support probiotic treatment for AUD. Bravo et al. found that a specific Lactobacillus strain affected brain GABA receptor expression and reduced stress and anxiety in mice[136]. A comprehensive review by Tsai et al. found that pro- biotics improved cognitive function, mood,

and alcohol appetite in AUD patients[137]. Probiotics also reduce pro-inflammatory molecules and prevent reward and craving brain regions from activating by restoring gut microbial balance and gut barrier function[138].
Savignac et al.[139] found that specific Bifidobacterium isolates significantly mitigated depressive and anxious behaviors in mice. Further, other research[140] revealed that *Bifidobacterium longum* attenuated responses to negative emotional stimuli in various brain regions by over 60% and reduced depression scores. On the other hand, *Lactobacillus* demonstrated antidepressant patterns[141]. The emerging understanding of psychobiotics show potential in aiding individuals with AUD. However, further clinical and preclinical studies are required[33].
Prebiotics, non-digestible dietary compounds, have been shown to selectively stimulate the growth and activity of beneficial bacteria in the gut, contributing to a healthier gut microbiota and overall gut health[142]. Studies have demonstrated the promising effects of prebiotics in mitigating symptoms and improving outcomes in individuals with AUD[142-144]. For instance, Ames et al.[145] found that increased consumption of dietary fiber was associated with beneficial changes in the gut microbiota in individuals with AUD, indicating a potential therapeutic effect. According to Carlson et al.[146], prebiotics bolster the gut microbiota on a larger scale, indicating potential therapeutic effects on mood disorders commonly associated with AUD[143].
Fecal microbiota transplant (FMT) has garnered attention as a novel intervention aimed at restoring a healthy gut microbiota composition and function[147]. Research has shown promising results regarding the effects of FMT on gut microbiota composition and alcohol-related behaviors. Studies have indicated that FMT from non-drinking donors can attenuate ethanol-induced liver damage, reduce alcohol preference, and modulate the brain's reward circuitry, thereby impacting alcohol-related behaviors[147]. Furthermore, FMT has been proposed as a therapeutic approach to restore gut homeostasis and reduce systemic inflammation in individuals with AUD[148]. Animal studies have indicated that FMT from non-drinking donors attenuated ethanol-induced liver damage and reduced alcohol preference, showcasing the potential role of FMT in modifying alcohol-related behaviors[149]. These findings suggest that FMT may modulate the brain's reward circuitry and improve abstinence rates in AUD patients.
Antibiotics can significantly alter microbial populations, potentially affecting the therapeutic response of AUD patients[150] and potentially causing collateral damage to gut microbiota diversity[151].
Modifications in diet can also rapidly shift gut microbial compositions[152]. As such, diet may serve as a significant non-pharmacological tool for improving gut health, helping to alleviate AUD symptoms.
Increasing attention has been paid to postbiotics and small molecules for their potential in managing AUD[150]. Yet, our understanding of these elements remains in its early stage.
Substantial opportunities exist to use the gut-brain axis as a therapeutic target in AUD, given the potential of non-pharmacological interventions like probiotics, prebiotics, and FMT. These interventions, supported by diet amendments, require comprehensive analysis and rigorous testing. The field is prepared for future research development, offering the potential for innovative techniques to address AUD holistically.

CONCLUSIONS

The relationship between the gut microbiota and the GBA is an emerging area of research in the study and treatment of AUD. Recent findings have shed light on the complex connections between alcohol and gut dysbiosis, highlighting how this condition could persist even after alcohol withdrawal. These insights suggest that it plays a significant role in the negative reinforcement patterns linked to alcohol consumption. Studies on FMT show gut bacteria's significant impact on the behavioral symptoms of AUD, suggesting it could be a promising new therapeutic approach.
Further investigation is required to fully understand the implications of the microbiota-gut-brain axis interaction for AUD, due to its inherent complexity. Exploring these intricate pathways offers a novel opportunity, potentially as a supplement or alternative to conventional AUD treatments. This research enhances our understanding of AUD and has the potential to improve its treatment and care.
Managing the gut microbiota through therapeutic interventions may treat AUD, according to growing research. Understanding gut microbiota complexities remains challenging, but rigorous scientific research is crucial for managing AUD and improving overall health outcomes.

Conflict of Interest:
The authors have no conflicts of interest to declare.

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