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Review article

Dietary fiber as a therapeutic strategy to protect intestinal barrier function and reduce neuroinflammation in alcohol use disorder: implications for depression and relapse

Fibra dietética como estrategia terapéutica para proteger la función de la barrera intestinal y reducir la neuroinflamación en el trastorno por uso de alcohol: implicaciones para la depresión y la recaída

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ABSTRACT

Introduction: Alcohol use disorder (AUD) and major depressive disorder (MDD) are highly comorbid conditions sharing a common neuroinflammatory substrate. Chronic alcohol consumption disrupts the intestinal barrier and induces gut dysbiosis, leading to bacterial lipopolysaccharide (LPS) translocation, systemic inflammation, and central neuroinflammation that persists during abstinence and increases relapse vulnerability. **Objective:** This perspective review discusses the mechanistic links between alcohol-induced gut barrier dysfunction, neuroinflammation, and neurotransmitter imbalances underlying depression and relapse in AUD, and proposes dietary fiber intake—as a source of intestinal butyrate through microbial fermentation—as a potential adjunct therapeutic strategy. **Discussion:** Butyrate, the principal short-chain fatty acid produced by colonic fermentation of dietary fiber, is the primary energy substrate of colonocytes and exerts anti-inflammatory effects through inhibition of NF-κB and histone deacetylases. It promotes intestinal barrier

integrity by upregulating tight junction proteins (ZO-1, occludin, claudin-1), reduces LPS translocation, and attenuates the peripheral-to-central inflammatory cascade. By reducing neuroinflammation, butyrate may contribute to restoring the balance of glutamate, dopamine, and serotonin, neurotransmitter systems disrupted by alcohol and critically implicated in depression and relapse. **Conclusions:** Increasing dietary fiber intake to enhance endogenous butyrate production represents a safe, accessible, and mechanistically grounded strategy to complement existing therapies for AUD-related depression and relapse prevention.

Keywords: alcohol use disorder; dietary fiber; butyrate; intestinal barrier; neuroinflammation; depression; relapse

RESUMEN

Introducción: El trastorno por uso de alcohol (TUA) y el trastorno depresivo mayor (TDM) son condiciones altamente comórbidas que comparten un sustrato neuroinflamatorio común. El consumo crónico de alcohol disrumpe la barrera intestinal e induce disbiosis intestinal, lo que conduce a la translocación de lipopolisacárido (LPS) bacteriano, inflamación sistémica y neuroinflamación central que persisten durante la abstinencia y aumentan la vulnerabilidad a la recaída. **Objetivo:** Esta revisión de perspectiva discute los vínculos mecanísticos entre la disfunción de la barrera intestinal inducida por el alcohol, la neuroinflamación y los desequilibrios en neurotransmisores que subyacen a la depresión y la recaída en el TUA, y propone el consumo de fibra dietética —como fuente de butirato intestinal mediante fermentación microbiana— como una estrategia terapéutica adyuvante. **Discusión:** El butirato, el principal ácido graso de cadena corta producido por la fermentación colónica de la fibra dietética, es el principal sustrato energético de los colonocitos y ejerce efectos antiinflamatorios mediante la inhibición de NF-κB y de las histona desacetilasas. Promueve la integridad de la barrera intestinal mediante la regulación al alza de las proteínas de uniones estrechas (ZO-1, ocludina, claudina-1), reduce la translocación de LPS y atenúa la cascada inflamatoria periférica hacia el sistema nervioso central. Al reducir la neuroinflamación, el butirato puede contribuir a restaurar el equilibrio de glutamato, dopamina y serotonina, sistemas de neurotransmisión alterados por el alcohol y críticamente implicados en la depresión y la recaída. **Conclusiones:** Aumentar el consumo de fibra dietética para potenciar la producción endógena de butirato representa una estrategia segura, accesible y mecanísticamente fundamentada para complementar las terapias existentes en la depresión relacionada con el TUA y la prevención de recaídas.

Palabras clave: trastorno por uso de alcohol; fibra dietética; butirato; barrera intestinal; neuroinflamación; depresión; recaída

1. INTRODUCTION

Alcohol use disorder (AUD) is one of the most prevalent mental and substance use disorders and constitutes a leading contributor to the global burden of disease. According to the World Health Organization, alcohol consumption accounts for approximately 4.7% of annual deaths worldwide and 5.1% of the global burden of disease [1]. Complicating the clinical picture, more than one-third of individuals with AUD meet diagnostic criteria for major depressive disorder (MDD) at some point during their history of alcohol use [2]. This comorbidity is associated with a more severe course of depression, higher rates of alcohol relapse, greater suicide risk, and poorer response to antidepressant treatment [3]. Despite decades of research, available pharmacological treatments remain insufficient to address this dual burden, underscoring the urgent need for novel therapeutic approaches.

A central and historically underappreciated mechanism linking AUD and MDD is neuroinflammation [4]. Chronic alcohol consumption activates innate immune pathways in both peripheral tissues and the central nervous system (CNS), leading to a sustained neuroinflammatory state that dysregulates neurotransmitter systems governing mood, reward, and motivation [5]. Critically, this neuroinflammatory state does not resolve spontaneously upon cessation of alcohol use; instead, it may persist for weeks or months of abstinence, contributing to negative affective states—anxiety, anhedonia, and dysphoria—that increase the risk of relapse [6,23].

A growing body of evidence implicates the gut-brain axis as a central driver of this neuroinflammatory cascade. Chronic alcohol consumption disrupts the intestinal epithelial barrier through direct toxic effects of ethanol and its metabolite acetaldehyde on tight junction proteins, and through alcohol-induced gut dysbiosis, which further compromises barrier integrity and reduces the abundance of beneficial butyrate-producing bacteria [7,8]. The resulting increase in intestinal permeability—commonly referred to as *leaky gut*—enables the translocation of bacterial lipopolysaccharide (LPS) into the portal and systemic circulation. LPS activates Toll-like receptor 4 (TLR4) in peripheral immune cells and, subsequently, in brain microglia, triggering the production of proinflammatory cytokines (TNF-α, IL-1β, IL-6) that disrupt neurotransmitter homeostasis in key brain regions involved in depression and reward [5,9].

Short-chain fatty acids (SCFAs), particularly butyrate, produced by microbial fermentation of dietary fiber in the colon, play a fundamental role in maintaining intestinal barrier integrity and containing both peripheral and central inflammatory responses [10,11]. Alcohol-induced dysbiosis reduces the abundance of butyrate-producing bacteria, thereby eliminating a key protective mechanism and amplifying intestinal barrier dysfunction [8]. This perspective review proposes that increasing fermentable dietary fiber intake—a safe, widely available, and low-cost nutritional strategy—could enhance endogenous butyrate

production, protect intestinal barrier function, attenuate neuroinflammation, and ultimately mitigate the depressive symptoms and relapse vulnerability associated with AUD.

2. ALCOHOL-INDUCED DISRUPTION OF THE INTESTINAL BARRIER: FROM LEAKY GUT TO BRAIN INFLAMMATION

The intestinal epithelial barrier is maintained by a network of intercellular junctions, with tight junctions (TJs) being the primary determinants of paracellular permeability. TJ proteins—including zonula occludens-1 (ZO-1), occludin, and claudins—form a selectively permeable seal that prevents the passage of microbial products into the submucosal immune compartment and the systemic circulation [12]. Both ethanol and its principal colonic metabolite, acetaldehyde, disrupt the expression and localization of TJ proteins through multiple mechanisms: activation of myosin light-chain kinase (MLCK), increased production of reactive oxygen species (ROS), activation of NF-κB, and dysregulation of the phosphorylation-dephosphorylation balance of TJ components [13,14,15].

This disruption is significantly amplified by alcohol-induced gut dysbiosis. Chronic alcohol consumption consistently reduces the abundance of SCFA-producing bacteria—such as *Lactobacillus* and *Bifidobacterium*—while enriching LPS-bearing Gram-negative Enterobacteriaceae [8,16]. The resulting reduction in microbial butyrate production deprives colonocytes of their primary energy source and eliminates a key anti-inflammatory and barrier-protective signal, further compromising TJ integrity [10,11]. The net consequence is increased intestinal permeability, or *leaky gut*, enabling the translocation of bacterial LPS into portal circulation.

A critical and clinically relevant feature of this process is that intestinal barrier dysfunction and dysbiosis do not resolve spontaneously upon cessation of alcohol consumption. In a pioneering study, Worthington et al. demonstrated that increased intestinal permeability in rats persisted for up to four weeks after alcohol withdrawal [17]. In humans, Yang et al. showed that ZO-1 and claudin-1 remained significantly reduced in the colon of abstinent subjects, with plasma LPS levels remaining elevated throughout the abstinence period [18]. Swanson et al., studying 178 subjects with at least 7 days of abstinence, found that colonic permeability remained elevated and that barrier resilience was reduced, even in patients without overt liver disease [19]. These findings establish that *leaky gut* is not merely a consequence of active drinking, but a persistent biological injury that continues to drive LPS translocation—and thus peripheral and central inflammation—well into abstinence.

The clinical correlates of this persistent gut-to-brain inflammation are well documented. In a seminal study, Leclercq et al. evaluated 60 AUD patients at two days and three weeks of abstinence: intestinal permeability correlated with higher craving, anxiety, and depressive symptom scores [20]. A subsequent report extended these findings from the

same group, which showed that persistent dysbiosis at three weeks was associated with the maintenance of depressive symptoms and craving even after some inflammatory markers had partially improved [20]. Together, these data support the concept of a self-sustaining gut-neuroinflammatory positive feedback loop that maintains psychiatric symptoms and relapse risk during abstinence [7].

3. NEUROINFLAMMATION AND NEUROTRANSMITTER DYSREGULATION: THE NEUROBIOLOGICAL BRIDGE TO DEPRESSION AND RELAPSE

LPS entering the systemic circulation binds TLR4 on circulating monocytes and macrophages, triggering the release of TNF-α, IL-1β, and IL-6, which can reach the brain directly—through areas of relatively permeable blood-brain barrier (BBB)—or by activating vagal afferents that relay inflammatory signals to hypothalamic and limbic regions [21]. Within the CNS, LPS-induced cytokines activate microglia and astrocytes, propagating neuroinflammation in regions critical for mood, reward, and executive function: the prefrontal cortex (PFC), hippocampus, and nucleus accumbens (NAc) [5,22]. Importantly, this microglial activation can persist for months after alcohol withdrawal [6,23], providing a neurobiological basis for the chronic nature of AUD-related depression.

The neurochemical consequences of this inflammatory state span three major neurotransmitter systems directly implicated in both depression and the maintenance of alcohol consumption.

3.1 Glutamatergic dysregulation

Neuroinflammation reduces the expression of the astroglial glutamate transporter GLT-1 in the NAc and PFC, elevating extracellular glutamate levels [24]. During active drinking, excess extracellular glutamate in the NAc drives dopamine release through mesolimbic circuits, reinforcing alcohol-seeking behavior [26]. During abstinence, ongoing GLT-1 dysfunction sustains glutamatergic dysregulation, contributing to excitotoxic stress, impaired executive control, and heightened stress reactivity—all hallmarks of relapse vulnerability. The clinical relevance of this pathway is underscored by the rapid antidepressant effect of ketamine, which acts by blocking NMDA glutamate receptors.

3.2 Dopaminergic dysregulation

During acute and chronic alcohol consumption, increased dopamine release in the NAc mediates the rewarding and reinforcing properties of alcohol [26]. However, during prolonged

abstinence, dopaminergic neurotransmission in the NAc becomes hypofunctional. This dopaminergic deficit constitutes the neurobiological substrate of anhedonia—the inability to experience pleasure—which is a cardinal symptom of both MDD and the abstinence phase of AUD [27]. Neuroinflammation contributes directly to this hypo-functionality: LPS suppresses dopamine synthesis and mesolimbic system function, in part through microglial activation that inhibits dopaminergic activity in the ventral tegmental area [28], while associated dysbiosis reduces tyrosine hydroxylase (TH) expression and upregulates the dopamine transporter (DAT) through depletion of bacterial metabolites such as SCFAs, thereby diminishing dopaminergic tone [29]. This hypodopaminergic state in the NAc drives further alcohol seeking as a compensatory mechanism, fueling the relapse cycle [30].

3.3 Serotonergic dysregulation and the kynurenine pathway

Serotonin (5-HT) is a critical modulator of mood, anxiety, and stress responses. During prolonged alcohol abstinence, extracellular 5-HT and its metabolite 5-HIAA (5-hydroxyindoleacetic acid) are reduced in the hippocampus and striatum, directly correlating with anxiety-like and depressive-like behaviors in animal models [31]. A mechanistically central pathway linking gut-derived inflammation to serotonin deficiency is the kynurenine pathway. Approximately 90% of total body serotonin is synthesized by enterochromaffin cells of the intestinal mucosa, and this production is directly regulated by microbiota-derived metabolites, including SCFAs [32]. Furthermore, systemic inflammation—driven by LPS and proinflammatory cytokines—activates the enzyme indoleamine 2,3-dioxygenase 1 (IDO1), which diverts the essential amino acid tryptophan (the precursor of 5-HT) away from serotonin synthesis and toward the kynurenine pathway [33].

Within the kynurenine pathway, the metabolic fate of kynurenine (KYN) is critically determined by the inflammatory state. In activated microglia, KYN is converted by kynurenine 3-monooxygenase (KMO) into quinolinic acid (QUIN), a potent NMDA receptor agonist with neurotoxic and excitotoxic properties. In astrocytes, by contrast, KYN is converted by kynurenine aminotransferase (KAT) into kynurenic acid (KYNA), an NMDA receptor antagonist with neuroprotective properties [33]. The balance between KYNA and QUIN determines whether the brain is in a neuroprotective or neurotoxic state [34,35]. In the neuroinflammatory context of AUD and abstinence, the balance shifts toward QUIN production, further amplifying glutamatergic excitotoxicity and contributing to depressive symptoms. In a clinical study of 57 AUD patients, Leclercq et al. demonstrated elevated QUIN and reduced KYNA levels during detoxification, with tryptophan levels correlating directly with depression severity; importantly, SCFA-producing bacteria were positively associated with neuroprotective kynurenine pathway metabolites [34].

The work of our own group has directly demonstrated the neurobiological consequences of alcohol-induced neuroinflammation on neurotransmitter systems in the context of depression. In León et al. [35], we showed that intermittent ethanol administration to rats produces anxiety-like behavior, increased immobility in the tail suspension test, elevated TNF-α, IL-1β, and IL-6 in the PFC and hippocampus, reduced BDNF expression in the PFC, and decreased dendritic arborization of pyramidal neurons. Treatment with fenofibrate—a PPAR-α agonist that inhibits NF-κB and reduces neuroinflammation—during the abstinence period reversed all of these behavioral and neurobiological deficits, including normalization of BDNF expression and partial restoration of dendritic complexity. Extending this line of work, Isla et al. demonstrated through *in vivo* microdialysis in alcohol-preferring UChB rats that fenofibrate administration during abstinence restored dopaminergic and glutamatergic homeostasis in the NAc, directly linking anti-inflammatory treatment to the recovery of neurotransmitter systems underlying depression and relapse [36].

Taken together, these data establish neuroinflammation—driven upstream by alcohol-induced intestinal barrier dysfunction and LPS translocation—as a convergent mechanism producing the glutamatergic, dopaminergic, and serotonergic imbalances that underlie both AUD-related depression and relapse vulnerability. This mechanistic framework identifies the gut as a critical therapeutic target.

4. BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF): A SHARED DEFICIT IN AUD AND DEPRESSION

BDNF is an essential neurotrophin for neuronal survival, synaptic plasticity, and mood regulation. Reduced serum BDNF levels have been consistently documented in patients with MDD compared to healthy individuals across multiple meta-analyses [37]. Clinical studies have demonstrated that BDNF normalization correlates with clinical improvement following antidepressant treatment [37,38]. In AUD, chronic alcohol exposure reduces BDNF gene expression in the PFC [39], and BDNF levels are altered in individuals with alcohol dependence [40]. The link is mechanistic: neuroinflammation and overexpression of proinflammatory cytokines in the CNS directly suppress BDNF expression [41], providing a molecular basis for the comorbidity between AUD and MDD.

The relevance of BDNF is not merely associative. BDNF signaling through its TrkB receptor activates the transcription factor CREB, a master regulator of dendritic morphology and synaptic plasticity [42]. The inverse correlation between depression severity and synaptic density —observed in postmortem and neuroimaging studies in humans with MDD [43]— may reflect the consequences of sustained BDNF suppression by neuroinflammation. In León et al. [35], we documented in our animal model that ethanol exposure reduced BDNF expression in the PFC by approximately 33% and was accompanied by a marked

reduction in dendritic arborization of PFC pyramidal neurons. Notably, both BDNF expression and dendritic complexity were rescued—at least partially—by the reduction in neuroinflammation mediated by fenofibrate during abstinence [35]. These findings underscore that the structural neuronal damage associated with AUD-related depression is potentially reversible when neuroinflammation is adequately controlled.

5. DIETARY FIBER, BUTYRATE, AND INTESTINAL BARRIER PROTECTION

Given the central role of intestinal barrier dysfunction and reduced butyrate production in the pathophysiology of AUD-related neuroinflammation and depression, strategies aimed at restoring intestinal integrity through increased butyrate availability represent a mechanistically compelling therapeutic approach. The most physiologically natural and clinically accessible route to increase intestinal butyrate is through dietary fiber fermentation.

Dietary fibers are non-digestible carbohydrates that reach the colon largely intact, where they serve as the primary substrate for fermentation by the resident microbiota. The major fermenting bacteria include species of *Faecalibacterium*, *Roseburia*, *Eubacterium,* and *Butyrivibrio*, all of which produce butyrate as the principal fermentation end product [44]. Importantly, these are among the taxa most depleted by chronic alcohol consumption [8,16]. Inulin and fructo-oligosaccharides (FOS) preferentially stimulate *Bifidobacterium* and *Lactobacillus*, which produce lactate and acetate, subsequently used as substrates by butyrate-producing bacteria; β-glucan, arabinoxylan, and resistant starch more directly stimulate butyrate-producing Firmicutes [44,45]. A diet rich in diverse fermentable fibers—fruits, legumes, whole grains, and vegetables—is therefore the most broadly effective strategy for restoring colonic butyrate production in individuals with AUD-associated dysbiosis.

Butyrate exerts its protective effects on the intestinal barrier through multiple complementary mechanisms. At the molecular level, it serves as the primary energy substrate for colonocytes, sustaining cellular metabolism and proliferation, which are essential for barrier renewal [10,11]. At the immune level, it inhibits NF-κB and histone deacetylases (HDACs), suppressing proinflammatory cytokine production by intestinal immune cells and reducing gut-derived inflammatory signals that reach the systemic circulation [7,11].

The preclinical evidence directly demonstrating these effects in the context of alcohol exposure is compelling. Cresci et al. showed that tributyrin—a butyrate prodrug—normalized ZO-1 and occludin expression, reduced endotoxemia, and attenuated hepatic inflammation in mice subjected to chronic-binge alcohol exposure [46]. The same group demonstrated similar protective effects in acute ethanol exposure models [47]. Siddiqui et al. confirmed that butyrate mitigates acute ethanol-induced intestinal mucosal disruption at the cellular level [48]. Most directly relevant to AUD behavior, Quintanilla et al. demonstrated

that intragastric administration of an SCFA mixture (including butyrate) to genetically alcohol-preferring UChB rats reduced voluntary ethanol consumption by 85–90%, while simultaneously normalizing neuroinflammatory parameters in the NAc [49]. This dramatic reduction in drinking behavior suggests that butyrate-mediated gut-brain axis protection can directly influence the neurobiological drivers of alcohol consumption. Indeed, increasing dietary fiber intake as a strategy to raise intestinal SCFAs and thereby modulate alcohol-induced neuroinflammation has been explicitly proposed by our group [7].

From a dietary perspective, several human studies and clinical trials have begun to explore fiber-based interventions in AUD and related conditions. Amadieu et al. conducted a pilot study in AUD patients in which inulin supplementation modulated microbiota composition—increasing *Bifidobacterium* and *Bacteroides*—and improved sociability and serum BDNF levels [50]. Although this study did not show significant effects on depression or craving versus placebo, it demonstrated the feasibility and safety of prebiotic supplementation in this population. Leclercq et al. showed that in AUD patients during early abstinence, those with greater bacterial butyrate-producing capacity showed faster resolution of intestinal permeability and lower craving scores [34]. A broader body of clinical evidence demonstrates that increased dietary fiber intake consistently raises fecal butyrate concentrations, improves intestinal barrier function, and reduces systemic inflammatory markers, including C-reactive protein and IL-6 [51,52].

The clinical rationale for focusing on dietary fiber rather than exogenous butyrate supplementation rests on several considerations. Dietary fiber produces butyrate in situ through a gradual, physiologically regulated process that avoids the variable bioavailability of orally administered butyrate, which is rapidly absorbed in the small intestine before reaching the colon. Furthermore, the fiber matrix supports the reestablishment of a diverse, butyrate-producing microbiota, addressing dysbiosis rather than merely supplementing one of its consequences. Additionally, dietary fiber interventions are economical, broadly acceptable to patients, and carry an excellent safety profile with no significant adverse effects at recommended intake levels (25–38 g/day for adults).

6. BUTYRATE AND NEUROTRANSMISSION RECOVERY: CONNECTING THE GUT TO THE BRAIN

Beyond its effects on the intestinal barrier, butyrate exerts direct and indirect influences on the neurotransmitter systems dysregulated by AUD-related neuroinflammation, providing additional rationale for its therapeutic potential in depression and relapse prevention.

Regarding serotonin, approximately 90% of total body 5-HT is synthesized in the gut by enterochromaffin cells, and this production is directly regulated by microbiota-derived metabolites, including butyrate [32]. Reigstad et al. demonstrated that SCFAs regulate the

expression of tryptophan hydroxylase 1 (TPH1) in enterochromaffin cells, thereby increasing intestinal serotonin production [53]. Furthermore, by inhibiting NF-κB, butyrate reduces IDO1 activation, favoring tryptophan metabolism toward serotonin rather than toward the neurotoxic QUIN branch of the kynurenine pathway [34,35]. Butyrate also shifts microglia toward an anti-inflammatory (M2) phenotype, reducing QUIN production and thereby restoring the KYNA/QUIN balance toward neuroprotection [34,35]. Collectively, these effects represent a significant contribution to serotonergic recovery during abstinence.

With respect to dopamine, butyrate, and other SCFAs regulate TH expression and DAT activity through cAMP-dependent mechanisms and histone acetylation [29]. By restoring the abundance of *Akkermansia muciniphila*—a species particularly depleted by alcohol-induced dysbiosis—fiber-enriched diets may help normalize TH and DAT expression, supporting recovery of dopaminergic tone in the NAc and thereby alleviating the anhedonia that is both a central symptom of depression and a driver of relapse [29,55]. This dopaminergic deficit is also the substrate of anhedonia in MDD [30].

BDNF, whose reduction is a common pathophysiological feature of both AUD and MDD [37,38], is also a target of butyrate action. In animal studies, manipulation of gut microbiota through dietary changes increases BDNF expression in the hippocampus and cortex, and this effect is at least partially attributable to HDAC inhibition by butyrate [54]. Since BDNF sustains dendritic arborization and synaptic plasticity through CREB activation [42], butyrate-mediated normalization of BDNF would, in theory, reverse the structural neuronal deficits documented in our animal model of AUD-related depression [35].

With respect to glutamate, the reduction in neuroinflammation achieved through butyrate's barrier-protective and NF-κB-inhibitory effects would presumably relieve the inflammatory suppression of GLT-1, allowing astrocytes to more efficiently clear extracellular glutamate in the NAc and PFC. This mechanism, demonstrated for anti-inflammatory agents such as fenofibrate in our own work [24], would reduce glutamatergic excitotoxicity and thereby the neurobiological drive toward alcohol seeking during abstinence.

7. EVIDENCE FROM HUMAN STUDIES AND CLINICAL RELEVANCE

Multiple studies have documented that individuals with AUD have markedly reduced abundance of butyrate-producing bacteria compared to healthy controls, and that this dysbiosis correlates with markers of intestinal permeability, systemic inflammation, and psychiatric symptom severity [8,16,20]. Proskynitopoulos et al. showed that during the first two weeks of alcohol abstinence, partial recovery of bacterial butyrate-producing capacity was associated with reductions in IL-8 and craving scores, supporting the idea that restoring this microbial function has clinical relevance [56]. In a study of 60 AUD patients

evaluated during early abstinence and at three weeks, Leclercq et al. found that those with persistent intestinal permeability and dysbiosis had significantly higher depression, anxiety, and craving scores—and greater subsequent relapse risk—than those whose barrier function partially recovered. [20].

From a broader nutritional perspective, multiple randomized clinical trials have demonstrated that increased dietary fiber intake reduces systemic inflammatory markers, including C-reactive protein, IL-6, and TNF-α [51,52], and that fiber-rich diets are associated with lower rates of depression in large epidemiological cohorts [57]. Dietary patterns rich in fermentable fiber (e.g., Mediterranean and plant-based diets) have been consistently associated with lower rates of depression and better mental health outcomes [58]. While these associations are largely observational and do not establish causality in AUD populations specifically, they are consistent with the mechanistic framework proposed in this article.

A particularly relevant human study is that of Leclercq et al. (2021) in 57 AUD patients undergoing detoxification, which directly linked the gut microbiota—and specifically SCFA-producing bacteria—to kynurenine pathway metabolites, depression severity, and craving [34]. This study demonstrated that a more robust butyrate-producing microbiota was associated with higher KYNA/QUIN ratios (indicative of neuroprotection) and lesser diversion of tryptophan toward the neurotoxic kynurenine branch. This represents one of the most direct human demonstrations of the gut-to-brain pathway proposed in this article.

8. AN INTEGRATED MODEL AND PROPOSED THERAPEUTIC FRAMEWORK

Based on the evidence reviewed, we propose the following integrated mechanistic framework: chronic alcohol consumption induces gut dysbiosis → reduces SCFA-producing bacteria and butyrate availability → disrupts TJ proteins and increases intestinal permeability → enables LPS translocation into the circulation → activates TLR4 in peripheral immune cells → generates systemic inflammation (TNF-α, IL-1β, IL-6) → proinflammatory cytokines reach the brain via the BBB and vagal pathways → activate microglia and astrocytes → reduce GLT-1, suppress BDNF, activate IDO1, and alter TH/DAT expression → produce excess glutamate, dopaminergic hypo functionality, and serotonin deficiency → generate depressive-like symptoms (anhedonia, anxiety, hopelessness) and maintain relapse vulnerability during abstinence (Figure 1).

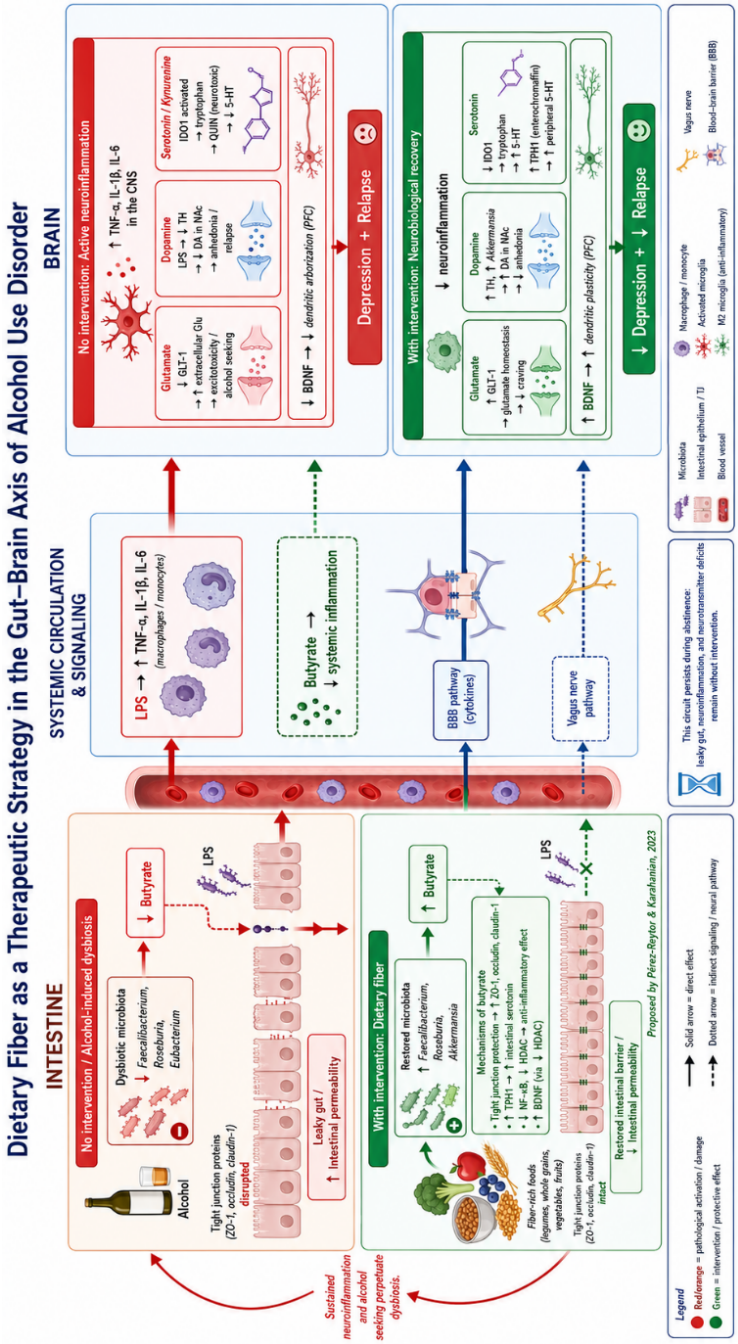

Figure 1.

Dietary fiber as a therapeutic strategy in the gut-brain axis of alcohol use disorder and depression

Critically, this circuit does not self-correct upon cessation of alcohol consumption. The intestinal barrier remains compromised, LPS translocation continues, neuroinflammation persists, and neurotransmitter imbalances are maintained, sustaining both the depressive phenotype and the neurobiological drive toward alcohol seeking.

Dietary fiber intervention—by restoring butyrate-producing microbiota, increasing colonocyte energy supply, upregulating TJ proteins, and inhibiting NF-κB—targets the upstream segment of this cascade, addressing the root cause rather than distal symptoms. This approach complements pharmacological interventions targeting downstream steps (e.g., anti-inflammatory agents, glutamate modulators, antidepressants) and may be particularly valuable during the early abstinence period.

We propose that dietary fiber intake should be systematically assessed and actively promoted as part of the clinical management of AUD, beginning during detoxification. Practical recommendations include increasing consumption of legumes (lentils, chickpeas, beans), whole grains (oats, barley, whole wheat), vegetables (onion, garlic, artichoke, asparagus—all rich in inulin and FOS), and fruits (apples, berries, bananas). For patients unable to substantially modify their dietary habits, prebiotic fiber supplementation (inulin, FOS, β-glucan) represents an accessible alternative that has proven safe and well-tolerated in AUD populations [50].

9. CONCLUSIONS AND FUTURE PERSPECTIVES

AUD-related depression and relapse vulnerability share a common neuroinflammatory substrate driven, in significant part, by alcohol-induced intestinal barrier disruption and dysbiosis. The consequent LPS-mediated activation of peripheral and central inflammatory pathways produces the glutamate, dopamine, and serotonin imbalances underlying anhedonia, hopelessness, and compulsive alcohol seeking during abstinence. Dietary fiber intake, by promoting the growth of butyrate-producing microbiota and thereby increasing endogenous butyrate production, targets this pathological cascade at its upstream source: the gut. Butyrate strengthens the intestinal barrier, reduces LPS translocation, inhibits NF-κB-driven neuroinflammation, promotes serotonin synthesis, restores dopaminergic tone, and may normalize BDNF and dendritic plasticity—mechanisms all highly relevant to both depression and relapse prevention in AUD.

The evidence base for this proposal spans from robust preclinical demonstrations of gut-brain axis disruption and recovery to human studies linking dysbiosis, butyrate deficiency, and psychiatric symptoms in AUD. While definitive randomized clinical trials specifically evaluating dietary fiber interventions on relapse rates and depressive outcomes in AUD populations are still lacking, the mechanistic coherence, favorable safety profile, and accessibility of this approach justify its integration into the clinical management of AUD as a complementary nutritional recommendation.

Future research should prioritize prospective clinical trials evaluating the effect of fiber-rich dietary interventions or prebiotic supplementation on markers of intestinal permeability (LPS-binding protein, zonulin), systemic and central inflammation, kynurenine pathway balance (KYNA/QUIN ratio), neurotransmission indicators, and clinically relevant outcomes, including depression scores, craving intensity, and relapse rates, in individuals with AUD during early and extended abstinence. Microbiome profiling will be essential to identify which fiber types and which bacterial taxa are most responsive in this population. These studies will help transform a mechanistically grounded hypothesis into an evidence-based therapeutic strategy.

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Conflict of interest

The authors declare no conflict of interest.

Data availability statement

This is a review and perspective article. No original datasets were generated or analyzed for this manuscript. All data supporting the conclusions are based on published studies cited in the references.

Author contributions

Conceptualization: EK, DPR. Original manuscript writing: EK. Revision and edition: DPR, EK.

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