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REVIEW

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Ethanol-induced changes to the gut microbiome compromise the intestinal homeostasis: a review

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ABSTRACT

The intestine is the largest organ in terms of surface area in the human body. It is responsible not only for absorbing nutrients but also for protection against the external world. The gut microbiota is essential in maintaining a properly functioning intestinal barrier, primarily through producing its metabolites: short-chain fatty acids, bile acids, and tryptophan derivatives. Ethanol overconsumption poses a significant threat to intestinal health. Not only does it damage the intestinal epithelium, but, maybe foremostly, it changes the gut microbiome. Those ethanol-driven changes shift its metabolome, depriving the host of the protective effect the physiological gut microbiota has. This literature review discusses the impact of ethanol consumption on the gut, the gut microbiota, and its metabolome, providing a comprehensive overview of the mechanisms through which ethanol disrupts intestinal homeostasis and discussing potential avenues for new therapeutic intervention.

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Introduction

The intestines are the largest, surface-wise, barrier organ in humans. The intestinal barrier is a complex structure that acts as a selectively permeable shield responsible for absorbing nutrients while safeguarding against harmful external factors. It consists of several layers: the gut microbiota, the unstirred water layer, glycocalyx and the mucosal layer (containing antimicrobial products from both Paneth cells and enterocytes), and epithelial cells separated by junctions built by tight-junction proteins.[1,2]

The gut microbiota, encompassing diverse bacteria and microorganisms within the gastrointestinal tract, is integral in maintaining host health. Recognition of its significance is steadily increasing, as evidenced by a growing number of dedicated studies.[3] It is fundamental for maintaining the proper function of the intestinal barrier, aiding in nutrient digestion and protecting against pathogens. This paper will focus on the bacteria that colonize the digestive tract, and for simplicity, we will refer to them as gut microbiota from this point on. The gut microbiota generates various metabolites that greatly influence the host's metabolism. These include short-chain fatty acids (SCFAs), branch-chained amino acids (BCAAs), tryptophan metabolites, bile acids (BAs), trimethylamine N-oxide (TMAO) and many more. Physiologically, *Firmicutes* and *Bacteroidetes* phyla constitute over 90% of the total bacterial population. A shift in the number and type of species that form the gut microbiota may facilitate the onset of various diseases, promote malnutrition, and induce inflammatory responses.

Ethanol abuse is widely recognized as a significant public health concern. In 2016, ethanol use was identified as the seventh leading risk factor for deaths and disability-adjusted life-years globally.[4] Its detrimental effects extend well beyond liver damage and addiction.[5] Not only does it damage the intestinal barrier, but emerging research has unveiled the profound impact of ethanol consumption on the gut microbiome.[6,7] Numerous studies have revealed that prolonged and excessive ethanol consumption can significantly alter the composition and diversity of the gut microbiota. These changes can impair its physiological function, potentially leading to various clinical consequences. Understanding the relationship between ethanol and the function of the gut microbiome may offer

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new therapeutic strategies in ethanol-related diseases of the gastrointestinal tract.

In this review, we will present ethanol's detrimental effect on the gut. First, we will discuss the effects of its inherent toxicity on the intestines. Then, we will explore its impact on the gut microbiota and its metabolites, which appear to be crucial in maintaining gut barrier function and intestinal balance.

Main text

Toxic effect of ethanol on the intestine and the gut barrier

Most of the ingested ethanol is absorbed in the small intestine through diffusion.[8,9] Ethanol has a direct toxic effect on the mucosal epithelium.[10] It is known to disrupt cell membranes, increasing their fluidity and, thus, permeability.[11] In experimental animals such as rodents and dogs, administration of ethanol at concentrations corresponding to those of commonly available alcoholic beverages leads to mucosal damage in the small intestine. This damage extends to the loss of epithelium at the tips of the villi, hemorrhagic erosions, and hemorrhage in the lamina propria.[12] Barona et al. observed concentration-dependent morphological changes in the duodenum and jejunum of rats fed with ethanol, particularly evident at the villi tips where significant cell loss occurred.[13] Broitman and Hoyumpa found similar changes in humans displaying villi damage in intestinal biopsies following ethanol consumption.[8,14] The changes included reduced villus height, reduced mucosal surface area of villi, increases in the number of intra-epithelial mononuclear cells, goblet cell hyperplasia, and gastric metaplasia.[15] Ethanol also increases the secretion of mucins by goblet cells and lowers the expression of heat shock proteins in a dose-dependent manner in murine models.[16,17]

Ethanol damages intestinal mucosa in a dose-dependent manner, compromising its barrier function by dismantling the microtubule skeleton and inducing oxidative stress.[18] Recent experiments have suggested that the initial event of gut response to alcohol is an influx of leukocytes accompanied by enhanced release of toxic mediators such as reactive oxygen species, leukotrienes, and histamine by mast cells.[19–21] However, duodenal or jejunal biopsies of actively drinking alcoholics taken after a few days of abstinence usually show no mucosal infiltrates of leukocytes or macrophages on routine histology or quantitative analysis compared to recently drinking alcohol-abusing subjects or controls.[22,23]

In the study by Palatino et al., ethanol increased the immunoreactivity of IL-6, MMP-9, and NF-κB in the jejunum.[24] MMP-9, IL-6, and TNF-α are mediators playing a crucial role in the progression of inflammation and increase of intestinal permeability in patients with inflammatory bowel diseases.[25,26]

Ethanol lowers the expression of tight junction proteins, such as zonula occludens-1 and claudin-1, in the Caco-2 intestinal cell in vitro model.[27] Ma et al. have shown that ethanol in Caco-2 monolayers can reversibly disrupt the intestinal epithelial tight junction integrity through myosin light chain kinase activation and subsequent modulation of perijunctional actin and myosin filaments.[28] Furthermore, incubation of Caco-2 cells with ethanol for 24 hours has been shown to induce nuclear factor-kB activation, resulting in F-actin cytoskeleton instability and intestinal barrier dysfunction.[29]

Significantly increased intestinal permeability in actively drinking alcoholics has been confirmed for both micro- and macromolecules.[30,31] It is supported by the observation of transient endotoxemia following acute alcohol consumption in healthy volunteers and in alcoholics with fatty liver.[32] Chronic alcohol consumption in mice increases intestinal permeability and causes steatohepatitis, with the colon being the primary site of increased gut leakiness. While small intestinal permeability was unaffected, whole gut permeability was elevated, indicating colonic hyperpermeability as the main factor in alcohol-induced gut leakiness.[33] In a study on healthy adults, acute binge drinking increased serum endotoxin and pro-inflammatory cytokine levels, proving that ethanol compromises the intestinal barrier, with this effect being more pronounced in women.[34]

Ethanol abuse induces alterations of the matrix network and increases the number of myofibroblast-like cells in the duodenal mucosa, findings

compatible with the development of fibrosis of the intestinal mucosa.[35]

In a murine model of alcohol liver disease, ethanol feeding caused intestinal hyperpermeability represented by high concentrations of plasma LPS, though plasma LPS was significantly lower in Muc2(-/-) mice. Hartmann et al. postulated that the increased mucin secretion creates an environment favorable to microbial overgrowth that ultimately leads to liver injury.[36] Germ-free mice fed with ethanol for seven days demonstrated only moderately higher intestinal permeability than control. In the same study, conventional mice had significantly higher intestinal permeability when exposed to the same level of ethanol consumption. This indicates that ethanol-induced alterations in the gut microbiome are the primary cause of increased intestinal permeability. Transferring these ethanol-modified gut microbes to germ-free mice resulted in high intestinal permeability and inflammation in the liver and intestines.[37]

We summarize the toxic effect of ethanol on intestine in Figure 1.

In this figure, we present the detrimental effect ethanol has on the intestinal tissue: 1) toxic damage of the intestinal cells, 2) hemorrhagic erosions and hemorrhage in the lamina propria, 3) lower expression of heat shock proteins (HSP), 4) increase in goblet cells and mucus production, 5) increased expression of nuclear factor kappa B (NF-κβ) and thus proinflammatory interleukin-6 (IL-6), matrix metalloproteinase-9 (MMP-9) and tumor necrosis factor α (TNF α), 6) decreased tight junction protein expression, 7) reduction of the height and surface of the villi, 8) influx of leukocytes which lead to release of toxic reactive oxygen species (ROS), leukotrienes (LTs) and histamine (H) by mast cells, 9) metaplasia.

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Impact of ethanol on the gut microbiome

The difference in the gut microbiome between the population overusing ethanol and healthy controls has been shown in several studies. Only one

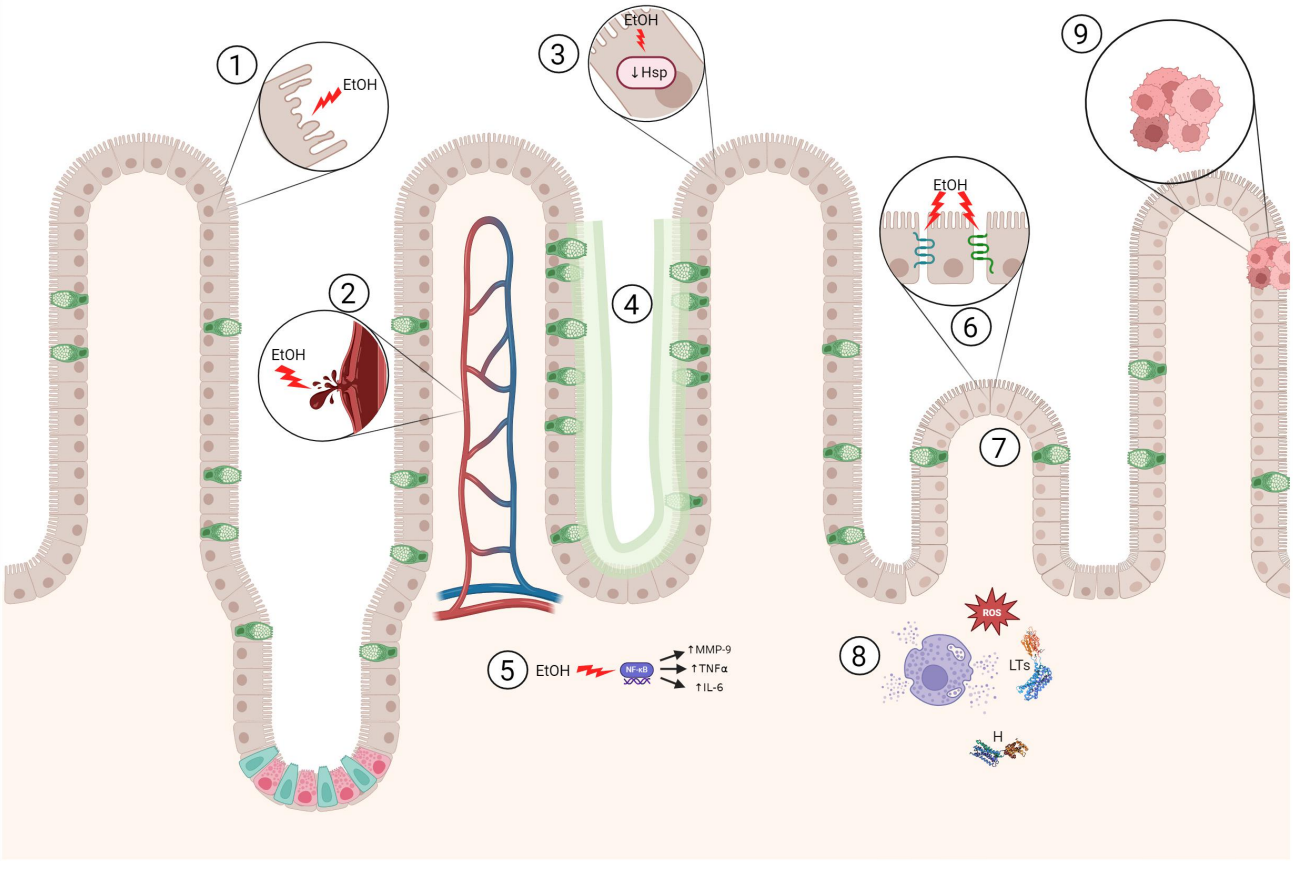

Figure 1. Detrimental effect of ethanol on intestine.

systematic review was published by Litwinowicz et al.[38] Changes in the gut microbiome observed in reviewed studies are presented in Table 1. Generally, there is a relatively higher abundance of *Proteobacteria* phylum in comparison to *Firmicutes*. Furthermore, there is a depletion of several bacterial genera. Almost all depleted genera are involved in producing SCFA, BCAAs, BAs and tryptophan derivatives. On the species level, the relative abundance of *Akkermansia muciniphila* and *Faecalibacterium prausnitzii* was consistently lower in the population with alcohol use disorder.

Proteobacteria

Proteobacteria is currently the largest bacterial phylum. It is characterized by Gram-negative staining. Many recognized human pathogens, such as *Helicobacter*, *Escherichia*, *Shigella*, *Salmonella* and *Yersinia*, belong to this phylum. Researchers postulate that the higher abundance of *Proteobacteria* might be a marker of intestinal dysbiosis. It is also associated with metabolic disorders, such as obesity and type 2 diabetes mellitus.[39]

Higher *Proteobacteria* prevalence promotes proinflammatory conditions. In mice that were genetically modified to be susceptible to inflammation, Carvalho et al. observed higher levels of Proteobacteria, which seemed to trigger chronic colitis.[67] IL-10^{-} mice had a higher abundance of *Proteobacteria* and an onset and progression of chronic colonic inflammation.[68] The excessive presence of *Proteobacteria* phylum characterizes inflammatory bowel disease patients and positively correlates with the severity of the inflammation.[69,70] Researchers also observed the growth of the *Proteobacteria* population with aging accompanied by increased intestinal permeability and chronic inflammation.[71] Low-grade chronic inflammation correlates with the development of age-related conditions and increased mortality.[72]

Akkermansia muciniphila

Ethanol abuse leads to the depletion of *Akkermansia muciniphila*. It is a mucin-degrading member of the *Verrucomicrobium* phylum, which can comprise up to 3% of the gut bacteria detected in human fecal samples.[73] It produces SCFAs and lowers endotoxemia by maintaining intestinal barrier integrity.[74,75] Extremely long-living people (i.e. over 100 years old) have a relatively higher abundance of *Akkermansia*.[76] Its lower abundance is being linked with various metabolic diseases, such as obesity, type 2 diabetes mellitus and non-alcohol fatty liver disease. Many consider *Akkermansia muciniphila* as a next-generation probiotic. Its supplementation was effective in the treatment of diet-induced obesity. It improved postprandial blood glucose, insulin sensitivity and total serum cholesterol. Furthermore, it seems to have a protective effect from cardiovascular diseases.[77,78]

Faecalibacterium prausnitzii

Faecalibacterium prausnitzii, a member of the *Clostridium* spp, is also depleted by excessive ethanol consumption. It is one of the most abundant butyrate-producing bacteria present in human fecal samples.[79] It colonizes the mucus layer and plays a vital role in preserving the intestinal barrier.[80,81] *Faecalibacterium prausnitzii* is often proposed as a marker of intestinal health. Patients with irritable bowel syndrome have a lower abundance of *Faecalibacterium* genus (including *Faecalibacterium prausnitzii*).[82] In both in vitro and murine models of colitis, it exerts anti-inflammatory effects. Furthermore, a preoperative lower relative abundance of *Faecalibacterium prausnitzii* was associated with a higher risk of postoperative recurrence of ileal Crohn's disease.[55] Llopis et al. postulated that *Faecalibacterium prausnitzii* was a key species associated with protection from alcohol hepatitis in a murine model.[83] Lower relative *Faecalibacterium prausnitzii* abundance was also found in patients with colorectal cancer.[84]

The gut microbiome metabolome and its response to ethanol consumption

Short-chain fatty acids

SCFAs are a group of fatty acids with a low number of carbon atoms predominantly produced in the colon through the bacterial fermentation of dietary fiber and other non-digestible carbohydrates.[85,86] Generally, the *Bacteroidetes* phylum produces acetate and propionate, while the *Firmicutes* phylum

produces butyrate.[45] The majority of SCFAs is absorbed in the cecum and large intestine, with the remaining portion excreted in feces.[87] In the following paragraphs, we will explore the diverse roles of SCFAs in intestinal health (Figure 2).

SCFAs, particularly butyrate, serve as the primary energy source for colonocytes, fulfilling around 90% of their energy needs, and contribute approximately 5–10% of the total daily energy requirements in humans.[88,89] Butyrate contributes to the production of tight-junction proteins, which play a critical role in maintaining the integrity of cell-to-cell junctions and regulating paracellular transport.[90,91]

The mucus forms a protective physical barrier that prevents harmful microorganisms and substances from reaching the epithelial surface.[92] In vitro studies indicated that SCFAs can regulate the thickness of this mucus layer and are involved in restoring the mucus layer in instances of injury.[93,94]

Paneth cells, situated at the base of the small intestinal crypts, are responsible for secreting various antimicrobial peptides crucial for the intestine's defense mechanisms.[95] In vitro and in vivo

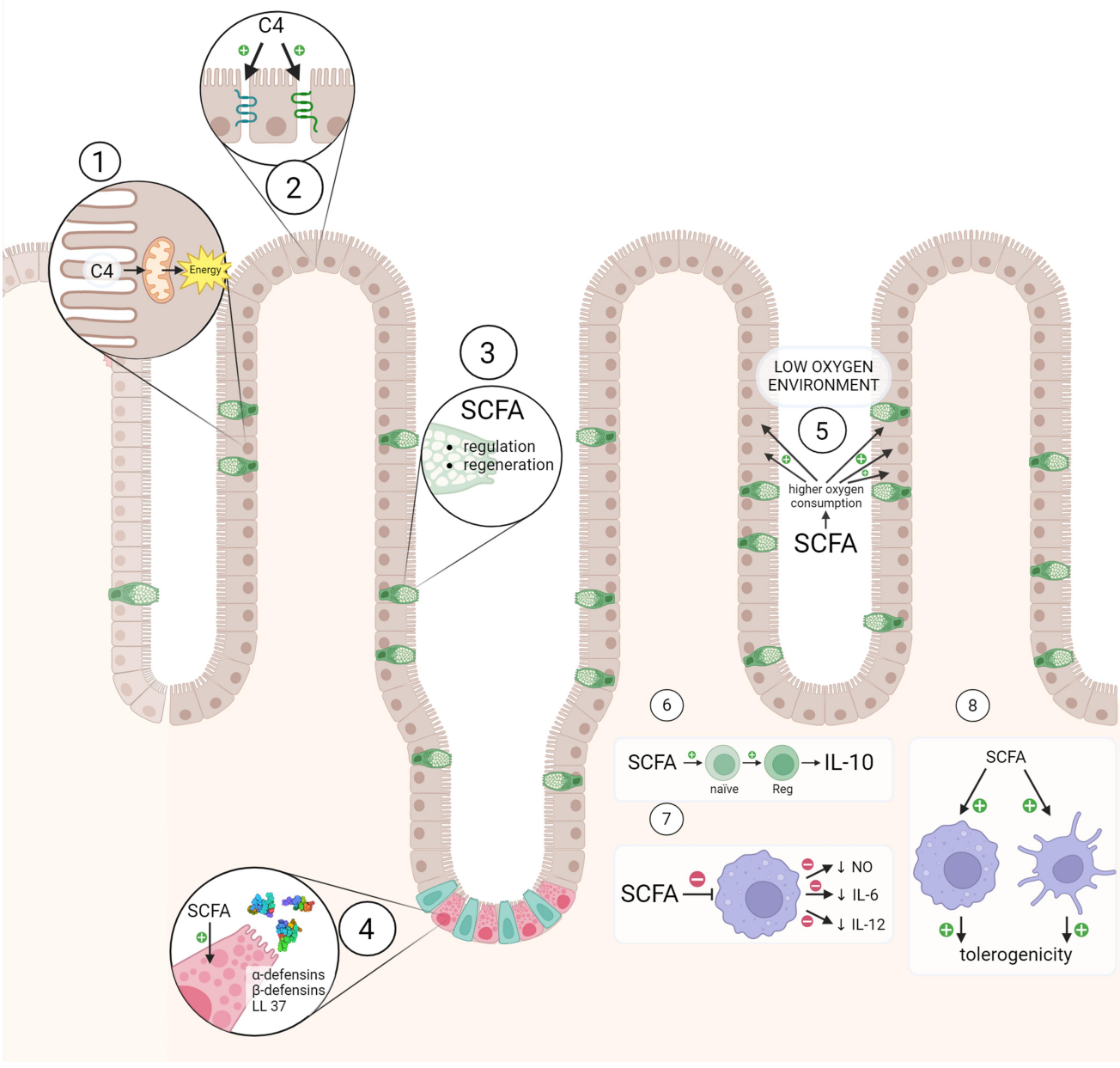

Figure 2. The impact of SCFAs on intestinal health.

studies indicate that SCFAs, especially butyrate, stimulate the production of antimicrobial peptides by Paneth cells, particularly alpha- and beta-defensins and LL-37.[96–99]

SCFAs participate in creating a favorable hypoxic environment that supports beneficial gut bacteria while inhibiting the growth of harmful pathogens. Butyrate stabilizes hypoxia-inducible factor transcription in intestinal epithelium cells, boosting oxygen consumption and fostering a physiologically advantageous hypoxic environment within the colon.[100,101]

SCFAs demonstrate potent immunomodulatory effects, particularly in the intestines, displaying notable anti-inflammatory properties. These effects operate through two primary pathways: G protein-coupled receptors (GPRs) and histone deacetylases (HDACs) inhibition.[102] Dendritic cells (DCs) treated with SCFAs induced differentiation of naïve T-cells into Treg1 cells producing anti-inflammatory IL-10.[103] Treatment of macrophages with n-butyrate led to the down-regulation of LPS-induced pro-inflammatory mediators, including nitric oxide, IL-6, and IL-12, while maintaining levels of TNF-α or MCP-1.[104] Moreover, activation of GPR109a by butyrate enhanced the tolerogenic response of colonic macrophages and dendritic cells, reduced colonic inflammation and promoted homeostasis in mice.[105] In a murine model of nonalcoholic steatohepatitis NASH, sodium butyrate treatment induced apoptosis of pro-inflammatory liver macrophages and promoted their differentiation into the anti-inflammatory M2 phenotype.[106] SCFAs exert an anti-inflammatory and tolerogenic effect not only in intestinal epithelial cells but also in other organs.

In this figure we present the detrimental effect ethanol has on the intestinal tissue: 1) toxic damage of the intestinal cells, 2) hemorrhagic erosions and hemorrhage in the lamina propria, 3) reduction of the height and surface of the villi, 4) increase in goblet cells and mucus production, 5) metaplasia, 6) lower expression of heat shock proteins (HSP), 7) dismantling of cytoskeleton, 8) decreased tight junction protein expression, 9) increased activity of proinflammatory interleukin-6 (IL-6), matrix metalloproteinase-9 (MMP-9) and nuclear factor kappa B (NF-κβ), 10) influx of leukocytes which lead to release of toxic reactive oxygen species (ROS), leukotrienes (LTs) and histamine (H) by mast cells.

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Impact of ethanol overconsumption on SCFA and SCFA-producing bacteria

Excessive ethanol consumption leads to a shift in SCFA-producing bacteria. There is a lesser abundance of *Bacteroidetes* on the phylum level and a lower *Firmicutes*/*Proteobacteria* ratio.[39,107] As presented in Table 1. on genus level, there is less *Akkermansia*, *Alistipes*, *Bacteroides*, *Clostridium*,

Table 1. Changes in the gut microbiota due to ethanol consumption based on the systematic review by Litwinowicz et al.

	Abundance	SCFA	BAs	Trp	BCAAs	TMA	Ref.
PHYLUM							
Proteobacteria	↑	–	–	–	–	+	39,40
Bacteroidetes	↓	+	+	+	–	+	40
FAMILY							
Enterobacteriaceae	–	–	–	–	–	–	
Ruminococcaceae	↑	–	+	+	–	–	
GENUS							
Akkermansia	↓	+	–	+	–	–	41–43
Alistipes	↓	+	–	+	–	–	44
Bacteroides	↓	+	+	+	+	–	45–49
Clostridium	↓	+	+	+	–	+	40,45,50–52
Collinsella	↓	+	–	–	–	–	53
Faecalibacterium	↓	+	–	–	+	–	54–56
Parabacteroides	↓	+	–	–	–	–	57
Paraprevotella	↓	–	–	–	–	–	
Prevotella	↓	+	–	–	+	–	58,59
Ruminococcus	↓	+	+	+	+	+	60–66

A plus sign in the table indicates that the given bacteria are involved in the metabolism of the specified metabolites (in the case of bile acids, in the conversion of primary bile acids to secondary bile acids). References indicate that the bacteria in question are involved in the metabolism of the specified metabolites.

(SCFA – short-chain fatty acids, BAs – bile acids, Trp – tryptophan derivatives, BCAAs – branch-chained amino acids, TMA - trimethylamine).

Collinsella, *Faecalibacterium*, *Parabacteroides*, *Prevotella* and *Ruminococcus*.

In mice, ethanol feeding causes colonic hyperpermeability, decreased butyrate to total SCFA ratio in the stool and steatohepatitis.[33] It inhibits intestinal stem cells essential to maintain the continuous renewal of the intestinal epithelium.[108] Ethanol feeding also suppressed Notch1 (the gene responsible for intestinal cell differentiation), resulting in gut leakiness, lower expression of tight-junction proteins and colonic inflammation.[109,110] This effect can be attributed to lower butyrate production by the intestines.[33] It is worth noting that the above effects happened only in the colon; none were observed in the jejunum. In an in vitro study of the intestinal cell model of ethanol abuse, treatment with a microbial synbiotic increased the relative abundance of SCFA-producing bacteria and butyrate and acetate production.[111] Cresci et al. proved that tributyrin (butyrate and glycerol ester) supplementation in a chronic ethanol murine model resulted in higher expression of tight-junction proteins and lower intestinal permeability.[112] Probiotic treatment with *Pediococcus pentosaceus* in chronic and binge ethanol murine models restored the relative abundance of SCFA-producing bacteria, improving the intestinal barrier function and reducing inflammation.[113]

Tryptophan and its derivatives

Tryptophan is one of the essential amino acids. Although most ingested tryptophan undergoes metabolism via kynurenine or serotonin pathways within the small intestine, the gut microbiome metabolizes a portion.[114,115] Certain bacteria utilize tryptophan as an energy source, generating by-products that influence the immunological homeostasis within the intestine.[116,117] In an experimental murine model, tryptophan deprivation led to a shift in the gut microbiome, notably an increase in *Actinobacteria*, *Proteobacteria*, and *Firmicutes*, alongside a decrease in *Bacteroidetes*.[118]

Tryptophan-derived microbial metabolites can function as ligands for the aryl hydrocarbon receptor (AHR). Within humans, AHRs are primarily situated at barrier sites, particularly in the intestines, contributing to maintaining immunological balance.[119] Activation of AHRs exerts multifaceted effects. It contributes to preserving the proper function of the intestinal barrier, promoting the production of anti-inflammatory cytokines (especially IL-22, which plays a crucial role in early defense against bacterial pathogens) and inhibiting the production of pro-inflammatory cytokines (such as IL-17 or IFN-γ).[120–124] AHR activation also helps regenerate the colitis model's intestinal barrier.[125]

One of the better-studied gut microbiome-derived tryptophan metabolites is indole propionic acid (IPA).[126] IPA is also involved in the maintenance of the intestinal barrier.[127] It up-regulates the production of mucins and tight-junction proteins, reducing the intestinal epithelium's permeability.[128,129] IPA induces the expression of anti-inflammatory IL-10 while suppressing the pro-inflammatory NF-κβ signaling.[130,131]

Indole-3-lactic acid (ILA) is another bacterial tryptophan derivative that exhibits anti-inflammatory activity by activating AHR.[132] Studies showed that it can reduce LPS-induced inflammation in intestinal epithelial cells and upregulate anti-inflammatory pathways in immature intestinal epithelial cells.[133,134] In mice, it decreases the accumulation of pro-inflammatory macrophages, thereby reducing susceptibility to DSS-induced colitis.[135] ILA increases the number of tryptophan-metabolizing bacteria, which results in increased production of indole-3-propionic acid and indole-3-acetic acid.[136]

A study by Li et al. demonstrated that indole-3-acetic acid, via an increase in the proportion of Treg cells, can alleviate DSS-induced colitis in an AHR-independent.[137] Furthermore, by enhancing the sulfation of mucins, indole-3-acetic acid supports intestinal homeostasis and protects it from inflammation.[138]

We present the impact of microbial-derived tryptophan metabolites on intestines in Figure 3.

Tryptophan-derived microbial metabolites: 1) partake in the creation of an anti-inflammatory environment by increasing the production of anti-inflammatory interleukin 10 (IL-10) and interleukin 22 (IL-22), 2) simultaneously inhibit the production of pro-inflammatory cytokines such as

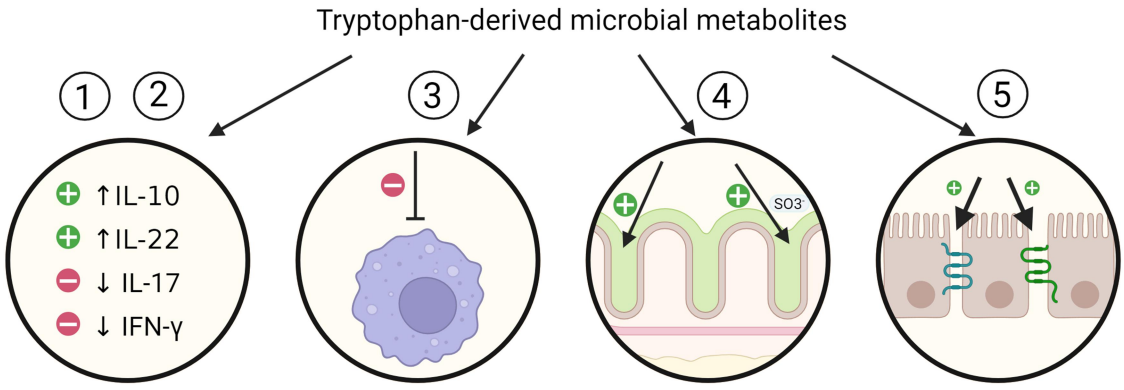

Figure 3. Impact of microbial-derived tryptophan metabolites on intestines.

interferon γ (IFN-γ) and interleukin 17 (IL-17), 3) decrease the accumulation of pro-inflammatory macrophages, 4) up-regulate mucus production and its sulfation, 5) up-regulate tight junction proteins production.

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Impact of ethanol abuse on tryptophan derivatives and the gut microbiota producing them

As presented in Table 1, ethanol abuse leads to a decrease in bacteria strains metabolizing tryptophan, namely *Bacteroidetes* phylum, *Ruminococcaceae* family and *Akkermansia*, *Alistipes* and *Clostridium* genus.

Ethanol consumption in mice led to intestinal dysbiosis, resulting in reduced levels of indole-3-acid – an AHR ligand involved in the regulation of the anti-inflammatory cytokine IL-22. Furthermore, patients with alcoholic hepatitis had lower fecal indole-3-acid compared to healthy controls. Feeding mice with *Lactobacillus reuteri* engineered to produce IL-22 reduced ethanol-driven liver damage, inflammation and bacterial translocation.[139] Intervention with Lactiplantibacilus plantarum in a murine alcoholic liver injury model altered gut microbiome and increased indole-3-acetamide levels, elevating AHR expression and exhibiting anti-inflammatory properties. It up-regulated AHR expression, exerting anti-inflammatory effects.[140] In a murine model of alcohol liver disease, prebiotic treatment leads to increased production of tryptophan-derived AHR ligands. It leads to a reduction in liver injury. However, this effect was absent in ahr knockout mice.[141] Patients with alcoholic hepatitis and liver cirrhosis exhibited diminished levels of tryptophan metabolites in both serum and fecal samples.[142]

While plasma levels of indole-3-propionic acid are lowered in people who abuse ethanol, Mrdjen et al. did not observe lower levels of indole-3-acetic acid or indole-3-lactic acid.[143]

Summing up, bacterial tryptophan metabolites improve and regenerate the intestinal barrier while mitigating inflammation by activating diverse anti-inflammatory pathways. Ethanol consumption leads to gut microbiome changes, resulting in decreased levels of beneficial tryptophan derivatives.

Bile acids

Primary bile acids (BAs), chenodeoxycholic acid (CDCA) and cholic acid (CA) are derivatives of cholesterol. The liver is the only organ that can produce primary BAs.[144] Once excreted into the intestine, more than 90% of BAs are absorbed in the ileum.[145] In the colon, resident microbiome transform remaining primary bile acids into secondary bile acids, primarily lithocholic acid (LCA) and deoxycholic acid (DCA).[146] This conversion involves deconjugation and dehydroxylation processes facilitated by specific enzymatic activity present in certain bacterial species. These include Gram-positive bacteria (mainly *Firmicutes*) and certain Gram-negative from the *Bacteroides* phylum.[147,148] We will focus on the relationship between BAs and the gut microbiota and how BAs help maintain immunological homeostasis in the intestines.

Relation between bile acids and gut microbiome

BAs can modify the gut microbiome. High concentrations of hydrophobic bile acids (BAs) exhibit direct antimicrobial effects by damaging bacterial membranes. Gram-positive bacteria are more vulnerable to BAs than Gram-negative bacteria, with secondary BAs typically displaying higher toxicity to bacteria than primary BAs.[146]

Wang et al. observed a significant shift in the gut microbiome in mice fed with CA, which led to impaired intestinal barrier function and mild intestinal inflammation.[149] Mice fed DCA displayed alterations in intestinal microbiome, alongside intestinal inflammation and the accumulation of fecal BAs.[150] Supplementation of obeticholic acid induced changes in the gut microbiome composition in both mice and humans, reducing endogenous bile acid levels and augmenting the proportion of *Firmicutes*, notably in the small intestine.[151] Interestingly, individuals with inflammatory bowel disease (IBD) often exhibit diminished primary bile acid conversion into secondary bile acids by their gut microbiome.[152]

Bile acids act as agonists for receptors found in various organs and cells. We will focus on receptors involved in preserving immunological balance within the intestines (Figure 4). Farnesoid-x-receptor (FXR) is a metabolic receptor expressed in several tissues, including the liver and the intestine.[153] It is mainly activated by primary BAs – CDCA and CA.[154] Its activation exerts several anti-inflammatory effects. It suppresses pro-inflammatory genes, reducing the expression of pro-inflammatory cytokines and leading to the attenuation of colitis in animal models.[155,156] FXR agonists increase plasma levels of anti-inflammatory Il-10.[157]

Secondary BAs, i.e. LCA and DCA, foremost activate the G protein bile acid receptor (TGR5). Primary BAs also activate TGR5 but at higher concentrations.[154] It can be found in the intestines, monocytes and macrophages. Activation of TGR5 in intestinal macrophages and monocytes shifts their phenotypes into anti-inflammatory promoting expression of ll-10.[158–160] BAs regenerate the intestinal epithelium via activation of TGR5 in intestinal stem cells.[161]

Both FXR and TGR5 promote inflammasome-mediated antimicrobial reactions in mice.[156]

The pregnane-x receptor (PXR) is expressed in the small intestine, colon and liver, as well as in CD4+ and CD8+ T lymphocytes, CD19+ B lymphocytes and CD14+ monocytes.[162,163] LCA is the most potent PXR activator, although CDCA and DCA also activate it.[164] PXR also takes part in the maintenance of intestinal homeostasis. Down-regulation of PXR by imidacloprid increased intestinal permeability, decreased the amounts of tight junction proteins and increased TNF-α and IL-1β levels, both in vitro and in vivo.[165] PXR agonist protected mice from colitis, decreasing macrophage and monocyte infiltration and inhibiting the production of pro-inflammatory cytokines.[166] Shah et al. observed that PXR agonists protected mice from colitis by reducing the mRNA expression of several NF-κβ target genes.[167]

The vitamin D receptor (VDR), located both in the liver and the intestine, is activated by LCA and DCA in addition to vitamin D.[168] Activation of VDR in dendritic cells inhibits the production of

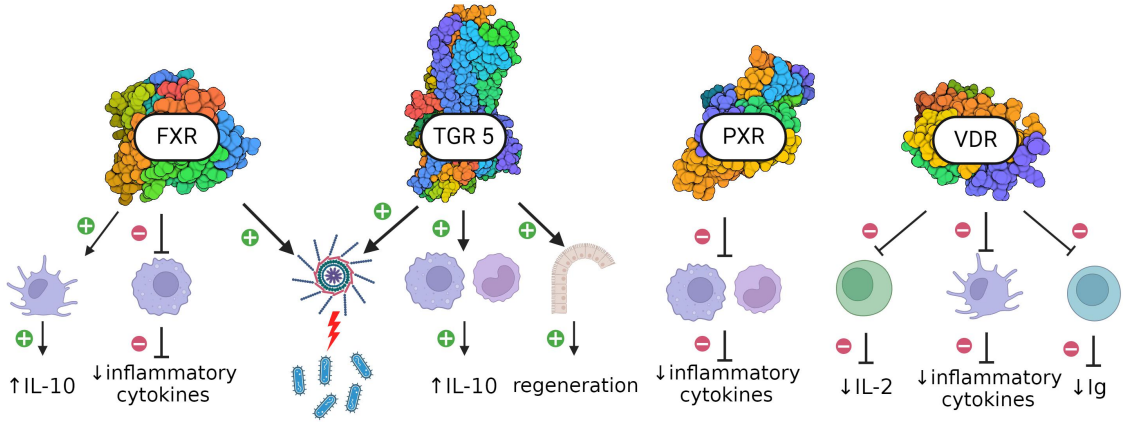

Figure 4. Bile acids receptors and intestinal health.

inflammatory cytokines and reprograms them to become tolerogenic.[169] Activation of VDR in CD8+ T lymphocytes reduces IL-2 production.[170] Activation of VDR in B lymphocytes reduces the production of immunoglobulins.[171]

Bile acids work as agonists for various receptors found in the gastrointestinal tract.

Farnesoid-x-receptor (FXR) activation suppresses pro-inflammatory genes and increases plasma levels of anti-inflammatory interleukin 10 (IL-10).

G protein bile receptor (TGR5) activation shifts the phenotype of intestinal macrophages and monocytes into anti-inflammatory, resulting in higher production of IL-10. TGR5 activation in intestinal stem cells promotes regeneration of intestinal epithelium.

Both FXR and TGR promote antimicrobial inflammasome-mediated reactions.

Pregnane-x receptor activation inhibits the production of pro-inflammatory cytokines by intestinal monocytes and macrophages and reduces the expression of several NF-κβ genes.

Vitamin D receptor activation in 1) intestinal CD8+ T lymphocytes reduces the production of pro-inflammatory interleukin-2 (IL-2), 2) intestinal dendritic cells inhibits the production of inflammatory cytokines, 3) B lymphocytes reduce the production of immunoglobulins (Ig).

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Ethanol consumption and bile acids

Ethanol stimulates bile acid synthesis in humans, possibly due to reduced feedback inhibition of bile acid synthesis caused by ethanol-driven diminished gall bladder contraction.[172,173] However, in patients with alcohol hepatitis, despite high serum bile acid levels, de novo bile acid synthesis is significantly decreased.[174] In mice, bile acid synthesis is regulated via ethanol-activated cannabinoid receptors in the liver.[175] Within the cirrhotic population, currently drinking patients had significantly higher levels of secondary bile acids in stool.[176]

Muthiah et al. observed no significant difference in total fecal levels of both primary and secondary bile acids between drinking and non-drinking patients. However, individuals who consumed ethanol exhibited decreased levels of deoxycholate (DCA), along with alterations in the concentration of other specific bile acids.[65] Ethanol increases the CDCA, DCA and LCA levels in the enterohepatic circulation.[177] In a murine model of alcohol-induced liver injury, fiber feeding lowered the BA levels in plasma and liver. It increased their levels in the stool, probably through reshaping of the gut microbiome.[178]

Other metabolites

Branch-chained amino acids

BCAAs are essential amino acids involved in various metabolic processes. Leucine is a critical stimulator of protein synthesis, supporting albumin production, liver health, and muscle tissue growth.[179] Elevated BCAA levels are associated with insulin resistance, type 2 diabetes risk, and hepatocellular carcinoma progression, but BCAA supplementation has shown benefits in liver diseases.[180–183] The gut microbiota has a bidirectional relationship with BCAAs, affecting their levels and producing or utilizing them.[184] Certain bacterial populations correlate with BCAA levels and insulin resistance.[183,185,186] In the murine model, chronic ethanol consumption lowers concentrations of all three of BCAA in the gastrointestinal tract.[187] However, as this review centers on exploring the relationship between gut microbiota and intestinal health, a detailed exploration of these aspects is beyond the scope of our focus.

Trimethylamine N-oxide

Trimethylamine N-oxide (TMAO) is another crucial microbial metabolite. The gut microbiota residing in the small intestine produces trimethylamine from choline and choline-containing compounds such as L-carnitine and betaine.[188,189] It is mainly produced by the *Firmicutes* and *Proteobacteria* phyla.[40] Then, in the liver, it is oxidized by the flavin monooxygenase family of enzymes forming TMAO.[190] High TMAO serum levels are linked with several detrimental effects in various organs and systems. Li et al.'s umbrella review found a positive association between

circulating TMAO serum levels and all-cause mortality, cardiovascular diseases, major adverse cardiovascular events, hypertension, diabetes mellitus and a decrease in glomerular filtration rate.[191] Furthermore, high TMAO serum levels were found in patients with breast, colorectal, gastric, liver and pancreatic cancers.[192] TMAO levels are also positively associated with the development of NAFLD.[193]

Limited data exist on TMAO's effects on the intestines. Still, it has been linked to the activation of NF-kB and NLRP3 pathways, contributing to inflammation and potentially the development of colorectal cancer. In vitro studies showed that TMAO activates NLRP3 inflammasomes and inhibits autophagy, suggesting a possible role in inflammatory bowel disease (IBD). However, one study found lower TMAO levels in IBD patients compared to a control group, indicating the need for further research.

There is insufficient data on the relationship between ethanol consumption and TMAO levels. Coulbalt et al. found no significant difference in serum TMAO levels between patients with alcohol use disorder and healthy controls, though the variability was greater in the ethanol group.[194] Similarly, Haas et al. reported no difference in TMAO levels between men who moderately drank red wine and those who abstained for an equal period.[195]

Intestinal stem cells

Intestinal stem cells (ISCs) are undifferentiated, multipotent cells located in the crypts of the intestinal epithelium, responsible for the continuous renewal and repair of the intestinal lining.[196,197] These cells give rise to the various cell types of the intestinal epithelium, including absorptive enterocytes, mucus-secreting goblet cells, hormone-producing enteroendocrine cells, and antimicrobial peptide-secreting Paneth cells.[198–200] The proliferation and differentiation of ISCs are tightly regulated by signaling pathways such as Wnt, Notch, and BMP to maintain intestinal homeostasis and prevent uncontrolled cell growth and differentiation.[201–203] The gut microbiota regulates ISC function and intestinal health through its metabolites. Butyrate, via the HDAC inhibition pathway, is a potent intestinal stem cell proliferation inhibitor. However, the unique architecture of the crypt structure usually shields intestinal stem cells from this effect, except during mucosal injury when they are exposed to butyrate.[204] Propionate, and to a lesser extent acetate, significantly induces Reg3B and Reg3G expression both in vitro and in vivo, stimulating intestinal stem cells upon tissue injury.[205] The probiotic bacterium *Akkermansia muciniphila* enhances ISCs function and epithelial development by producing SCFAs and activating the Wnt signaling pathway.[206]

At physiological levels, secondary bile acids act through FXR to regulate Wnt-β catenin signaling and ISCs proliferation, whereas lower levels can disrupt this regulation, potentially leading to carcinogenesis.[207] Pai and colleagues found that low doses of DCA (5 to 50 μM) stimulate colonic cancer cell proliferation and migration via Wnt/β-catenin signaling, while higher concentrations (100 μM) inhibit these processes.[208] Similar results were observed by Milovic et al. in an in vivo model.[209] Sorrentino et al. demonstrated that bile acids (both isolated secondary bile acids as well as a mix) promote epithelial regeneration by activating the TGR5 receptor in intestinal stem cells. The BA-TGR5 axis was essential for reprogramming the intestinal epithelium into a proliferative, repairing tissue.[161]

Tryptophan metabolites influence intestinal stem cells (ISCs) by regulating the aryl hydrocarbon receptor (AHR), which controls WNT signaling and β-catenin levels, maintaining intestinal barrier integrity and preventing tumorigenesis.[125] Park et al. showed that indole-3-carbinol, an AHR-dependent tryptophan metabolite, promotes goblet cell differentiation by regulating key transcription factors, underscoring its role in intestinal health and regeneration.[210]

Ethanol consumption and ISCs

There are still some conflicting data regarding ethanol's effect on intestinal stem cells. Ethanol feeding in mice decreases Notch1 expression in the colon, associated with impaired cell integrity, decreased expression of tight junction proteins and colon inflammation.[33,109,211] Ethanol exposure decreases ISC markers Lgr5 and Bmi1 by

dysregulating β-catenin signaling, impairing small intestine stem cell proliferation and function in *in vitro* and *in vivo* models.[212] On the other hand, in the NIAAA murine model, ethanol consumption alters small intestinal epithelium morphology by increasing crypt depth, proliferative activity, and migration of intestinal epithelial cells, upregulating ISC markers Lgr5 and Bmi1 and enhancing Wnt signaling-dependent ISC activity and IEC proliferation while leaving goblet cell numbers and Notch-1 pathway unchanged.[213]

The effect of probiotic treatment on the gut in ethanol abuse

Several clinical trials have explored the efficacy of probiotic treatment in ethanol-related diseases. They used predominantly animal models to simulate ethanol abuse. In mice, ethanol feeding increases the abundance of *Proteobacteria* and *Actinobacteria* while decreasing the abundance of *Bacteroides* and *Firmicutes*.[214] In the following paragraphs, we will discuss how probiotic treatment can revert ethanol-induced changes to the gut microbiome and alleviate ethanol-induced intestinal injury.

Lactobacillus rhamnosus GG

Lactobacillus rhamnosus GG is Gram-positive, facultative anaerobic or microaerophilic bacteria. It preserves intestinal integrity, exerts anti-inflammatory effects in the intestines, and prevents dysbiosis.[215] It is probably the most studied probiotic in the treatment of alcohol disease.

Treatment with *Lactobacillus rhamnosus* GG prevents ethanol-induced dysbiosis and increases the abundance of BSH-producing bacteria recovering ethanol-suppressed FXR activation.[214,216] In vitro, *Lactobacillus rhamnosus* GG inhibits miR122a, increasing the occludin expression in Caco-2 intestinal monolayers treated with ethanol and restoring their barrier function.[217] The same effect was observed in animal models where *Lactobacillus rhamnosus* GG recovered ethanol-induced damage to the intestinal villi and tight-junction proteins.[218,219] It is, at least in part, mediated through exosome-like nanoparticles. They act through the AHR pathway, increasing the production of tight-junction proteins leading to improved intestinal barrier function.[220] Furthermore, *Lactobacillus rhamnosus* GG reduces gut leakiness and decreases oxidative stress and inflammation in both the intestine and the liver, significantly ameliorating alcoholic steatohepatitis.[221] In a murine model of alcohol-induced liver injury, Zhu et al. found that administration of *Lactobacillus rhamnosus* GG and inosine reversed ethanol-induced changes to the population of Treg and Th1 lymphocytes, alleviating inflammation in the intestines.[218] Supernatant of *Lactobacillus rhamnosus* GG caused restoration of the intestinal barrier function and increased the expression of HIF 2α in mice.[222]

Other probiotics

Lactobacillus plantarum ST-III restored standard histological architecture of the intestine in ethanol-fed rats and mice.[223] It has also restored the distribution of tight-junction proteins and the expression of P-gp protein (a protein that protects the intestine from harmful substances).[224] In the DSS model of colitis treatment with *Lactobacillus delbrueckii*, it increased the expression of anti-inflammatory IL-22 and attenuated ethanol-induced exacerbation inflammation.[225] In the small intestine, *Lactobacillus fermentum* inhibited inflammation by lowering the expression of IL-6 and transcription of TNF-α. Furthermore, it upregulated the production of tight-junction proteins, restoring the intestinal barrier function.[24]

Administration of another probiotic – *Kluyveromyces marxianus* YG-4 – to ethanol-fed mice increased the number of tight-junction proteins and the number of goblet cells in the colon; furthermore, it reduced oxidative stress and inflammation in the liver.[226]

Pediococcus pentosaceus CGMC C7049 in mice restored ethanol-depleted abundance of SCFA-producing bacteria. It lead to increased SCFA levels in stool and increased expression of tight-junction proteins and the antimicrobial peptide Reg3B. Dissection of the murine livers showed lesser ethanol-induced injury in comparison with control and decreased levels of endotoxin and inflammatory cytokines.[113]

Interestingly, Jiang et al. engineered a recombinant strain of *Lactococcus lactis* that produced human alcohol dehydrogenase. Mice treated with the aforementioned probiotic not only showed greater tolerance for ethanol consumption but also were protected from ethanol-induced intestinal and liver damage.[227]

Compound probiotic (containing Lactobacillus, Bifidobacterium and Streptococcus) used together with metformin protected the intestine from ethanol-induced damage in vivo, in vitro and in silico. It has up-regulated tight junction proteins, reduced oxidative stress and alleviated inflammation.[228]

Concluding section

Ethanol's detrimental impact on the intestines extends beyond its inherent toxicity. The gut microbiome, through the production of its metabolites, plays a vital part in maintaining intestinal homeostasis. Its modification caused by ethanol abuse creates a pro-inflammatory environment and compromises the intestinal barrier function. Several studies suggest that probiotic interventions have, at least partially, reversed these changes and restored immunological balance. Thus, further exploration of the gut microbiome in relation to ethanol consumption represents a promising research topic which may deliver new therapeutic options in ethanol-related gastrointestinal diseases.

Further studies are needed to address gaps in the current knowledge. In our opinion, data on the impact of ethanol abuse on the composition of the gut microbiota remain too sparse and too heterogeneous. Due to the ethical impossibility of conducting prospective randomized studies on the effects of ethanol on the microbiota in humans, we rely solely on observational studies. Therefore, more research on this topic is still needed to provide sufficient data for meta-analyses. The impact of ethanol on the gut microbiota in the small intestine, which constitutes the largest part of the digestive tract, is an almost unexplored area. Finding a method to non-invasively determine the composition of the microbiota there would be extremely valuable. The vast majority of studies assessing the impact of prebiotics, probiotics, and postbiotics on the gut microbiota in the context of ethanol abuse have been conducted on animals. Human studies are necessary.

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Views expressed in this paper are our own.

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Data availability statement

The data supporting this study's findings are openly available in cited papers.

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