

CRITICAL REVIEW

Inflammation, oxidative stress and gut microbiome perturbation: A narrative review of mechanisms and treatment of the alcohol hangover

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Abstract

Alcohol is the most widely abused substance in the world, the leading source of mortality in 15–49-year-olds, and a major risk factor for heart disease, liver disease, diabetes, and cancer. Despite this, alcohol is regularly misused in wider society. Consumers of excess alcohol often note a constellation of negative symptoms, known as the alcohol hangover. However, the alcohol hangover is not considered to have long-term clinical significance by clinicians or consumers. We undertook a critical review of the literature to demonstrate the pathophysiological mechanisms of the alcohol hangover. Hereafter, the alcohol hangover is re-defined as a manifestation of sickness behavior secondary to alcohol-induced inflammation, using the Bradford-Hill criteria to demonstrate causation above correlation. Alcohol causes inflammation through oxidative stress and endotoxemia. Alcohol metabolism is oxidative and increased intake causes relative tissue hypoxia and increased free radical generation. Tissue damage ensues through lipid peroxidation and the formation of DNA/protein adducts. Byproducts of alcohol metabolism such as acetaldehyde and congeners, sleep deprivation, and the activation of nonspecific inducible CYP2E1 in alcohol-exposed tissues exacerbate free radical generation. Tissue damage and cell death lead to inflammation, but in the intestine loss of epithelial cells leads to intestinal permeability, allowing the translocation of pathogenic bacteria to the systemic circulation (endotoxemia). This leads to a well-characterized cascade of systemic inflammation, additionally activating toll-like receptor 4 to induce sickness behavior. Considering the evidence, it is suggested that hangover frequency and severity may be predictors of the development of later alcohol-related diseases, meriting formal confirmation in prospective studies. In light of the mechanisms of alcohol-mediated inflammation, research into gut permeability and the gut microbiome may be an exciting future therapeutic avenue to prevent alcohol hangover and other alcohol-related diseases.

KEYWORDS

alcohol, gut microbiome, gut permeability, hangover, inflammation

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INTRODUCTION

Background to alcohol and hangovers

Ethanol (hereafter alcohol) is the most widely available psychoactive drug in the world with an estimated global consumption of 50 billion liters per annum (TWH Organisation, 2018). Alcohol is the seventh leading cause of morbidity and mortality worldwide (GBDA Collaborators, 2018). In 15–49-year-olds, alcohol is the leading cause of mortality, causing 4% of female and 12% of male deaths annually (GBDA Collaborators, 2018). Any level of alcohol consumption is shown to cause harm and alcohol consumption is a risk factor for a multitude of diseases including ischaemic heart disease, liver disease, diabetes, and cancer (GBDA Collaborators, 2018; Hyun et al., 2021). As a result, the high prevalence of alcohol abuse carries a significant socioeconomic burden, with a 6–10-fold increase in the risk of alcohol-related admission or death for heavy drinkers across all social groups (Katikireddi et al., 2017).

Alcohol consumption can lead to alcohol hangover, defined as “the combination of negative mental and physical symptoms which can be experienced after a single episode of alcohol consumption, starting when blood alcohol concentration (BAC) approaches zero” (van Schooten et al., 2016; Verster, Scholey, et al., 2020). The broad range of symptoms may include fatigue, nausea, vomiting, headache, anxiety, apathy, sweating, and concentration problems but symptoms vary by person and quantity of alcohol consumed (Verster, van de Loo, et al., 2020). There is no standard amount of alcohol that induces hangover and symptoms can be experienced across any range of BACs, after any number of drinks (de Haan et al., 2012; Kruisselbrink et al., 2017).

The array of physical and mental symptoms of hangover leads to serious economic impact. A 2019 survey of 3400 workers estimated that the annual number of work days each person spent intoxicated or hungover was 0.6–0.7, implying that 75,000–89,000 people in the United Kingdom are hungover per day, at an economic cost of £8.3–8.5 billion per annum (Studies, 2019). In the United States in 2010, the economic cost of hangovers exceeded \$250 billion (Sacks et al., 2015). In addition to sick days, increasing hangover frequency predicts more severe hangovers, alcohol dependence, and the development of alcohol use disorder (AUD; Courtney et al., 2018; Vatsalya et al., 2019; Verster et al., 2019). While popular, interventions to improve hangover symptoms are ineffective (Roberts et al., 2022).

Due to a general lack of research interest in alcohol hangover, its pathogenesis has been poorly described and is generally unknown, forming the basis of the rationale of this review (GBDA Collaborators, 2018). This review describes the evidence for inflammation as the cause of hangover following acute alcohol intake, through oxidative stress, perturbation of the gut microbiome, congeners, and sleep disturbance. A better appreciation of the pathogenesis of hangovers may provide the basis for treatments that can modulate alcohol-related harm and associated alcohol-seeking behavior simultaneously.

Alcohol-related inflammation causes alcohol hangover

The Bradford-Hill criteria set forth nine viewpoints, which have become the most important and frequently cited framework for causal inference in epidemiological studies (Hill, 1965). The nine points: plausibility, consistency, the strength of association, specificity, temporality, biological gradient (dose–response), coherence, experiment, and analogy are described in further detail to illustrate how inflammation causes the hangover.

Plausibility

Inflammation refers to an immune response to a perceived noxious stimulus that results in tissue damage. The inflammatory response to alcohol is well-characterized: chronic inflammation from alcohol consumption leads to hepatosteatosis, steato-hepatitis, liver fibrosis, and eventually cirrhosis, as well as extrahepatic effects including brain damage and changes in the gut microbiota that impact gut health (Wang et al., 2010). Inflammation induces sickness behavior, characterized by weakness, depression, lethargy, inability to concentrate, malaise, little interest in activity or surroundings, and reduced food and water intake (Dantzer, 2004; Hart, 1988). Sickness behaviors are an adaptive response to infection and inflammation that evolutionarily were critical for the host response to invasion by a pathogen to enhance survival (Alford et al., 2020; Furman et al., 2019; Scholey et al., 2019). Hangover symptomatology recapitulates these sickness behaviors.

Sickness behaviors are triggered by pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor alpha (TNF α), which in general may be released due to tissue damage or by recognition of microbial antigens such as lipopolysaccharide (LPS), a constituent of Gram-negative bacterial cell walls. Meta-analysis has demonstrated how IL-1 and IL-6 are pivotal in the development of sickness behaviors (Shattuck & Muehlenbein, 2016). Cerebral increases of IL-1 and TNF α are noted in a dose–response manner following acute intoxication with alcohol in rat models (Dantzer, 2004; Doremus-Fitzwater et al., 2014; Tiwari et al., 2009; Valles et al., 2004). Alcohol bingeing behavior stimulates LPS release into the systemic circulation by leakage across the gut epithelium (Bala et al., 2014). Mice and humans administered LPS demonstrate raised pro-inflammatory cytokines and thereafter typical sickness behaviors (Lasselin et al., 2021; Musaelyan et al., 2018). LPS is a major mediator of inflammation and its increase following alcohol consumption, combined with its demonstrable ability to cause sickness illustrates a highly plausible mechanism for hangover.

A commonly cited factor suggested to manifest sickness behavior in hangovers is acetaldehyde. Commercial products have long proposed that acetaldehyde is indeed responsible for the alcohol hangover, and the evidence for this is that the pharmacological inhibitor of acetaldehyde dehydrogenase, disulfiram, causes symptoms some symptoms similar to hangover, including flushing, headache, nausea, vomiting, weakness, sweating, and thirst.

However, it can also cause a variety of other symptoms including hyperventilation, tachycardia, hypotension, syncope chest pain, palpitations, dyspnoea, uneasiness, vertigo, blurred vision, and confusion which are not typical of hangover (Lanz et al., 2023). Experiments from 1948 showed that IV infusion of acetaldehyde recreated the negative symptomatology for disulfiram (Hald & Jacobsen, 1948). More recent animal studies have demonstrated that a number of these symptoms may be explained by mast cell degranulation with subsequent histamine and other vasoactive mediator releases (Berg et al., 1977; Ruiz & Gomes, 2000). Moreover, acetaldehyde concentrations in the plasma do not correlate with the severity of the hangover—acetaldehyde is not detected in plasma after 12h, whereas ethanol remains along with hangover symptoms (Mackus et al., 2020; van de Loo et al., 2020).

Dehydration and electrolytes are also commonly believed to result from alcohol consumption. Evidence on the topic is remarkably scant, but a number of studies have shown no electrolyte imbalance resulting from acute intoxication with alcohol, though acid-base status may well be affected (Ylikahri et al., 1974). Moreover, the diuretic effect of alcohol is at best transient and mild, with the strongest evidence from randomized controlled trials showing modest differences up to 4h postalcohol intake and no difference thereafter (Jimenez-Pavon et al., 2015; Maughan et al., 2016; Polhuis et al., 2017; Shirreffs & Maughan, 1997).

Consistency

Consistent results increase the likelihood of a causal inference. Temporal studies in rats have demonstrated how pro-inflammatory cytokines are elevated following acute alcohol consumption and how the cytokine response increases with time postalcohol consumption (Doremus-Fitzwater et al., 2014). In human studies, there is the greatest consistency in elevated levels of IL-6 and IL-10; evidence from a randomized placebo-controlled trial demonstrated that the cytokines IL-6 and IL-10 were elevated following acute alcohol consumption and positively correlated with hangover scores (Kim et al., 2017). In saliva samples, a night of self-reported heavy drinking increased levels of IL-6 and IL-10 compared to no alcohol (van de Loo et al., 2021). IL-10 elevations are recurrently noted in studies of hangovers; IL-10 is an anti-inflammatory cytokine that downregulates the acute inflammatory response. Its expression is commonly seen to be elevated in other pro-inflammatory states as a method of cytokine regulation and may directly antagonize the potentiation of inflammation seen with IL-1 and IL-6 (Dantzer, 2004; Shattuck & Muehlenbein, 2016), although IL-10 may be responsible for mood changes and depressive symptoms expressed by some individuals with hangover (Mesquita et al., 2008). Elevations in cytokine levels vary depending on the method of collection, but macrophage chemotactic protein 1 (MCP-1), IL-1, IL-6, IL-8, IL-10, IL-12, interferon-gamma (IFN γ), TNF α , and CRP are elevated in different studies (Adams et al., 2020; Gonzalez-Quintela et al., 2000; Neupane et al., 2016).

Strength of association (effect size)

The strength of association between alcohol intake and inflammation also supports this inflammatory theory of hangover. The larger the alcohol intake, the greater the level of endotoxemia (considered a measure of systemic inflammation caused by leaky gut) in normal healthy adults as well as patients with liver disease (Bode et al., 1987; Fukui et al., 1991). Moreover, increased frequency of alcohol intake causes worsening endotoxemia (Bjarnason et al., 1984). In mice, quantitative experiments have shown that increasing ethanol intake results in more endotoxemia, liver inflammation, and brain inflammation, with brain cytokine levels remaining elevated for up to 10 days (Qin et al., 2008). Hence volume of alcohol consumed is the major moderator of endotoxemia and inflammation, as well as forming the major risk factor for alcohol hangover and hangover severity (Courtney et al., 2018; Vatsalya et al., 2019; Verster et al., 2019), evidencing a strong association between alcohol intake, inflammation, and hangover.

Specificity

Associations are more likely to be causal when specific. Alcohol consumption is the single cause of hangover, meaning it is highly specific. Preservation of observed endotoxemia in response to alcohol intake is seen in the full spectrum of healthy adults to cirrhotic patients with AUD (Bode et al., 1987, Fukui et al., 1991). Studies using patients as their own controls showed that, when consuming alcohol, there were significant increases in both IL-6 and IL-10 the following day illustrating that inflammation was specific to the alcohol intake as the only independent variable (van de Loo et al., 2021). Unfortunately, no study has yet sought to measure endotoxemia, inflammation, and hangover together, highlighting a gap within the evidence base that calls for further research. Interestingly, factors that make hangovers worse, such as reduced sleep quality and congeners, also cause inflammation and/or oxidative stress adding further weight to the specific link between alcohol, inflammation, and hangovers.

Temporality

To infer causation, the cause must occur before the observed effect. Acute alcohol intake is known to be a potent activator of neuroinflammation, which potentially activates sickness behavior due to the proximity to central cytokine receptors in the anterior olfactory nucleus, thalamus, hypothalamus, amygdala, and cerebellum (Dantzer, 2004). This is evidenced through experimental measurement of brain cytokines in animal models (Doremus-Fitzwater et al., 2014, 2015). Toll-like receptors (TLRs) are an essential family of antigen-recognition receptors that mediate the innate immune response against pathogens by recognizing antigens like LPS. Studies in mice have shown that administration of LPS mimicked the

systemic effects of alcohol intake on inflammation which is mediated by the TLR4 receptor (Rivera et al., 1998). Human studies have shown how cerebral concentrations of TLR4 in patients with AUD correlate to lifetime alcohol intake; ethanol priming of this receptor may mediate alcohol craving (Crews et al., 2017; Karoly et al., 2018). By recognizing antigens such as LPS, TLRs trigger nuclear factor kappa B (NF- κ B) activation which is responsible for initiating the pro-inflammatory cascade in response to a pathogen, with marked cytokine release and demonstrating the clear temporal relationship (Akira & Takeda, 2004). Neurones also express TLRs, increasing levels of TLR2 and TLR4 in response to IFN γ -related energy deprivation and IFN γ levels have been correlated with hangover severity (Kim et al., 2003; Tang et al., 2007). The presence of TLR2 and TLR4 ligands together augment the inflammatory response to alcohol (TNF- α protein and mRNA levels and NF- κ B activation) in human monocytes (Oak et al., 2006). Both acute and chronic alcohol administration has been shown to activate TLR4 signaling in astrocytes, microglia, and macrophages in the brain (Blanco et al., 2005; Davis & Syapin, 2004; Fernandez-Lizarbe et al., 2008). In addition to the pro-inflammatory activation of microglia and astrocytes, murine studies have demonstrated that chronic alcohol intake stimulates the migration of peripheral macrophages into the central nervous system, particularly the hippocampus (Lowe et al., 2020). Inhibition of macrophage chemotactic protein 1 (MCP-1) signaling via CCR2 blockade decreased the alcohol-induced expression of inflammatory cytokines (Lowe et al., 2020). In human experimental studies, MCP-1 drops acutely with alcohol intake then steadily increases, remaining elevated once blood alcohol reaches zero (Neupane et al., 2016). Alcohol bingeing causes systemic increases in MCP-1, as well as IL-6 and TNF α , in response to stimulated endotoxemia (Bala et al., 2014). Altogether, temporality is clearly seen, with alcohol administration leading to inflammation which predicates hangover symptoms.

Biological gradient (dose-response)

In a causal relationship, an increased exposure should lead to an increased risk of the diseased state. However, this is difficult to control clinically in alcohol trials, as between individuals, different quantities of alcohol cause hangovers of differing severity. Of particular interest, a study that used patients as their own controls showed that patients with hangover had increased production of IL-10, IL-12, and IFN- γ when exposed to phytohemagglutinin as compared to alcohol intake. The levels of IL-12 and IFN- γ demonstrated a dose-response relationship with multiple measures of hangover severity (Kim et al., 2003).

The dose-response relationship is also seen biochemically when considering the tissue-specific alterations in cytokines in animal models. Neuroinflammation, mediated by TLRs, markedly contributes to neurodegeneration and is seen across several disease states including chronic alcohol intake, ischaemic stroke, and multiple sclerosis (Okun et al., 2009). Neurodegeneration is worse with repeated alcohol exposure, leading to both structural and functional

changes in the brain (Crews, 2008). Experiments with TLR4 genetic and small interfering RNA (siRNA) knockdown demonstrate that abolishing TLR4 signaling protects against neuroinflammation measured by TNF- α , IL-1 β , and IL-6 and neurodegeneration in a mouse model of ethanol-induced brain damage including (Alfonso-Loeches et al., 2010; Alfonso-Loeches & Guerri, 2011). Cerebral IL-1 and TNF α are elevated in a dose-response manner in rats following ethanol intake (Dantzer, 2004; Doremus-Fitzwater et al., 2014; Tiwari et al., 2009; Valles et al., 2004). cAMP responsive element binding (CREB) family proteins promote neuron survival through protection from excitotoxicity and apoptosis (Bison & Crews, 2003; Zou & Crews, 2005). CREB binding is reduced progressively with increasing ethanol concentrations, while NF- κ B binding is increased, highlighting the neuroinflammatory and neurodegenerative mechanism of alcohol metabolism, through oxidative stress-induced apoptosis (Zou & Crews, 2005). While evidence from animal trials demonstrating neuroinflammation following alcohol intake constitutes dose-response, clearly the lack of corresponding behavioral changes that correlate with expected hangover-like symptoms makes this evidence circumstantially weak and highlights an obvious area for further work in the field.

Coherence

Coherence between clinical and laboratory experiments increases the likelihood of a causal relationship. Mice treated with ethanol show marked pro-inflammatory cytokine release TNF- α , MCP-1, IL-1, IL-6, and tissue-dependent changes in IL-10 levels (Alfonso-Loeches et al., 2010; Doremus-Fitzwater et al., 2014; Qin et al., 2008). MCP-1 is a chemotactic protein for macrophages, known to perpetuate neuroinflammation, that remains significantly elevated following significant alcohol intake (Lowe et al., 2020; Neupane et al., 2016). Further studies have demonstrated elevated IL-6, C-reactive protein (CRP), and TNF- α in-vivo and correlated these to hangover severity in patients with AUD as compared to healthy controls (Alho et al., 2004; Garcia-Calvo et al., 2020; van de Loo et al., 2020; Xu et al., 2020).

Experiment

Experimental manipulation has demonstrated the role of anti-inflammatory medicines in reducing hangover severity, and strengthen the evidence for inflammation as the cause of hangovers. Three placebo-controlled randomized trials of nonsteroidal anti-inflammatory drugs (NSAIDs) have demonstrated that cyclooxygenase inhibition, and therefore the production of pro-inflammatory mediators like prostaglandins and thromboxane A₂, significantly improved hangover symptoms (Hara et al., 2020; Kaivola et al., 1983; Verster, Dahl, et al., 2020). Prostaglandins are known to have an inhibitory effect on NF- κ B, a central pro-inflammatory mediator (Poligone & Baldwin, 2001). Treatment with cyclooxygenase inhibitors is also seen to potentiate anti-inflammatory IL-10 production by

macrophages, through PGE2 and TXB2 inhibition, which are significantly elevated following acute alcohol intake (Kaivola et al., 1983; Mandrekar et al., 1996). Hara et al. demonstrated that Loxoprofen was superior to a placebo for hangover headache but not general fatigue; general hangover severity was not measured (Hara et al., 2020). The two remaining studies reported improvements in other symptoms including nausea, vomiting, irritation, tremors, thirst, and dryness of mouth, though not all of the noted associations were statistically significant (Kaivola et al., 1983, Verster, Dahl, et al., 2020). Alcohol is known to augment TLR4 signaling in glial cells, triggering both inflammatory mediator production and cell death, and this induction of TLR4 also induces increased levels of COX-2 mechanism (Alfonso-Loeches et al., 2010). This mechanism demonstrates why NSAIDs (well-characterized COX inhibitors) are the only treatment which has provided hangover symptom relief in randomized controlled trials. Given that LPS is a major proposed mechanism of alcohol-mediated inflammation and TLR4 is the effector of this endotoxemia, the experiments offer a clear rationale for the observed treatment effect.

Analogy

Looking at other sources of systemic inflammation adds support to the inflammatory theory of hangover. Sickness behaviors are exhibited by both humans and animals in response to recognized pathogens and toxins such as LPS (Lasselin et al., 2021; Musaelyan et al., 2018). In humans, sickness behaviors are seen with a variety of pathogens but additionally, patients with chronic inflammatory conditions such as cardiovascular diseases, type 2 diabetes, and rheumatoid arthritis are also seen to exhibit elements of sickness behaviors (Dantzer et al., 2008). As extensively reviewed by Dantzer et al., treatments with pro-inflammatory mediators for tumors and hepatitis C, such as IL-2 and IFN α , resulted in flu-like symptoms, fatigue, anorexia, pain and sleep disorders, and depression (Dantzer et al., 2008). Peripherally produced cytokines act within the brain to generate sickness behaviors and therefore the notable peripheral production of cytokines following acute alcohol intake is a logical cause of the collection of sickness behaviors grouped together as hangover (Dantzer, 2004).

As such, there is a wealth of evidence consistent with alcohol-related inflammation as being a major contributory cause of hangover symptoms. Because inflammation is associated with tissue damage, this infers that hangovers may be associated with long-term harm to health; a discrete inflammatory event as part of the pathogenic process for fatty liver, alcoholic liver disease, dementia, or cardiovascular disease. This is a paradigm shift in the way the alcohol hangover is currently perceived, from a research, clinical, and popular culture perspective. Moreover, it demands that clinicians and scientists understand the pathological process by which alcohol causes inflammation, to innovate new treatments for patients with a spectrum of alcohol-related diseases that may act directly to reduce inflammation and thereby improve disease outcomes down the line.

ALCOHOL AS A PRO-INFLAMMATORY MEDIATOR

To understand how alcohol generates the inflammation that causes hangovers, it is necessary to understand the metabolism of alcohol, its effect on the gut microbiome, the additional substances (congeners) present within all alcohol, and the impact of alcohol on sleep and hydration.

Alcohol metabolism and oxidative stress

Oxidative stress describes the imbalance between the production of reactive oxygen species (ROS) and the ability to process/eliminate these highly reactive intermediates. Following consumption, alcohol is metabolized in the liver, through both oxidative and nonoxidative pathways. The major pathway of alcohol metabolism is oxidative, and within oxidative metabolism there are three sub-pathways present in various tissues to varying degrees. The major alcohol pathway utilizes alcohol dehydrogenase, present in the cell cytoplasm, and is chiefly expressed in hepatocytes of the liver. The microsomal ethanol oxidizing system (MEOS), utilizes the cytochrome P450 2E1 (CYP2E1) in microsomes of the endoplasmic reticulum and is inducible, being present in all cells to varying degrees, but especially hepatocytes. The catalase system makes a minor contribution to alcohol metabolism and is present in all bodily tissues (3). The activity of all these enzymes converts alcohol into acetaldehyde using oxygen, yielding hydrogen ions and reduced NAD/NADP (hereafter NADH/NADPH) (please see Figure 1). The acetaldehyde is subsequently converted into acetyl co-enzyme A (Acetyl-CoA) through combination with co-enzyme A and NAD by acetaldehyde dehydrogenase, producing NADH and hydrogen ions as byproducts. Acetyl-CoA can then be metabolized in peripheral tissues through Kreb's cycle to produce energy. The oxidative metabolism leaves the liver in a highly reduced state, with an excess of NADH/NADPH, in which it is susceptible to damage from ROS, radiation, and tobacco smoke among others (Wu & Cederbaum, 2003).

ROS are intermediate oxygen products that are usually formed in the body during aerobic respiration, a series of reactions that uses energy within the glucose molecule to reduce oxygen to water and produce ATP for cellular processes. During aerobic respiration, intermediate products are formed including superoxide, peroxide, and the hydroxyl radical (Wu & Cederbaum, 2003). During normal respiration only around 2–3% of the oxygen used is converted into ROS, which are so reactive that the majority react with each other, protons or oxygen to form water. As a normal byproduct of aerobic respiration, mechanisms exist to eliminate ROS through antioxidants like glutathione, vitamin E, and vitamin C, as well as supporting enzymes to catalyze these reactions including superoxide dismutases, catalase, and glutathione peroxidase (Wu & Cederbaum, 2003).

Alcohol metabolism is oxidative and therefore generates ROS. Additionally, ROS produced from aerobic respiration can react directly with alcohol to produce the toxic 1-hydroxyethyl

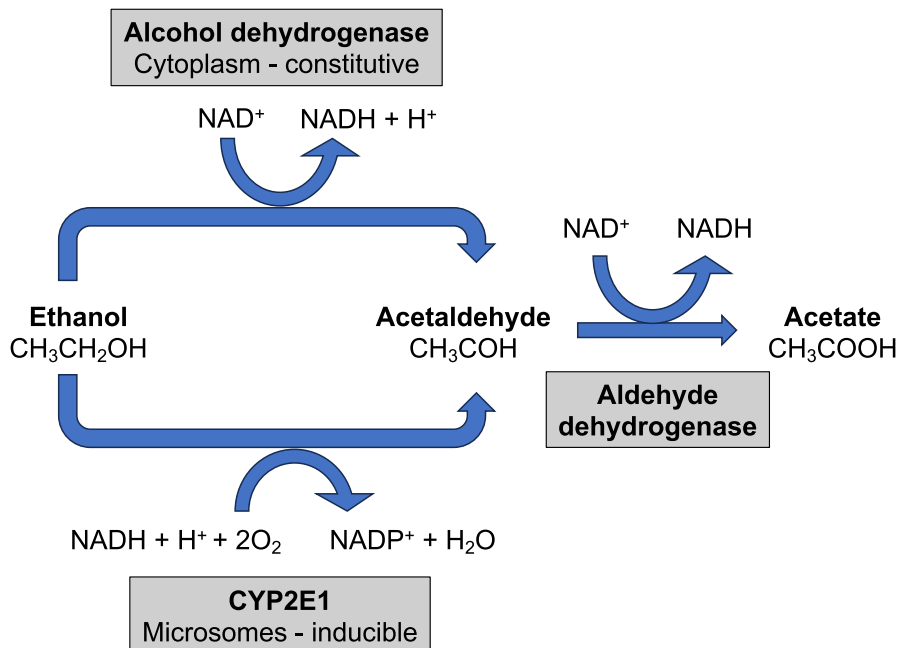


FIGURE 1 Two of the main alcohol metabolism pathways: the major pathway relies on the alcohol dehydrogenase enzyme present in the cytoplasm of specialized cells such as hepatocytes and the microsomal endothelial system (MEOS) which utilizes the inducible CYP2E1 enzyme on the surface of microsomes within any cell.

radical or change the phenotype of xanthine dehydrogenase to xanthine oxidase to contribute to further radical formation (Wu & Cederbaum, 2003). Alcohol induces hypoxia due to high metabolic demand for oxygen leading to tissue hypoxia and further radical formation (Wu & Cederbaum, 2003). As such, it is seen that alcohol causes significant oxidative stress following its consumption, leading to hypoxia, inflammation, cell death, and tissue damage.

Additional ROS formation is seen with increased alcohol exposure. While the capacity of alcohol dehydrogenase activity in the liver is largely fixed, CYP2E1 is inducible in the endoplasmic reticulum of any alcohol-exposed cells, but especially in the liver. Repeated alcohol intake leads to a relative increase in CYP2E1 activity relative to alcohol dehydrogenase, producing many times greater ROS, extra-hepatic acetaldehyde, and activating other drugs, including paracetamol, to their toxic metabolites (Lieber, 2004). The extra-hepatic induction of CYP2E1 in the gastrointestinal and respiratory tracts may explain the observation of increased risk of cancers of the mouth, pharynx and larynx, esophagus (squamous cell carcinoma), liver, colorectal, stomach, and breast cancer with alcohol intake (Rumgay et al., 2021).

Oxidative stress has been linked to hangover severity. Markers of oxidative stress, including 8-isoprostane and malondialdehyde, are elevated in hangovers and correlated with severity scores (van de Loo et al., 2020). The authors suggested that oxidative stress may be one of the principal causes for the additional elevations in inflammatory markers observed in this study, including IL-6, $\text{TNF}\alpha$, and CRP (van de Loo et al., 2020). The significance of oxidative stress, causing ROS production, hypoxia, lipid peroxidation, and cell death, is well described in neuronal injury and neuroinflammation (Haorah

et al., 2008). As previously described, neuroinflammation is thought to be essential to the pathogenesis of hangover and this therefore explains the significance of oxidative stress. However, oxidative stress is not just experienced in the brain, but anywhere alcohol metabolism takes place. CYP2E1 can be induced by high alcohol concentrations, as seen in the liver and the gut.

Gut microbiome perturbation

The gut microbiome is a community of 100 trillion microbial organisms that reside in the intestines (Guinane & Cotter, 2013). Gut microbes exist in a symbiotic relationship with the host human and may include bacteria, fungi, bacteriophages, protozoa, and viruses that can modulate a huge variety of health outcomes including cardiovascular disease, liver disease, systemic inflammation, and infections (Backhed et al., 2005; Bajaj, 2019).

Though the majority of alcohol is absorbed through the stomach and small intestine, colonic concentrations of ethanol become significant within hours of consuming relatively small doses of alcohol (0.8 mg/kg) (Halsted et al., 1973). Disruption of the gut microbiome may itself trigger systemic inflammation (Furman et al., 2019). Alcohol is a known potent factor in gut microbiome perturbation, as evidenced by disease flares in 70% of patients with inflammatory bowel disease when alcohol is consumed (Swanson et al., 2010). Mechanisms of gut microbiome disturbance following alcohol intake center on damage to gut epithelial integrity, alterations in microbial richness and diversity, and the favored growth of pathogenic organisms over probiotic species.

Intestinal barrier function

The intestinal epithelium forms the gut lining and contains multiple physical and immunological mechanisms to ensure a healthy symbiotic relationship between the host organism and the microbial organisms living therein (extensively reviewed in Vancamelbeke and Vermeire (2017)). Goblet cells are incorporated within the intestinal epithelium and produce a thick mucous layer that acts as a physical barrier, protecting epithelial cells from bacterial toxins. In the mucous, the secretion of soluble immunoglobulin type A (IgA) and antimicrobial peptides further protect against overwhelming infection. The concentration of these peptides is highest within the thick mucous close to the epithelium and their concentration decreases to the outer layer. Commensal microorganisms reside in the outer mucous layers and act as further protection against pathogenic bacteria that may seek to colonize the colon. Mucin gene deficiency using genetic knock out in mice leads to overwhelming gut infections (Hasnain et al., 2010).

The integrity of the intestinal epithelium is regulated by tight junctions, adherens junctions and desmosomes ensuring cell-cell adhesion is maintained in a tight cellular monolayer. However, to absorb the products of digestion for nutrition it is necessary that the intestinal epithelium is permeable, vascularised, and has a high surface area—factors at odds with preventing microbial invasion. As

such, the lamina propria contains a huge amount of gut-associated lymphoid tissue; granulocytes and lymphocytes that regulate the immune response to bacterial and food antigens, as well as toxins (Figure 2). Disruption of the intestinal barrier, in terms of gut mucous production or integrity of the epithelial barrier leads to increased permeability, exposure of microbial antigens such as LPS to immune cells, and dissemination of microbes via the portal circulation, leading to a systemic inflammatory response (Spadoni et al., 2015).

Although the liver is the primary organ of alcohol metabolism, both oxidative and nonoxidative alcohol metabolism occur in the (Forsyth et al., 2014). CYP2E1 is inducible in gut epithelial cells with acute alcohol exposure to metabolize alcohol. The activity of CYP2E1 has been correlated to increased intestinal permeability (Forsyth et al., 2013), and overall differences in the induction of the enzyme in the gut correlate with the development of alcoholic liver disease (Seitz & Wang, 2013). Oxidative metabolism yields oxidative stress through ROS production and accumulation, causing direct cellular damage and apoptosis of epithelial and goblet cells, compromising the integrity of the intestinal epithelium (Forsyth et al., 2014).

Damage to the gut epithelium also derives from acetaldehyde, nonoxidative alcohol metabolism. Acetaldehyde and alcohol can form chemical addition products with other molecules, termed adducts. As an extremely reactive aldehyde molecule, acetaldehyde can react with proteins, lipids, and DNA to form lipid, protein, or

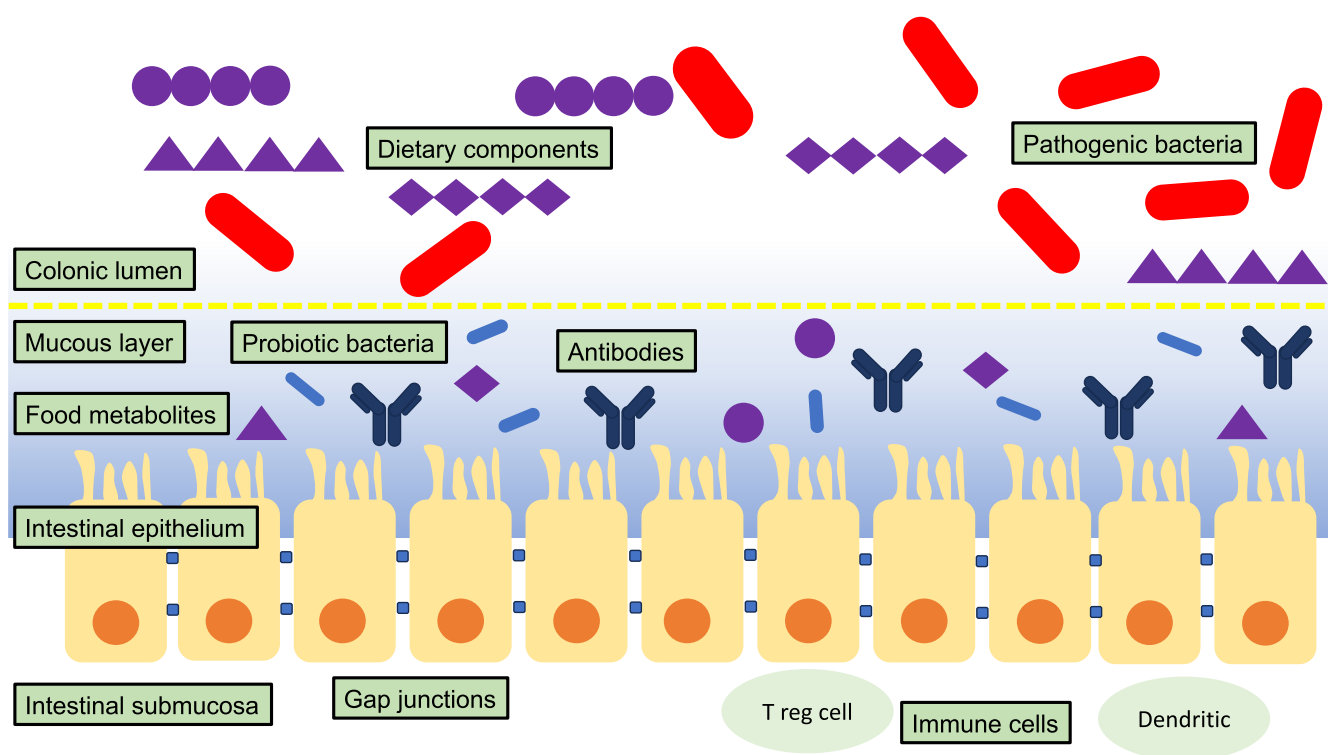


FIGURE 2 The normal intestinal lumen. Intestinal epithelial cells (pale yellow) are apposed by gap junction protein complexes (blue squares). The epithelial cells maintain and separate the luminal contents from the immune cells residing within the submucosa. Goblet cells in the epithelial layer produce mucous (blue gradient) which is at the highest density close to the epithelium and lowest further away. Dietary components (purple triangles, circles, and diamonds) are absorbed from the intestinal lumen and/or further metabolized by intestinal bacteria, some of which have pathogenic potential (red), and others of which are probiotic/ commensal (blue). Antibodies to recognize pathogenic bacterial antigens (dark blue) are secreted into the intestinal lumen.

DNA adducts (Wu & Cederbaum, 2003). Acetaldehyde is therefore classed as pro-inflammatory, pro-fibrotic, mutagenic, carcinogenic, and mediator of oxidative stress (extensively reviewed previously (Setshedi et al., 2010)). Similarly, in nonoxidative alcohol metabolism, alcohol is conjugated with endogenous metabolites such as fatty acids, phosphatidyl choline, glucuronide, and sulfate molecules to form adduct compounds (Hyun et al., 2021). The impact of these adducts varies; conjugation of alcohol/acetaldehyde with fats leads to lipid peroxidation generating further ROS and inflammation (Wu & Cederbaum, 2003). Protein adducts reduce protein efficacy, for example, alcohol metabolism enzymes and antioxidant enzymes (Wu & Cederbaum, 2003), and interfere with adherent and tight junctional integrity through its effects on E-cadherin and β -catenin phosphorylation (Seth et al., 2004; Sheth et al., 2007). Acetaldehyde can form protein adducts with the CYP2E1 enzyme, thereby impairing the functional capacity for acetaldehyde removal (Niemela, 1999), as well as binding to glutathione to inhibit free radical scavenging to exacerbate oxidative stress and lipid peroxidation, considered to be the primary mechanisms of alcohol-induced liver injury and disease (Setshedi et al., 2010). DNA adducts cause severe DNA damage leading to cellular apoptosis of intestinal epithelial cells and compromising the integrity of the intestinal barrier (Figure 3).

Alcohol additionally exerts epigenetic effects that impact the integrity of the gut lining. Alcohol interferes with the cytoskeleton of intestinal epithelial cells, through gene expression and phosphorylation of tight junctions (TJs) (MAPK isoforms p38, ERK, and JNK) (Elamin et al., 2014). Moreover, alcohol-induced expression of micro

RNAs in the chronic alcohol-feeding model augments gut permeability, endotoxemia, and gut-derived expression of TNF α and NF- κ B (Lippai et al., 2014). Hence, factors in addition to oxidative alcohol metabolism and ROS production also contribute to the loss of gut barrier integrity that renders the body susceptible to endotoxemia and inflammation.

The result of decreased gut epithelial integrity is leakage of bacterial antigens, such as LPS in the cell wall of Gram-negative bacteria (endotoxemia), to the immune cells in the lamina propria. LPS, among other microbial antigens and toxins, stimulates the inflammatory cascade through the transcription factor NF- κ B and overproduction of nitric oxide, resulting in the formation of reactive nitrogen species, causing further oxidative stress, directly interfering with tubulin in the epithelial cell cytoskeleton and perpetuating barrier dysfunction and leakiness (Banan et al., 2000, 2007; Vallance et al., 2004). Studies in rats demonstrate that initial gut leakiness and endotoxemia precede steatohepatitis and alcoholic liver disease in rats chronically fed alcohol over 10 weeks (Keshavarzian et al., 2009). In mice, a single dose of ethanol by oral gavage is sufficient to produce endotoxemia (Petrasek et al., 2012). Multiple human studies have also shown that a single instance of acute alcohol binge can yield increased intestinal permeability through endotoxemia, as well as 16S rDNA, a marker of bacterial translocation from the gut (Bala et al., 2014; Keshavarzian et al., 1994). Stimulation with LPS in vivo in these experiments yielded increases in TNF α , IL-6, and MCP-1, with serum endotoxin remaining elevated for hours after acute alcohol intake (Bala et al., 2014). Increased TNF α leads to phosphorylation

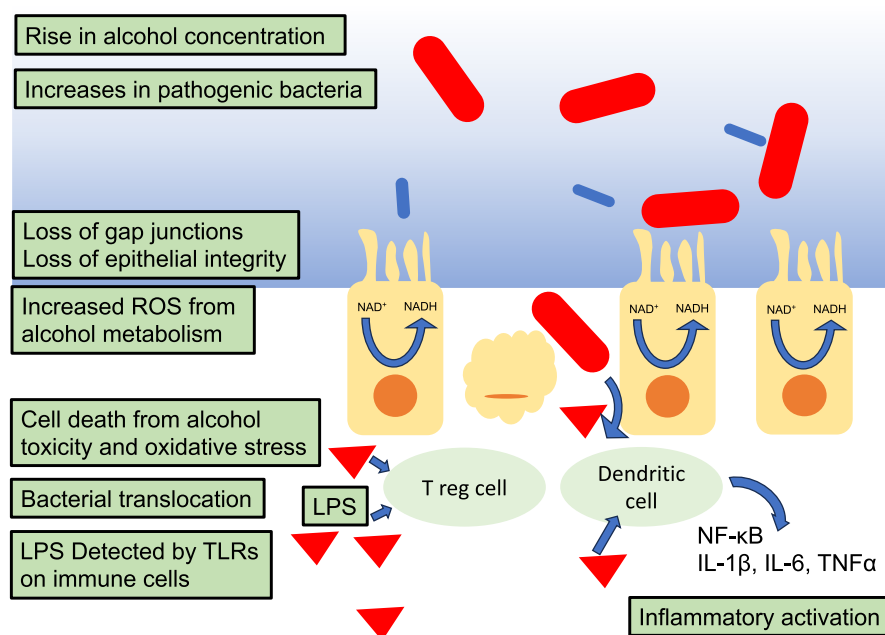


FIGURE 3 Acute alcohol intake causes a rise in luminal alcohol concentration, favoring the growth of potentially pathogenic bacteria (red) which increase in number. Alcohol metabolism exerts significant oxidative stress, leaving epithelial cells highly reduced (NAD⁺ → NADH) and susceptible to further damage. Oxidative stress is worsened by congeners and sleep deprivation. The free radical generation leads to DNA, protein, and lipid adducts that can lead to local tissue damage in the intestinal epithelium. Bacteria may translocate across the damaged intestinal epithelium and the presence of the lipopolysaccharide (LPS) antigen (red triangles) within the cell wall of Gram-negative bacteria activates toll-like receptors (TLRs) antigen-presenting cells (green ovals) which produce pro-inflammatory cytokines.

of the Forkhead Box Other protein 4, which regulates intestinal permeability through the expression of tight junctions, another mechanism perpetuating endotoxemia, hepatic inflammation, and injury in a mouse model of alcoholic liver disease.

Conversely, improving gut barrier integrity to reduce endotoxemia has been shown to benefit inflammatory markers, as well as subsequent alcohol seeking behavior and health outcomes. A randomized controlled trial of fecal microbiota transplant (FMT) in patients with cirrhosis reduced endotoxemia, improved microbial diversity, reduced inflammation as measured by IL-6, reduced alcohol craving and consumption, and reduced adverse events compared to placebo (Bajaj et al., 2021). Given that acute alcohol bingeing stimulates endotoxemia and subsequent inflammation (Bala et al., 2014), the cause of hangover, targeting gut permeability is an important future therapeutic avenue that justifies future research to limit alcohol-related harm. Studies of FMT and probiotics indicate that, as well as epithelial integrity, specific microbial species may be critical in mediating/limiting inflammation secondary to alcohol (Gu et al., 2019; Kirpich et al., 2008; Mishra et al., 2023; Saab et al., 2016; Sarin et al., 2019).

The effect of alcohol on microbial species

There are at least 1000 different bacterial species that form part of the human microbiome (Guinane & Cotter, 2013). Indeed, microbial species richness, as well as other markers of microbiome health like stool transit times, stool consistency, enterotypes, and community composition have been shown to indicate overall gut health and susceptibility to disease (Vandeputte et al., 2016). Different microbes are adapted to different growth conditions and alcohol promotes the growth of Gram-negative bacteria that contain LPS within the cell wall (Purohit et al., 2008). Some bacteria in the gut also ferment ethanol to acetaldehyde, exacerbating inflammation in individuals with enterotypes containing increased numbers of these bacteria, through mechanisms previously addressed. In rats, microbial diversity indices in the colon were markedly reduced with alcohol intake by oral gavage over a 10-week period as compared to a dextrose control (Mutlu et al., 2009). In a human study, people who were currently (or who had previously) misused alcohol had decreased diversity and connectivity of the microbial network, and signs of gut microbiome disturbance—known markers of poor gut health (Vandeputte et al., 2016).

When fed an alcoholic diet versus control for a period of 6 weeks, mice had fewer *Bacteroidetes* and *Firmicutes*, with increases in *Proteobacteria* and *Actinobacteria* as well as *Alcaligenes* and *Corynebacterium* (Bull-Otterson et al., 2013). These microbiome alterations led to significant increases in plasma endotoxin, fecal pH, hepatic inflammation, and injury (Bull-Otterson et al., 2013). The increased endotoxemia and inflammation may have been related to the significant increases in *Proteobacteriae*, species of which include well-known pathogenic organisms: *Escherichia*, *Salmonella*, *Vibrio*, and *Helicobacter*. Patients with

AUD also have reduced levels of *Bacteroidetes* and increased levels of Gram-negative *Proteobacteriae*, in addition to increases in other Gram-negative anaerobes, coliforms, endospore-forming rods, *Enterobacteriaceae* among others (Bode et al., 1984; Chen et al., 2011; Mutlu et al., 2012). Recent evidence in the Lancet has even demonstrated that microbiome changes act as a biomarker of future alcohol problems and AUD (Carbia et al., 2023), suggesting that microbes may be able to modulate behavior via the gut-brain axis. This hypothesis is supported by evidence from randomized controlled trials and yields another interesting future avenue for treatments to prevent alcohol-related inflammation and health impact (Bajaj et al., 2021).

Interventions containing probiotic bacteria, that is, bacteria beneficial for host health, have shown evidence of restoration of gut microbiome homeostasis and reduced systemic inflammation. In animals, supplementation with *Lactobacillus rhamnosus* GG resulted in improved intestinal permeability, reduced endotoxemia, reduced alcohol-related inflammation, and hepatic injury (Bull-Otterson et al., 2013; Forsyth et al., 2009; Mutlu et al., 2009; Wang et al., 2011, 2013). Similar findings have been demonstrated with other probiotic bacterial supplements containing *Lactobacilli* and *Bifidobacteriae* (Chang et al., 2013). Dietary supplementation with oats, which contain antioxidants and prebiotic fiber to bolster probiotic bacterial populations, has also been seen to improve intestinal barrier integrity, ameliorating alcohol-induced oxidative stress and endotoxemia in a model of chronic alcohol intake (Mutlu et al., 2009; Tang et al., 2009). The authors suggest that oats could be a novel intervention to prevent alcohol-related oxidative stress, but at a dose of 10g/kg/day, that would equate to 10 bowls of porridge per 70kg human, which could be considered excessive by many. In cirrhotic patients, 30 days of symbiotic treatment ameliorated gut microbiome perturbation, with a reduction in pathogenic *Escherichia coli* and *Staphylococcal* species, increases in *Lactobacilli* and reductions in ammonia, endotoxemia, as well as improvement in encephalopathy parameters (Liu et al., 2004). Improvements in encephalopathy have been additionally demonstrated previously with *Lactobacillus acidophilus* supplementation (Macbeth et al., 1965). Five days of supplementation with *Bifidobacterium bifidum* and *Lactobacillus plantarum* 8PA3 reduced liver enzymes and ameliorated gut microbiome disturbance, while also improving biochemical markers of alcoholic hepatitis in a subset of patients with the condition (Kirpich et al., 2008). One trial used a probiotic supplement containing *Lactobacilli* and *Bifidobacteriae* but did not find any impact on hangover symptoms nor severity, however no inflammatory measures such as systemic cytokine levels or endotoxemia were measured in the trial and relatively conservative alcohol doses of 0.8g/kg were administered, the equivalent of two pints of 4.8% alcohol by volume beer for a 70kg male (Jung et al., 2021).

The evidence presented demonstrates the multitude of complex mechanisms by which perturbation of the gut microbiome contributes to systemic inflammation, through endotoxemia and gut permeability, leading to steatohepatitis and alcoholic liver disease. The great concern, therefore, is that the inflammation, from gut

microbiome disturbance and oxidative stress, is the common pathological cause of all alcohol-related harm and therefore hangovers may represent a previously unrecognized health burden.

Sleep disturbance

Drowsiness is the most common and severe component of an alcohol hangover (Penning et al., 2012; Verster, van de Loo, et al., 2020). Sleep disruption perpetuates the pro-inflammatory effects of oxidative stress and gut microbiome disturbance. One of the critical functions of sleep is to act as an antioxidant and eliminate ROS produced during wakefulness; sleep disturbance, through both circadian misalignment and acute sleep loss, significantly increases oxidative stress (Hill et al., 2018; Teixeira et al., 2019). Circadian disruption impacts circadian rhythm *CLOCK* gene expression in gut epithelial cells, exacerbating intestinal permeability and endotoxemia (Summa et al., 2013). In mice, this promoted hepatic inflammation and the advancement of liver disease (Summa et al., 2013). In humans, circadian misalignment has been shown to cause insulin resistance and inflammation, independent of sleep loss (Leproult et al., 2014).

Fascinatingly, a multi-organ analysis in animals showed that ROS production and oxidative stress during acute sleep deprivation occur in the gut, rather than the brain. Animals with acute sleep deprivation showed premature death, which was rescued by antioxidant administration and overexpression of antioxidant enzymes in the gut rather than in the brain (Vaccaro et al., 2020). Acute sleep loss as well as circadian misalignment can also cause pro-inflammatory activation, with elevated IL-1 β , IL-6, and TNF α leading to increased risk of type 2 diabetes and cardiovascular disease (Mullington et al., 2010; Tobaldini et al., 2019). Alcohol metabolism exerts significant oxidative stress in the gut as previously described, hence the additional impact of sleep deprivation, a frequently-reported neurological effect of alcohol (Colrain et al., 2014; Penning et al., 2012; Spanagel et al., 2005), drives ROS accumulation, alterations in the gut microbiome, intestinal permeability, and inflammation. It is, therefore, perhaps unsurprising to see that nightly awakenings, sleep quality, and total sleep time all correlate with hangover severity (Ayre et al., 2021; van Schrojenstein Lantman et al., 2017).

Congeners

Congeners are products other than ethanol that are produced during the fermentation process and may include a variety of compounds including other alcohols such as methanol, acetaldehyde, acetone, esters, and polyphenolic compounds (tannins) (Nathan et al., 1970). Typically, darker drinks such as whisky or red wine contain more congeners (Nathan et al., 1970), which exacerbate both oxidative stress and neuroinflammation.

Two studies have demonstrated a link between hangover severity and congeners; one randomized controlled trial of 95 patients comparing high-congener Bourbon whiskey, lower-congener whiskey, and

placebo (diet cola), demonstrated that patients in the high-congener drink group had more severe hangovers by symptom severity, although outcomes in cognitive tests matched the low-congener group (Rohsenow et al., 2010). In another study of 18 men, it was demonstrated that blood methanol concentration was directly correlated to hangover subjective scale score, even after controlling for blood ethanol concentration (Woo et al., 2005). Urinary methanol concentrations have been linked specifically to headache, nausea, and vertigo in one nonrandomized study of 20 individuals (Bendtsen et al., 1998). Methanol is metabolized more slowly by alcohol dehydrogenase, competing with alcohol directly, and is metabolized to toxic byproducts formaldehyde and formic acid (Barceloux et al., 2002). These products inhibit cytochrome oxidases for respiration and oxidative metabolism of alcohol, increase NADH:NAD ratio, and worsen oxidative stress. Moreover, profound acidemia from the formic acid and leukotriene-driven neuroinflammation leads to CNS toxicity and death (Barceloux et al., 2002; Zakharov et al., 2017). The severity of inflammation correlated to long-term morbidity and mortality in patients with acute methanol poisoning (Zakharov et al., 2017). Fortunately, concentrations of highly toxic congeners like methanol are generally low in alcoholic drinks but nonetheless are seen to be pro-inflammatory and correlated with the severity of hangover symptoms.

CONCLUSION

Alcohol is a widely abused pro-inflammatory drug and excessive consumption leads to high degrees of oxidative stress and ROS production. In this review, we have highlighted the wealth of evidence demonstrating that alcohol hangovers are pro-inflammatory, causing both neuroinflammation and systemic inflammation. Central to this mechanism is oxidative stress, already correlated to hangover severity and gut microbiome perturbation. The production of ROS, toxicity of acetaldehyde, and direct effects of alcohol have a direct impact on the gut epithelium, promoting cellular damage and permeability, as well as altering microbiome composition. Endotoxemia and bacterial translocation ignite the inflammatory cascade through TLRs and the presence of these receptors in the brain is well-documented to perpetuate neuroinflammation and sickness behaviors. The co-existence of congeners and sleep deprivation serves to exacerbate inflammation and oxidative stress, demonstrating why these factors have been correlated with hangover severity.

An effective hangover remedy could be theorized to reduce oxidative stress and inflammation by promoting the integrity of the gut epithelium, favoring probiotic bacterial populations, and reducing oxidative stress in the gut, which are all central to the mechanism of inflammation.

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CONFLICT OF INTEREST STATEMENT

None.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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