Vascular Health and Risk Management

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REVIEW

Mechanisms of Acetaldehyde-Induced Organ Injury via Impairment of Vascular Endothelial Cells

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Abstract: Acetaldehyde, a metabolite of alcohol, accumulates in the body through excessive alcohol consumption. This accumulation triggers a range of vascular endothelial cell damage, including changes of signaling pathways, and ultimately results in organ and tissue damage. In this review, we highlight the role of acetaldehyde in vascular endothelial cell damage, including DNA damage, oxidative stress, and changes in signaling pathways. Particularly concerning the role of the NEIL3 pathway in DNA repair, the NEIL3 pathway is prioritized over the Fanconi anemia pathway, which may result in genomic rearrangements and the cleavage of the crosslink. Insulin, and estrogen receptors α damage induced by acetaldehyde. Notably, we describe the mechanisms by which long-term acetaldehyde exposure causes DNA damage, oxidative stress, imbalance in Ca^{2+} homeostasis, inflammatory response, and signaling pathway changes. We provide novel insights into the intervention of acetaldehyde exposure-mediated vascular endothelial cell disorders.

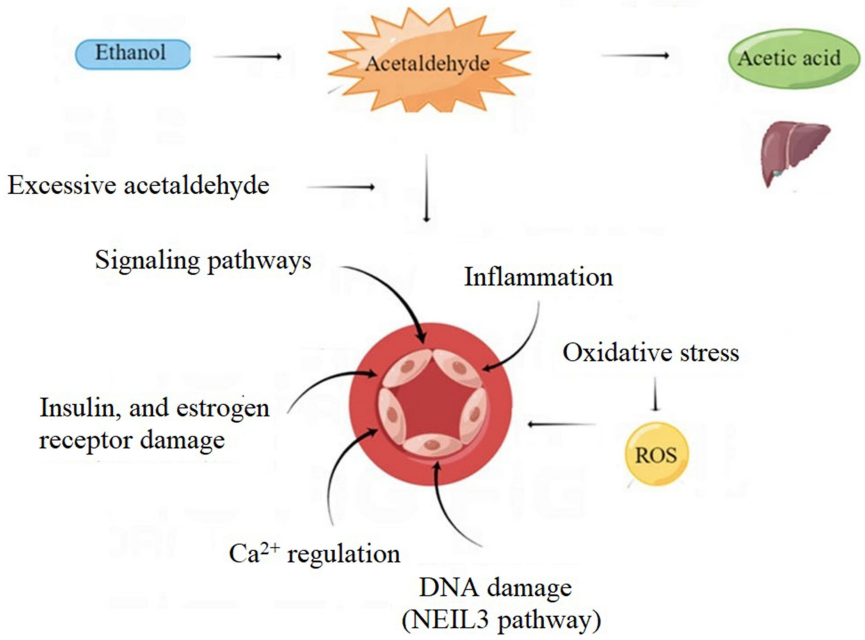
Keywords: acetaldehyde, laboratory targets, toxicity, vascular injury

Introduction

Excessive alcohol consumption can lead to severe organ damage, and alcohol abuse has become a significant public health issue.[1–3] Alcohol-induced cardiomyopathy, atherosclerosis, hypertension, stroke, and other cardiovascular complications arise from elevated blood pressure and the promotion of vascular endothelial dysfunction, oxidative stress, and inflammation—key factors in the development of cardiovascular disease.[4] This is particularly true for individuals with alcohol addiction. The second leading cause among those deaths was digestive diseases, of which 95% were due to cirrhosis.[5] Approximately 10% of hypertension is caused by alcohol consumption.[6,7] Patients who abuse alcohol are at higher risk of complications after coronary artery bypass grafting, which include higher cardiogenic shock (8.31% vs 7.43%, $p = 0.03$), mechanical ventilation (11.51% vs 7.96%, $p < 0.01$), hemorrhage/hematoma (57.49% vs 54.75%, $p < 0.01$), superficial (0.99% vs 0.61%, $p < 0.01$) and deep wound complications (0.37% vs 0.18%, $p = 0.02$), and reopen surgery for bleeding control (0.92% vs 0.63%, $p = 0.03$).[8] A total of 10% of all cancers in men and 3% of all cancers in women can be attributed to alcohol consumption across Europe.[7] Those who heavily drank alcohol (ie, more than 14 drinks/week) were at a 1.2-fold higher risk of developing dementia[9–11] or disease in other organ tissues.[12,13] Approximately 90–98% of consumed ethanol is metabolized in the liver to acetaldehyde (AA) via the oxidative pathway.[14] As the first metabolite of ethanol oxidation, AA is internationally recognized as a carcinogen and has a negative impact on human health.[15,16] AA is a highly reactive low molecular weight organic compound that is colorless, flammable, and volatile, with an irritating odor.[17] AA is catalyzed by AA dehydrogenase to produce acetic

Received: 14 August 2025
Accepted: 30 November 2025
Published: 8 December 2025

Graphical Abstract



acid, which is oxidized and decomposed into carbon dioxide and water. However, most acetic acid evades liver metabolism and is distributed to various tissues. Unoxidized AA accumulates in the body, causing damage that requires repair through multiple DNA repair pathways, oxidative stress, and other detrimental mechanisms (Figure 1).[18–22]

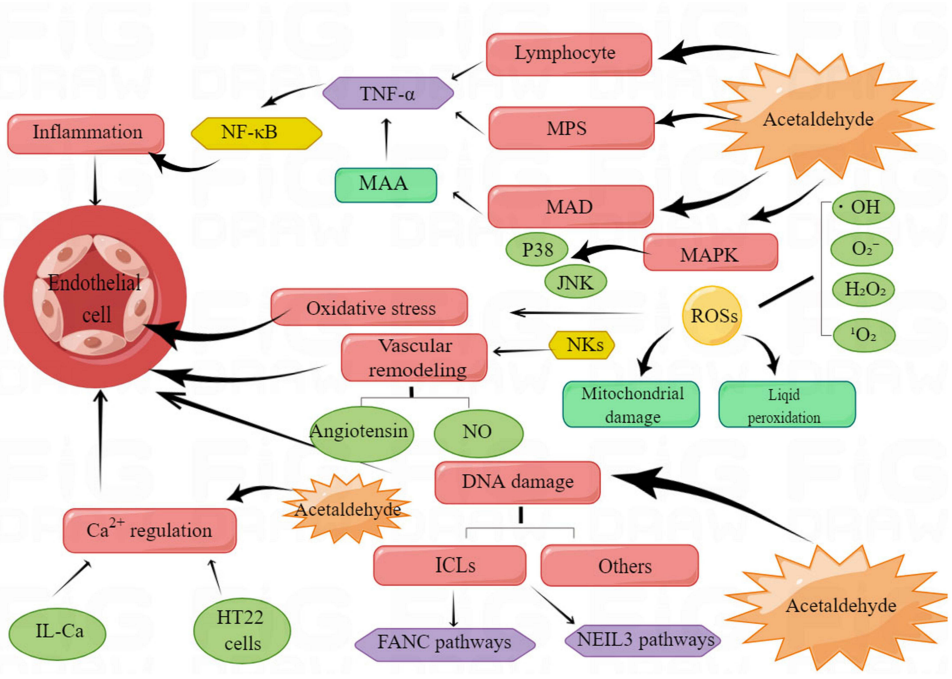


Figure 1 Metabolic pathways of ethanol and its metabolite acetaldehyde (AA) in the human body. Excess AA accumulates, causing DNA damage, oxidative stress, and other mechanisms such as damage to insulin and estrogen receptor α.
Abbreviations: AA, acetaldehyde; NEIL3, DNA Endonuclease VIII-like 3.

Exposure to ethanol and its metabolite AA adversely induces changes in vascular endothelial cells (VECs).[23] VECs act as a simple passive barrier between circulating blood and surrounding tissues. They have multiple functions, such as modulating vascular homeostasis and cellular function, mediating inflammatory and immune responses, and preventing thrombosis. VEC dysfunction shows strong effects on cardiovascular diseases,[24] owing to their active role in ethanol metabolism. VECs are directly affected by ethanol and AA, which leads to endothelial monolayer integrity disruption.[25] Numerous studies have shown that alcohol and its by-product, AA, contribute to DNA damage, primarily by forming DNA interstrand crosslinks (ICLs), a type of DNA adduct. ICLs induce severe DNA damage by disrupting transcription and replication,[26] negatively affecting endothelial cell structure and function, and are typically repaired through the FANC pathway.[27] Recently, some studies have identified a FANC-independent ICL repair pathway involving DNA endonuclease VIII-like 3 (NEIL3) glycosylase, which facilitates the removal of crosslinks and may represent a potential target for future therapeutic strategies.[28–31] However, the specific contributions of alcohol and AA-induced DNA damage to repair mechanisms—whether through the FANC pathway, the NEIL3 glycosylase pathway, or a cooperative interaction between the two—remain unclear. Many studies have showed methylglyoxal,[32] acrolein,[33] and alcohol[34] damage insulin receptors, but AA has not been implicated in this effect.

To elucidate the mechanisms underlying AA-induced vascular endothelial cell dysfunction, the manuscript first outlines the background of how AA damages vascular endothelial cells and its clinical manifestations. The focus then shifts to the mechanisms by which AA induces endothelial cell damage, including DNA damage, oxidative stress, vascular inflammation, Ca^{2}+ imbalance, and vascular remodeling. Next, the manuscript examines the impact of light to moderate alcohol consumption on human health and, based on current literature, discusses the effects of varying alcohol doses. Finally, the manuscript concludes with a summary of the key findings.

Clinical Manifestations of AA Exposure

The impact of AA exposure on the human body can be viewed from two perspectives. On one hand, there are positive clinical effects, such as AA potentially being a component of the complex postprandial hyperemia reflex. This reflex induces vasodilation of the mesenteric vasculature and relaxes the superior mesenteric artery (SMA) through an endothelium- and nitric oxide (NO)-dependent mechanism;[35] On the other hand is the negative clinical manifestations. Acute exposure to AA causes body dysfunction resulting in swelling of the eyes, redness, and increased sputum, consequently triggering allergic reactions and headaches. In addition, AA causes damage to skeletal muscles;[36,37] Ethanol's metabolite, AA, can cause DNA damage, inhibit DNA synthesis and repair, and disrupt DNA methylation, leading to cancers of the upper aerodigestive tract, liver, colorectum, and breast;[38] Inhalation of high AA concentrations can result in asphyxiation, respiratory paralysis, and increased incidence of pneumonia in individuals with alcohol use disorders;[39,40] AA is teratogenic,[41] and exposure during pregnancy may lead to fetal alcohol syndrome;[42] AA exposure by acute intravenous alcohol injection adversely affects attention and working memory, whereas moderate alcohol concentrations negligibly affect speed and accuracy;[43] AA contributes to the pathogenesis of alcoholic liver disease[44] and induces toxicity in the endocrine pancreas.[44]

Additional toxic effects on the vascular endothelium have been reported. First, AA stimulates a sympathetic-like effect that triggers the release of endogenous catecholamines, contributing to alcoholic cardiomyopathy;[10] Second, AA induces oxidative stress (OS) in vivo, leading to vascular endothelial damage;[25] Third, AA promotes peripheral vasodilation and central vasoconstriction (to a greater extent than ethanol);[45] Finally, AA participates in an extremely potent lipid peroxidation reaction, which is highly toxic and damages the vascular endothelium, contributing to atherosclerosis.[46] Collectively, these findings suggest that AA has a more substantial toxic impact than alcohol itself.

Mechanism of Endothelial Cell Damage by AA

AA is a mono-formaldehyde that affects endothelial cell function through various pathological processes. The major process affected by AA are induction of gene mutations, formation of DNA adducts, promotion of OS, disruption of Ca^{2+} homeostasis, induction of inflammatory responses, and alteration of vascular remodeling (Figure 2).

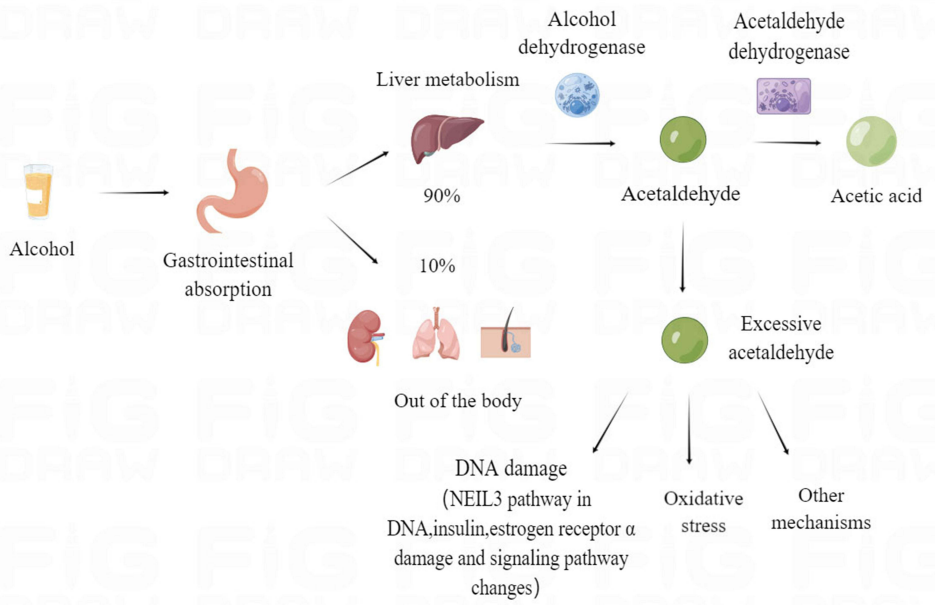


Figure 2 Various injuries induced by AA in vascular endothelial cells, including DNA damage, oxidative stress, Ca^{2+} homeostasis imbalance, inflammatory responses, alterations in signaling pathways, and damage to vascular endothelial growth factor, insulin, and estrogen receptor α.

Abbreviations: AA, acetaldehyde; HT22, Mouse Hippocampal Neurons; IL, interleukin; ICLs, DNA interstrand crosslinks; MAPK, mitogen-activated protein kinase; MPS, mononuclear phagocyte system; MAD, malondialdehyde; MAA, MAD-AA adducts; NEIL3, DNA Endonuclease VIII-like 3; JNK, Jun N-terminal kinase; NKs, natural killer cells; NO, Nitric Oxide; P38, p38 kinase; TNF, tumor necrosis factor; NF-Kb, nuclear factor kappa B.

DNA Damage

AA elicits VEC damage by inducing DNA mutations and forming adducts with DNA. AA causes DNA deletion mutations that cause structural and functional abnormalities in tissues, including VECs, leading to metabolic disorders and cancer. AA reportedly induces deletions of four bases or longer, which may be a feature of the monogenic aldehyde mutation pattern.[47,48] In addition, AA can form adducts with nucleotides, proteins, phospholipids, epinephrine, and dopamine,[49,50] which are the main mechanisms responsible for endothelial cell damage.[18] Therefore, AA-induced DNA damage and repair is important in cell damage and carcinogenesis.[51,52]

DNA adducts have been identified in the human body, and in vitro analysis of multiple induced decellularized DNA exocyclic adducts revealed adducts in white cells, with a high number of changes at the level of all adducts.[53] AA reacts with guanine to form N2-proguanine, which interacts with the N2-amine of guanine to form ICLs, a form of DNA adducts. ICLs induce severe DNA damage by damage transcription and replication; this damage negatively affects endothelial cell structure and function.[26]

The primary repair mechanism of aldehyde-induced ICL damage is the Fanconi anemia (FANC) pathway. Studies investigating the ICL model have identified a FANC-independent ICL repair pathway, which may serve as a potential target for future drug therapies.[27] Another pathway is the NEIL3 glycosylase pathway, which facilitates the removal of the crosslink. The tumor necrosis factor receptor-associated factor (TRAF)-interacting protein regulates the choice between the FANC pathway and the simpler NEIL3 pathway.[28] NEIL3 not only initiates replication-dependent ICL repair as an alternative to the FANC pathway.[30] But also participates in maintaining replication fork stability and telomere integrity. Furthermore, NEIL3 is strongly associated with the progression of cancers, as well as cardiovascular and neurological diseases.[31] In endometrial cancer, high NEIL3 expression in tumors correlates with worse overall survival outcomes in patients.[29] Additionally, tumors with high NEIL3 expression are linked to a higher number of mutations and chromosomal instability. As such, NEIL3 may serve as a potential prognostic biomarker to stratify endometrial cancer patients and as a target to enhance immunotherapy responses in this context.[29–31] In AA-induced DNA damage, the primary mechanism involved is the generation of DNA double-strand breaks (DSBs); A previous

study demonstrated that treatment with epicatechin mitigated AA-induced DNA damage and protected vascular endothelial cells by inhibiting double-strand break (DSB) formation through scavenging of AA, without affecting repair kinetics.[54]

Oxidative Stress

Induction of Reactive Oxygen Species (ROS) Production

OS, caused by an imbalance between ROS and antioxidant factors, is a threat to the genome and enhances the toxic effects of pathogenic factors. Excess ethanol consumption promotes OS.[48,55–57] In addition, unmetabolized AA accumulates in the body and prompts an increase in the production of ROS, which results in a dynamic imbalance between ROS production and removal, causing OS.[58] Excess ethanol consumption can damage Akt phosphorylation, which induces insulin dysfunction,[21] and increase the AA concentration, which stimulates cardiovascular dysfunction by ROS and nitric oxide (NO) molecules[59] through estrogen receptor α (ERα) and ERβ.[60]

Oxidized-low-density lipoprotein, formed during OS conditions, induces inflammatory products to promote monocyte adherence and migration to the arterial intima. It can also induce macrophages to express scavenger receptors and increase the uptake of lipoproteins to form foam cells, ultimately leading to VEC damage and atherosclerotic plaque formation.[61] AA-induced cardiomyocytes produce large amounts of oxygen radicals, which drives OS in vivo, and high ROS activates the intracellular apoptosis-inducing pathway. In vitro studies have shown that AA enhances the production of ROS and reactive nitrogen species (RNS), decreases the activity of related metabolic and binding enzymes, disrupts the antioxidant defense system, inhibits the cellular total antioxidant capacity, alters cell morphology, and causes irreversible damage to cells.[62]

AA promotes OS by activating the mitogen-activated protein kinase (MAPK) pathways.[55,63,64] MAPK plays a crucial role in relieving pressure such as OS, apoptosis, and inflammatory responses.

In summary, the accumulation of AA causes an increase in ROS production and MAPK pathway activation, which promotes OS and results in VEC dysfunction.

Impairment of Mitochondria (Mit) Function

Mit are involved in many biological processes, including adenosine triphosphate (ATP) production. AA induces Mit remodeling: it induces Mit swelling, cristae and membrane disruption, and Mit deletion.[65] These alterations affect Mit function and result in intracellular ATP depletion, which induces ROS overproduction. ROS accumulation leads to Mit damage, including Mit dysfunction and structural damage. Mit damage further affects AA oxidation,[66] which causes cells to enter a cycle of continuous AA accumulation and Mit dysfunction that affects cellular energy production throughout the body and in VECs. The altered Mit function causes irreversible damage to the VECs.[33] For example, Blanca Eugenia et al[34] reported that AA might disrupt endothelial cell redox regulation. The viability of AA-treated cells is severe compared with untreated cells. In addition, AA induces hyperphosphorylation of dynamin-related protein 1 (Drp1), which promotes excessive Mit division and leads to irreversible endothelial cell damage and Mit autophagy. Pretreatment of SH-SY5Y cells with the autophagy inhibitor 3-MA inhibited the toxic effect of AA. These results indicated that AA induces autophagy via ROS overproduction.[62] Studies on human small intestinal cells revealed that AA significantly increases intracellular ROS production, decreases Mit function, and could induce apoptosis.[67] Overall, the accumulating evidence suggests that AA induces structural and functional Mit damage via ROS overproduction and Mit hyperdivision; these changes promote autophagy and lead to VEC destruction.

Induced Vascular Inflammatory Response

The vascular inflammatory response is closely related to endothelial cell injury. When VECs undergo AA-induced injury, lymphocytes, monocytes, and macrophages[68] are stimulated to produce large amounts of inflammatory factors, including interleukin 6 (IL-6) and TNF-α. These inflammatory factors influence various vascular cell functions and can cause damage to VECs. TNF-α can regulate endothelial cell remodeling and injury via the nuclear factor kappa B (NF-κB) signaling pathway. TNF-α binds to immunologically relevant receptors and activates the kinase inhibitor of kappa

B (IkB), which phosphorylates IkBa and stimulates ubiquitination. NF-κB (nuclear factor kappa B, NF-κB) activates and exposes the nuclear localization domain, initiates target gene expression, and generates an inflammatory response.[69]

AA and malondialdehyde (MAD) are highly reactive aldehydes that bind to proteins to produce an antigenically unique protein adduct called MAD-AA adducts (MAA). MDA and AA react together with endogenous proteins to generate an antigenically distinct protein adduct, termed the MAA adduct. Intrahepatic MAA adduct formation may be the result of the metabolism of ingested ethanol, which generates AA in combination with hepatic lipid peroxidation, which produces MAA.[70] MAA adduct proteins induce the production and release of TNF-α from cultured rat heart and VECs, and upregulate the expression of endothelial adhesion molecules, which are important for the adhesion of related cells to VECs, which facilitates inflammatory cell infiltration into tissues.[70] MDA-oxidized LDL adducts have been implicated in eliciting immune responses. Cytokines (TNF-a, monocyte chemoattractant protein-1, and macrophage inflammatory protein - 2) and adhesion molecules (intercellular cell adhesion molecule-1, vascular cell adhesion molecule-1) have been shown to be upregulated in liver endothelial cells in response to MAA-adducted proteins. Exposure of rat heart endothelial cells to MAA–BSA resulted in a pronounced morphological change in the endothelial cells and, more importantly, the upregulation of a number of adhesion molecules. These data would be consistent with the infiltration of more monocytes followed by CD4+ and CD8+ T cells into the area of inflammation. Although there is little evidence for cytotoxic reactions within plaques, a number of proinflammatory cytokines (IL-1, IL-6, and TNF-a) are secreted into the plaque.[70] Intrahepatic MAA adduct formation may be the consequence of the metabolism of ingested ethanol which results in AA generation in combination with hepatic lipid peroxidation which produces MAA.

Atherosclerosis is a chronic inflammatory vascular disease. Studies have shown that MAA-modified protein is present in vascular-related tissue. Saleena et al[71] demonstrated that AA-induced OS at the blood-brain barrier initiates cerebrovascular inflammation and damages VECs, which leads to the development of neurovascular inflammation. A significant inflammatory response in blood vessels causes VEC damage, which regulates coagulation and anticoagulation (including the fibrinolytic system). This dysregulation causes blood hypercoagulability, promoting the formation and progression of the prethrombotic state and triggering the formation of pathological thrombosis.[72]

Ca^{2+} Imbalance

Ca^{2+} is an indispensable ion required for all physiological activities and is transported throughout the body via calcium channels. These channels are located in the cell membrane and primarily maintain the intracellular concentration gradient (extracellular Ca^{2+} is much higher than the intracellular Ca^{2+}). Ca^{2+} is essential for normal heart function,[73] blood coagulation, excitatory conduction of cardiac muscles and nerves, maintenance of cardiac myocyte cell membrane permeability, and activation of various enzymes. The normal adult mammalian heart comprises 30% cardiomyocytes and 70% VECs.[74] VECs and cardiomyocytes work together to maintain the normal physiological function of the heart.

AA reportedly increases the L-type calcium current (IL-Ca) in bullfrog atrial myocytes. This increase further enhances contractility, action potential overshoot values, and plateau periods. These results indicate that AA-induced prolongation of IL-Ca or altered action potential timing contributes to the development of alcoholic arrhythmias and cardiomyopathies by affecting intracellular calcium movement in cardiomyocytes and VECs or producing cardiac nonresponse.[75]

Excessive alcohol consumption can lead to arrhythmias and ventricular insufficiency, and the acute and chronic toxic effects of ethanol and its metabolite AA on the heart are of clinical importance.[76] AA causes prolongation of IL-Ca or causes changes in the action potential time course, which in turn affects the movement of Ca^{2+} in the myocardium and endothelium. AA significantly increases intracellular Ca^{2+} concentration in HT22 cells, which disrupts cellular redox homeostasis and induces apoptosis.[20] In cardiomyocytes, AA activates Ca^{2+} channels at low concentrations (1–10 μmol), whereas long-term exposure and high concentrations (100 μmol) decrease cellular Ca^{2+}, inhibit cardiomyocyte contractile function, and negatively impact cardiomyocyte and endothelial cell function.[22] In summary, AA activates ROS production, induces OS, regulates Ca^{2+} overload, induces Drp1 phosphorylation and translocation to Mit, promotes excessive Mit division, and ultimately impairs Mit function, which leads to VEC toxicity.[77]

Vascular Remodeling

The effect of AA on vascular remodeling remains controversial, and further investigation is required to determine the specific effects of different doses of AA on vascular remodeling (Table 1).

Light to Moderate Alcohol Consumption Has Effects on Human Health

Low levels of AA are cardioprotective, whereas high levels are damaging in an ex vivo model of ischemia/reperfusion injury. Additionally, ALDH2 is a major, though not the sole, regulator of cardiac AA levels and plays a key role in protecting the heart from ischemia/reperfusion injury.[87] Confirming the threshold value that distinguishes high and low doses of ethanol is difficult because different research show different dose ethanol (Table 2).

Antagonism of AA Damage to Endothelial Cell Function

Cigarettes and alcoholic beverages are significant sources of AA exposure. Brassington et al[93] demonstrated that chronic cigarette smoke exposure promotes oxidative damage and perturbs cell function, which leads to endothelial-type NO

Table 1 The Effect of AA on Vascular Remodeling

Model	Dose	Effect and Reference
Men and nonpregnant women	Moderate (men: 280 g, women: 168 g) and heavy (men: 280 g, women: 168 g) alcohol consumption were compared with low intake (men: 168 g, women: 112 g).	Increase in mean systolic and diastolic pressures by 4 mmHg[78]
Sheep model system	The absence (0 mg/dL; Control) or presence of two alcohol doses were administered, including a lower dose (LD, 300 mg/dL) group and a higher dose (HD, 600 mg/dL) group.	Assessment of uterine vascular adaptation through angiogenesis revealed that alcohol negated the dose-dependent proliferative effects of estradiol-17β, thereby inhibiting angiogenesis.[79]
Human	Treated with/without EtOH (25 mM)	AA inhibits Notch signaling-mediated proliferation of vascular smooth muscle cells, leading to alterations in vascular structure and function.[80]
Rodent model (Conventional sexually mature stock of outbred CF-1 mice)	Adult female mice were orally exposed to 10% (w/v) ethanol or provided with water alone (Control) in their drinking water. This perigestational ethanol model resulted in a blood alcohol concentration of 24 mg/dL by day 10 of gestation.	Induces a reduction in the expansion of spiral arterial lumens and decreases both the proliferation of spiral arteries and the number of natural killer cells. It also lowers the levels of vascular endothelial growth factor and its receptor 2, which contributes to deficiencies in decidual tissue and results in incomplete vascular smooth muscle remodeling.[81]
Rodent model (Male Wistar rats)	Four groups were established: a normal group, a 1.8 g/kg ethanol (40% v/v) group, a 200 mg/kg Z. zerumbet extract plus ethanol group, and a 400 mg/kg Z. zerumbet extract plus ethanol group.	Long-term heavy alcohol consumption, along with its metabolite acetaldehyde (AA), can lead to cerebral arterial remodeling and cerebrovascular dysfunction, characterized by an endothelium-dependent reduction in diastolic function.[82]
Rodent model (Male Wistar rats)	Drank either water (Control) or a 5.2% ethanol mixture for 4 weeks.	Short-term moderate alcohol consumption has been shown to damage the respiratory system and circulatory system, with changes in right ventricular structure occurring as a secondary effect of AA-induced pulmonary revascularization.[83]
Rodent model (Adult male Sprague Dawley rats)	Daily intraperitoneal injections of 20 mg/kg/day bovine serum albumin-derived advanced glycation end products, or an equal volume of unmodified BSA (control), were administered for 6 weeks.	Acetaldehyde-modified proteins can induce structural remodeling and functional abnormalities in the aorta, leading to cardiac pressure overload.[84]
Rodent model (S100β-EGFP /Cre/ERT2 transgenic mice and Ai9 mice)	A 20 g mouse was gavaged with 18.75 μL of ethanol in 200 μL of water. This "daily moderate" alcohol feeding regimen was resumed 1 day post-ligation and continued daily for up to 2 weeks, after which the animals were anesthetized and their vessels harvested. The control group was gavaged with a calorically matched water-cornstarch mixture.	Intermittent alcohol abuse or chronic excessive alcohol consumption leads to the excessive accumulation of ethanol and AA, contributing to the development of atherosclerosis. However, small amounts of AA promote the proliferation of vascular endothelial cells, which may play a critical role in preventing vascular atherosclerosis.[85]
Rodent model (Sca1-eGFP transgenic mice)	A 20 g mouse was gavaged with 18.75 μL of ethanol in 200 μL of water. This "daily moderate" alcohol feeding regimen was resumed 1 day post-ligation and continued daily for up to 2 weeks, after which the animals were anesthetized and their vessels harvested. The control group was gavaged with a calorically matched water-cornstarch mixture.	AA has been shown to reduce arterial vascular remodeling by inhibiting the expansion of stem cell antigen-1-positive precursors, which are stimulated by Sonic Hedgehog signaling.[86]

Table 2 Light to Moderate Alcohol Consumption Has Effects on Human Health

Model	Doses	Effect and Reference
Rodent model (Homozygous knock-in mice)	50μM acetaldehyde	Increased ALDH2 activity was associated with reduced cardiac injury in the hearts of wild-type mice.[87]
Rodent model (Wistar albino rats)	0.1 mL of 10% ethanol was applied around the deep circumflex iliac pedicle vessel.	Significantly increased the mean flap survival area, blood flow, microvascular density, and levels of VEGF.[88]
Human	Microdoses of alcohol were infused bilaterally through the three needles into the adventitial space (0.30 mL per artery, 37 arteries total).	It affects perivascular sympathetic nerve innervation and can be used to alleviate renal hypertension.[89]
Human	The subjects were divided into five groups: non-drinkers (0 g/week), light drinkers (>0 to 140 g/week), moderate drinkers (>140 to 280 g/week), heavy drinkers (>280 to 420 g/week), and excessive heavy drinkers (>420 g/week).	Flow-mediated vasodilation (FMD) is impaired with alcohol consumption, and FMD is significantly smaller even in light alcohol drinkers compared to non-drinkers. Alcohol intake itself may be detrimental to vascular function[90]
Human	For men aged 65 years and younger, the NIAAA recommends no more than four alcoholic drinks per day and no more than 14 drinks per week. For women of all ages and men over 65, the NIAAA recommends no more than three alcoholic drinks per day and no more than seven drinks per week.	Most older Americans who drink are light to moderate drinkers, yet a substantial proportion of them engage in drinking behaviors that are either harmful or hazardous to their health.[91]
Human	Thirty-two healthy women and twelve healthy men (34 ± 9 years of age) were randomized to consume 150 mL of red wine per day for women (16 g ethanol/day) or double that amount for men (33 g ethanol/day), or to abstain from alcohol for 90 days.	Moderate consumption of red wine over three months increased hepatic triglyceride content in subjects who did not have steatosis at baseline.[92]

synthase downregulation in Sprague–Dawley rats. They found that treatment with ebselen can promote endothelial cell function through easing inflammation and oxidative damage induced by AA. AA dehydrogenases (ALDHs) are enzymes excreted to the outside of the body that are essential for the metabolism of AA. The major metabolite of quercetin glycosides protects cells from damage by enhancing aromatic hydrocarbon receptor-dependent activity of ALDHs induced by AA.[94] Silymarin is widely used in clinical practice for the treatment of cardiovascular injury. Silymarin reduces the expression of Mit division-related protein and kinesin-related protein 1, effectively attenuates AA-induced Mit division and apoptosis, and protects VECs.[95] Disulfiram inhibits the enzyme mitochondrial aldehyde dehydrogenase with a low Km (michaelis constant) for acetaldehyde.[96] Naltrexone binds to the opioid receptors and attenuates the pleasant sensations associated with alcohol drinking.[97] Acamprosate is sold under the brand name campral and is thought to stabilize the balance of neurotransmitters in the brain that would otherwise be disrupted by alcohol withdrawal.[98]

AA Metabolism and Toxic Thresholds

Previous research has shown variations in AA metabolism and toxic thresholds. Roach et al reported that[99] blood AA concentrations in alcoholics (1.4 to 2.4 pM) were elevated compared to controls (1.1 to 1.9 pM) after ethanol intake, with alcoholic relatives exhibiting levels between 65 to 78 pM. The mean AA plateau level was significantly ($p < 0.001$) higher in alcoholics (42.7 ± 1.2 mM) than in non-alcoholics (26.5 ± 1.5 mM), particularly when the mean blood ethanol concentration reached 24 mM;[100] Furthermore, AA concentrations were reported to be approximately 3.6 mg/mL following a dose of ethanol (0.5mL/kg) and around 2.2 mg/mL in controls.[101]

These differences in AA metabolism and toxic thresholds across studies may be influenced by several factors:

(1) The threshold for harmful effects of ethanol metabolism into AA varies among races and animal models, depending on the activity of ALDH and ADH enzymes.
(2) The AA formation reaction is more prominent in the blood of alcoholics and their relatives.
(3) The rate of AA clearance from human blood during preparation for analysis differs between alcoholics, their relatives, and controls.

Conclusions

AA, a metabolite of ethanol, inflicts damage on various tissue cells, including VECs, cardiomyocytes, and neuronal cells. This damage occurs through multiple mechanisms, such as DNA damage, exacerbation of OS, ROS accumulation, mitochondrial dysfunction, inflammatory response induction, Ca^{2+} dysregulation, and vascular structure remodeling. Notably, novel insights reveal that TRAIP regulates the choice between the NEIL3 and FANC pathways for ICL repair induced by AA. Additionally, the oxidation of thioredoxin contributes to oxidative stress, as well as insulin and estrogen receptor α damage induced by AA.

NEIL3 as a potential prognostic biomarker for patient stratification: NEIL3 not only initiates replication-dependent ICL repair as an alternative to the FANC pathway but also plays a critical role in maintaining replication fork stability and telomere integrity. Moreover, NEIL3 is strongly associated with the progression of various cancers, as well as cardiovascular and neurological diseases. Future research should focus on elucidating the mechanisms by which TRAIP regulates the choice between the NEIL3 and FANC pathways in ICL repair induced by AA.

Abbreviations

AA, Acetaldehyde; ALDH, Acetaldehyde dehydrogenase; ATP, Adenosine triphosphate; Drp1, Dynamin-related protein 1; DSB, Double-strand break; ERα, Estrogen receptor α; ERβ, Estrogen receptor β; FANC, Fanconi anemia; FMD, Flow-mediated vasodilation; ICL, Interstrand crosslink; IkB, Inhibitor of kappa B; IkBa, Inhibitor of kappa Ba; IL-Ca, L-type calcium current; IL-6, Interleukin 6; MAA, Malondialdehyde-acetaldehyde adducts; MAD, Malondialdehyde; MAPK, Mitogen-activated protein kinase; Mit, Mitochondria; NEIL3, DNA Endonuclease VIII-like 3; NF-κB, Nuclear factor kappa B; NK, Natural killer cell; NO, Nitric oxide; OS, Oxidative stress; RNS, Reactive nitrogen species; ROS, Reactive oxygen species; SHH, Sonic Hedgehog; SMC, Smooth muscle cell; TNF, Tumor necrosis factor; TRAF, Tumor necrosis factor receptor-associated factor; VEC, Vascular endothelial cell; VEGF, Vascular endothelial growth factor.

Data Sharing Statement

Data used to support conclusions are referenced in the article.

Ethics Statement

Ethical review and approval were not required for this submission.

Acknowledgments

We would like to thank Editage for English language editing, and Hai-Xia Chu has read and approved the final paper. Images were drawn using FigDraw software.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study was supported by the Open Project Program of the First Affiliated Hospital of Xinxiang Medical University [XZZX2022006].

Disclosure

The authors declare no conflicts of interest relevant to this article.

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