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Alcohol Consumption and its Effects on the Liver

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Abstract

Thousands of people die each year in the United States from alcohol related deaths. Why does the metabolism of alcohol cause severe damage to the body? Ethanol enters the body in the form of wine, and other alcoholic beverages and travels through the digestive system and then to the liver where it is metabolized. There are a series of steps involved in the breakdown of ethanol, and toxic byproducts are formed such as reactive oxygen species (ROS). These oxygen radicals can lead to damaged deoxyribonucleic acid (DNA) and to the formation of adducts. Chronic alcohol consumption can lead to liver inflammation and liver failure. Researchers are continuing to study and understand the specific mechanisms of liver damage as well as possible interceptions and cures.

Introduction

There are approximately one-hundred-forty-thousand alcohol related deaths in the United States each year, which is more than three-hundred-eighty deaths per day. The deaths are primarily a result of heavy episodic drinking (HED) that led to liver disease, heart disease, and cancer (Centers for disease Control and Protection, 2022). Alcohol consumption is a serious risk factor for many diseases because of its toxic effects on the body.

The Centers for Disease Control and Prevention (CDC) established guidelines for what is considered excessive alcohol consumption. Binge drinking is defined as consuming four or more drinks on one occasion for a woman and five or more drinks for a man. A woman drinking eight or more drinks a week and a man drinking fifteen or more is considered heavy drinking (Centers for Disease Control and Prevention, 2022).

There are some observed trends with alcohol consumption among gender, race, and age. In the United States, over 55% of adults aged 26 and older consume alcohol each month, and one in every four adults in this age bracket engage in HED (Witkiewitz, Litten, & Leggio, 2019). Men are more likely to engage in HED, possibly due to peer pressure or to achieve the feeling of masculinity. There is a correlation between white American males overconsuming alcohol more than other races (Wade, 2020). Alcohol abuse affects both men and women, but men are more likely to develop alcohol related diseases and die from them. Men are four times more likely than women to develop cirrhosis and liver cancer (Yerby, 2022).

Long term consumption of alcohol correlates to the development of many diseases. Alcohol consumption has been shown to have a detrimental impact on the development of infectious diseases such as tuberculosis, human immunodeficiency virus (HIV), and pneumonia since alcohol negatively affects the immune system. It is not fully understood how, but there is a correlation between heavy alcohol consumption and the development of cancer. Some say that the acetaldehyde, a product of alcohol metabolism, is itself carcinogenic. Additional diseases that alcohol consumption is related to include: diabetes, cardiovascular diseases, neuropsychiatric disorders (like epilepsy), and liver and pancreatic diseases (Rehm, 2011).

Alcohol is one of the leading causes of death in humans, and a leading risk factor in many diseases. What is it about alcohol that makes it so toxic to the human body, specifically to the liver, and is there any way to intercept the process from causing severe liver damage and eventual death?

Methods

The research acquired for this paper was compiled from the databases of Touro College Online Libraries and was supplemented by additional websites. Keywords used to aid in finding relevant articles include: alcohol, liver, acetaldehyde, and reactive oxygen species.

Discussion

Alcohol has negative effects on the entire body; the liver suffers the most severely since it is the primary location of alcohol metabolism (Cioarca-Nedelcu, Et. Al. 2021). This paper analyzes common alcohol metabolic pathways and the harm of the byproducts formed.

Pathway Through the Body

"The effects of alcohol on various tissues depend on its concentration in the blood over time (Zakhari, 2006)." The rate that alcohol is absorbed, metabolized, distributed, and excreted determines the blood alcohol concentration (BAC). Environmental factors such as how fast one drinks, or what they drink, as well as genetic factors can contribute to one's BAC levels. Rate of alcohol elimination varies among individuals and things like age, time of day, and chronic drinking can all affect the rate of alcohol elimination from the body (Zakhari, 2006).

Alcohol enters the body through the oral cavity and a very small amount is directly absorbed into mucosal tissue and then into the blood stream. The majority of the alcohol then travels down the esophagus to the stomach. Once in the stomach, the mucosal layer of the stomach absorbs a small amount of the alcohol and sends it directly into the blood stream and then to the liver. This is why there is an almost immediate alcohol rush response soon after drinking.

The vast majority of alcohol will be absorbed into the blood stream from the intestines. From the stomach, alcohol travels through the pyloric sphincter to the small

intestines. If alcohol is consumed on an empty stomach, the sphincter will be fully open, allowing the alcohol to enter the intestines all at once and ultimately hit the bloodstream faster. However, if there is food in the stomach, the sphincter will open only slightly, so the alcohol will steadily reach the bloodstream (Cottle, 2021).

The alcohol encounters the enzyme alcohol dehydrogenase which converts ethanol to acetaldehyde - a more toxic substance than the ethanol itself. Another enzyme converts acetaldehyde to acetate which is less toxic. However, if one consumes too much alcohol that overwhelms the liver, some of the ethanol will escape into the blood stream without first being converted to something less toxic (Cottle, 2021).

From the liver, the blood goes to the heart, and the heart sends the blood to the lungs. Some of the ethanol actually leaves the body simply by breathing, but the percentage that does not travels back into the heart. The heart pumps and sends the rest of the ethanol first to the brain and then to the rest of the body. Ethanol affects the majority of the body aside from bone and fatty tissue. Ethanol is water soluble and fat tissue is lipids so they will not mix, which is why women who have more fatty tissue and less blood volume than men are affected more by alcohol consumption (Cottle, 2021).

Ethanol triggers the sympathetic nervous system – fight or flight, causing rapid heart rate and sweating (Cottle, 2021). In the brain, ethanol will affect the function of neurotransmitters. Ethanol will increase the function of inhibitory neurotransmitters like GABA, glycine, and adenosine, causing people to feel sedated. At the same time, ethanol inhibits the function of excitatory neurotransmitters like glutamate, also contributing to the alcohol induced feeling of sedation (Valenzuela , 1997). Additionally, the hypothalamic-pituitary axis will recognize the ethanol and, in an effort to maintain homeostasis, it will trigger the adrenal glands to release cortisol, epinephrine, and norepinephrine causing the feelings of stress and adrenaline. The pituitary will also produce less antidiuretic hormone (ADH). Typically, ADH affects the amount of blood flowing through the vessels in the kidney and thereby controls the amount of urine produced. With limited ADH, the vessels in the kidney will dilate and thus allow more urine production, which is why people have frequent urination when they consume alcohol. This results in dehydration since the body has lost so much fluid (Cottle, 2021).

Alcohol Metabolism

One chemical mechanism alone will not account for alcohol induced damage in a person. Rather, a series of processes will occur when one consumes alcohol, and combined, they will lead to critical damage (Wu & Cederbaum, 2003).

Alcohol is metabolized in the liver through a series of steps known as oxidative metabolism. The major oxidative pathway for metabolism of alcohol in the liver involves an enzyme called alcohol dehydrogenase. When alcohol enters the liver, it encounters the alcohol dehydrogenase enzyme in the cytosol of hepatocytes. This enzyme converts alcohol into acetaldehyde, a toxic and highly reactive molecule (Tuma & Casey, 2003).

Then, the enzyme aldehyde dehydrogenase converts acetaldehyde into acetate. The oxidation of alcohol reduces nicotinamide adenine dinucleotide (NAD+) by two electrons to form a nicotinamide adenine dinucleotide (NADH) molecule-the starting material for the cellular respiratory chain. "As a result, alcohol oxidation generates a highly reduced cytosolic environment in liver cells," leaving the liver vulnerable to the reactive byproducts of alcohol metabolism (Zakhari, 2006). During the respiratory chain, oxygen radicals, such as hydroxyl, peroxide and superoxide, are produced as intermediates. These oxygen radicals are, for the most part, converted to water before they can damage any cells. With increased alcohol intake there is a greater volume of NADH and possibility for oxygen radical formation (Cederbaum & Wu, 2003).

The enzyme cytochrome P450 2E1, located mainly in the endoplasmic reticulum of hepatocytes in the liver, can also be used to convert alcohol into acetaldehyde in an oxidative process. However, this chemical mechanism also produces highly reactive oxygen species (ROS) as a byproduct (Tuma & Casey, 2003).

Another oxidative pathway in metabolizing alcohol involves the enzyme catalase, located in the peroxisomes of cells. Catalase oxidizes ethanol in the presence of hydrogen peroxide. Researchers have found increased catalase activity and hydrogen peroxide production in the liver of rats who were given alcohol over time. This is a minor pathway in metabolizing alcohol (Zakhari, 2006).

Reactive Oxygen Species

A significant process leading to alcohol induced damage was found to be the production of reactive oxygen species (ROS). "Both acute and chronic alcohol exposure can increase production of ROS and enhance peroxidation of lipids, protein, and deoxyribonucleic acid (DNA) (Wu & Cederbaum, 2003)."

"Repeated formation of these reactive oxygen species, especially in heavy drinkers, surpasses the liver's capacity for fighting oxidative stress by consuming all resources of the local enzymatic and non-enzymatic antioxidant molecules (Cioarca-Nedelcu Et. Al. 2021)." Excessive

production of ROS or limited activity of antioxidants can lead to oxidative stress and eventually result in cell death (Tuma & Casey, 2003).

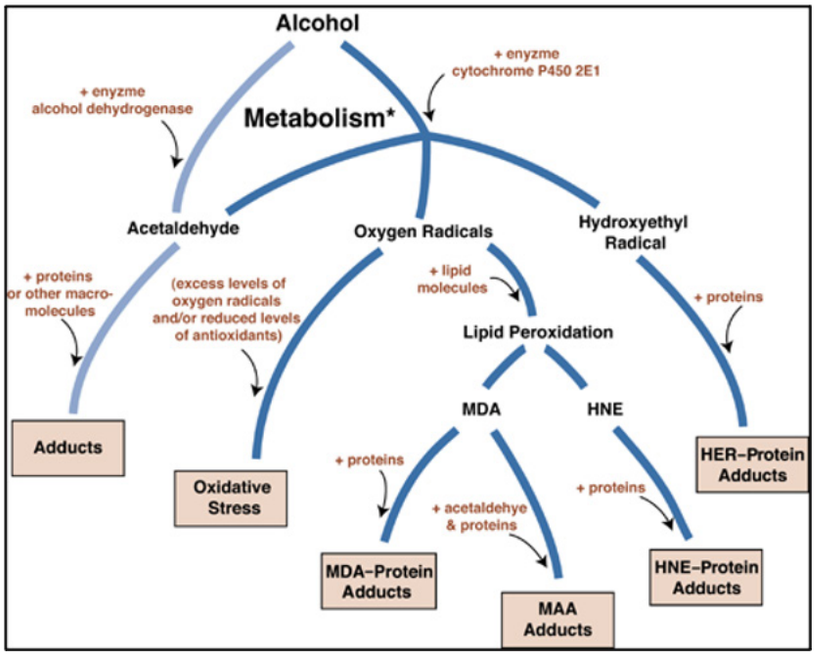
The oxygen radicals are toxic because they can interact with polyunsaturated fat molecules in cell membranes, in a process called lipid peroxidation." The result of ROS interacting with phospholipids is the formation of electrophiles that are reactive aldehyde derivates: malondialdehyde (MDA), 4-hydroxy-2,3-alkenal, and 4-hydroxy-2-nonenal (HNE), similar to acetaldehyde (Tuma & Casey, 2003). Di Luzio, in 1966, was the first to discover the peroxidation of lipids after alcohol consumption, and this was confirmed by other studies (Galicia-Moreno & Gutiérrez-Reyes, 2014). "In addition to damaging cells by destroying membranes, lipid peroxidation can result in the formation of reactive products that themselves can react with and damage proteins and DNA (Wu & Cederbaum, 2003). These lipid peroxide derived compounds can induce a strong inflammatory response in the liver, also known as alcoholic hepatitis (Cioarca-Nedelcu, Atanasiu, & Stoian, 2021).

The oxidative modification of proteins can alter their function and structure eventually leading to proteolysis. First, proteins will be slightly modified, but they can still function. Next, proteins will slightly unfold, exposing the hydrophobic regions of proteins. If the damaged protein has not yet been degraded, "it forms an aggregate with other proteins, lipids, and sugars (Galicia-Moreno & Gutiérrez-Reyes, 2014)."

Acetaldehyde along with the lipid peroxide derivatives MDA and HNE can interact with proteins and other complex molecules forming adducts as a product. The aldehydes typically interact with the lysine amino acid and most commonly affect the following proteins: hemoglobin, albumin, tubulin, lipoproteins, collagen, cytochrome, and ketosteroid reductase. Research has found that these adducts that are formed from the metabolism of alcohol are a leading cause of alcohol induced liver disease (Tuma & Casey, 2003). In other words, the ROS oxidation of lipids yields products that interact with proteins and can cause changes to the protein's three-dimensional structure and cross linking of proteins (Wu & Cederbaum, 2003).

Research has been done to confirm that adducts are indeed formed in-vitro as a result of alcohol consumption. The first study done detected antibodies for aldehyde adducts, like acetaldehyde, MDA, and HNE, in the blood of chronic alcohol consumers. The adducts formed were seen as foreign, and therefore, elicited an immune response and production of antibodies. Further studies proved adduct formation in the liver, specifically in the primary liver cells-hepatocytes. Acetaldehyde adducts were primarily found in the perivenous regions of the liver, an area around the vein carrying blood out of a lobule in the liver. MDA and HNE adducts were found in damaged parts of the livers of chronic alcohol consumers (Tuma & Casey, 2003).

Research has found a link between adduct formation resulting from alcohol consumption and liver dysfunction and disease. Liver damage has been seen in the same area where acetaldehyde adducts accumulate, indicating a correlation. Additionally, acetaldehyde adducts were found in areas of inflammation and fibrosis (scar tissue formation) in advanced liver disease. MDA adducts were found in the same places as acetaldehyde adducts. Aldehydes were found to interact specifically with the lysine amino acid, and evidence was found showing dysfunction in lysine reliant enzymes like calmodulin and a cytoskeleton protein: tubulin. Research has found that modification of even five percent of a person's tubulin molecules by acetaldehyde can impair one's cytoskeleton function. This explains the observed protein transport pathway and protein secretion dysfunction in the liver of alcoholics. The altered tubulin can also lead to disorganized hepatocytes which can



Tuma & Casey, 2003

lead to more severe liver damage (Tuma & Casey, 2003).

Research has found the extracellular matrix (ECM) in the liver to also be affected from adducts. Disorder in the ECM production can result in scar formation in the liver, hepatic fibrosis. Accumulation of irregular ECM is associated with the stage of alcohol induced liver disease prior to cirrhosis. Another study found that alcohol consumers with aldehyde adducts trigger a specific immune response producing antibodies that can harm the liver. This hypothesis was supported by an experiment where a guinea pig with aldehyde adducts was given alcohol, resulting in hepatitis (Tuma & Casey, 2003).

ROS, specifically the hydroxyl radical, reacts with the carbon atoms in the nitrogenous bases of DNA, and they abstract hydrogen from thymine and 2-deoxyribose. Guanine has the greatest tendency to become damaged from oxidation, and if it is not repaired, it can become mutagenic since it will pair with adenine instead of cytosine. There is a hypothesis that the ethanol induced morphological and functional abnormalities in the hepatocytes are due to the loss of integrity in DNA pairing, leading to inaccurate protein synthesis. Studies were done with rats where they were given alcohol over time, and modified DNA was seen in the rats' mitochondria (Galicia-Moreno & Gutiérrez-Reyes, 2014).

Alcohol Intake Causing Liver Disease

Since ROS are naturally produced, the body has mechanisms, including the use of an antioxidant Glutathione (GSH), to rid the body of them. However, with long term alcohol consumption, these mechanisms become impaired, so ROS can accumulate and lead to liver damage. (Wu & Cederbaum, 2003).

Liver Diseases

Researchers have found that many liver diseases resulting from alcohol are due to the products of alcohol breakdown in the liver (Tuma & Casey, 2003).

The liver reacts to alcohol causing fatty liver, inflammation, and the breakdown of liver cells. Hepatic steatosis, also known as a fatty liver, is when a minimum of five percent of the liver weight is made up of intrahepatic triacylglycerols. Hepatic steatosis is the primary response when the liver is overly exposed to alcohol. It is considered a reversable process once a person stops drinking alcohol (Cioarca-Nedelcu, Atanasiu, & Stoian, 2021).

Long time alcohol consumers are prone to develop Alcoholic Steatohepatitis, a chronic liver disease described as inflammation of a fatty liver. Kupffer cells, macrophages located in the sinusoids of the liver, defend the liver when it is exposed to pathogens from the portal venous tract (a vein carrying blood from the GI tract, gallbladder, and spleen to the liver). With chronic alcohol intake, Kupffer cells can switch from anti-inflammatory to a pro inflammatory state. Activated Kupffer cells generate reactive oxygen radicals and nitrogen species that trigger the release of several cytokines like TNF alpha, chemokine, and interleukins, which ultimately will attract leukocytes to the liver causing inflammation (Cioarca-Nedelcu, Atanasiu, & Stoian, 2021).

"The main trigger of Kupffer cells' immune response in subjects with chronic ethanol consumption is an endotoxin known as lipopolysaccharide (LPS)," an endotoxin found in the gut. Alcohol has the ability to increase intestinal permeability and destroy tight interepithelial junctions between intestinal cells, allowing pathogenic bacteria and endotoxins to leak into the portal system. The process of bacteria translocating from the gut to the liver is known as endotoxemia. LPS reaches the liver, the Kupffer cells respond by generating reactive oxygen and nitrogen species, and ultimately inducing liver inflammation and damage. "In conclusion, there is a strong connection between high endotoxemia and the progression of alcoholic liver disease from liver steatosis to alcoholic hepatitis (Cioarca-Nedelcu, Atanasiu, & Stoian, 2021)."

Cirrhosis is a progressive disease of the liver where hepatocytes are replaced with scar tissue. There are four stages of this disease beginning with hepatitis: inflammation of the liver. Abdominal discomfort is usually felt at this stage, and if the inflammation is treated at this point, it can inhibit the progression to stage two. Next, there is scarring as result of the inflammation, obstructing the blood flow to the liver. At this point if treated, the liver may be able to recover or slow the progression of liver disease. The third stage is cirrhosis where liver tissue that was destroyed over time is replaced by scar tissue. This scarring is permanent damage to the liver, making the liver hard and lumpy.

The scar tissue will eventually block the blood flow through the portal vein into the liver, causing the blood to travel to the spleen resulting in additional problems. The final stage is liver failure. At this stage, if no immediate medical intervention is done, like a transplant, a person will die. "Cirrhosis of the liver caused by years of alcohol abuse or being overweight can be avoided by making changes in the early stages of the disease… Once your liver is severely damaged and scarred, there is no way to repair the damage (Kumar, 2002)."

A primary function of the liver is to filter out toxins from the blood. When the liver is replaced by scar tissue due to alcohol induced damage, it struggles to filter toxins, resulting in the accumulation of toxins in the blood

continuing onto the heart, lungs and then the brain. Some of the blood from the portal system will not even enter the liver and rather bypass the liver in a phenomenon known as portal–systemic shunting and continue onto the brain. The toxins, such as ammonia and manganese, can build up in the brain and lead to a disorder known as hepatic encephalopathy. Researchers have confirmed this when they found ammonia and manganese in the brains of those with severe liver disease. Symptoms of hepatic encephalopathy include cognitive dysfunction and problems with motor function such as tremors and poor coordination. Eventually, patients can end up in a coma called a hepatic coma since it was the dysfunction of the liver which led to the toxic accumulation. Lactulose, a sugar molecule that is not absorbed by the body, draws ammonia into the intestines and eliminates it with the undigestible sugar. This is the primary treatment for chronic hepatic encephalopathy (Butterworth, 2004).

The liver, the second largest organ in the body, has the capability to regenerate. Regeneration is different than scarring in that it is actually reproducing liver tissue as opposed to scar tissue. The liver has this feature because it is in charge of metabolizing toxins in the body (Cottle, 2021). With chronic alcohol consumption and development of cirrhosis, the liver can no longer regenerate, and the liver fails to function. Most doctors will require patients needing a liver transplant due to alcohol abuse to be sober for at least six months. Many people are not candidates for a liver transplant because they have medical problems such as cancer, hypertension, or substance abuse disorder (Feng, Roayaie, & , 2023).

Possible Treatments

There are numerous treatments for alcohol use disorder including the use of drugs and treatment programs like Alcoholic Anonymous. Acamprosate, a drug that targets the glutamate system in the body, works to inhibit alcohol dependency. Another drug, Naltrexone, reduces alcohol cravings. Naltrexone does have a risk of causing hepatotoxicity if more than the approved amount is taken. Therefore, patients with active liver disease, and acute hepatitis or liver failure should not use Naltrexone. The first FDA approved drug in 1951 was Disulfiram. Disulfiram works by inhibiting aldehyde dehydrogenase, the enzyme that converts acetaldehyde into acetate. With the enzyme disabled, if alcohol is consumed it will cause acetaldehyde to accumulate, resulting in unpleasant symptoms like tachycardia, headaches, nausea, and vomiting (Witkiewitz, Litten, & Leggio, 2019).

For treating the excessive production of ROS: "Numerous investigations have found that administering antioxidants, agents that reduce the levels of free iron, or agents that replenish GSH levels can prevent or ameliorate the toxic actions of alcohol (Wu & Cederbaum, 2003)."

Where Research is at Now

"Innovative approaches to better identify the mechanisms through which adducts cause liver injury remain challenging goals. The development of new therapeutic interventions for patients with alcoholic liver disease aimed at modifying or preventing adduct formation also poses a challenge for investigators. Both of these endeavors represent fertile areas for future research and should provide valuable information concerning alcohol's toxic effects on the liver and the treatment of alcoholic liver disease (Tuma & Casey, 2003)."

"Nowadays, multiple studies targeting alcohol-induced liver disease have shown that administration of agents that eradicate superoxide anions, such as a superoxide dismutase and agents that restore reduced glutathione, such as N-acetyl cysteine, can successfully counteract oxidative stress. Moreover, through their anti-inflammatory activity, corticosteroids can decrease the local release of cytokines and the local collagen production, especially in alcoholic hepatitis. Last but not least, silymarin, which is a strong antioxidant, is a strong cell membrane stabilizer and an antifibrotic agent (Cioarca-Nedelcu, Atanasiu, & Stoian, 2021)."

Conclusion

Alcohol has short term effects on the body, affecting the lining of the digestive tract, the neurotransmitter function, and cognitive function. Over time, alcohol consumption can have more detrimental effects on the body. The liver suffers the most severely, first with inflammation, then steatosis, and finally with cirrhosis. The breakdown of alcohol yields byproducts called reactive oxygen species that are toxic to lipids, proteins, and DNA. ROS interacting with parts of the body causes damage and formation of adducts. Adducts were found in the liver of long-term alcohol consumers. There are some medications to help the effects, but if consumption of alcohol is not stopped, the only option at times is a liver transplant. Research is focused on trying to inhibit the ROS from causing damage.

References

Butterworth, R. F. (2004). Hepatic Encephalopathy. National Institute of Alcohol Abuse and Alcoholism .

Centers for Disease Control and Prevention. (2022, July 11). Excessive Alcohol Use. Retrieved from National

Center for Chronic Disease Prevention and Health Promotion : https://www.cdc.gov/chronicdisease/resources/publications/factsheets/alcohol.htm

Cederbaum, A. I., & Wu, D. (2003). Alcohol, Oxidative Stress, and Free Radical Damage. Alcohol Research & Health , 27(4), 277-284.

Centers for disease Control and Protection. (2022, July 6). Retrieved from https://www.cdc.gov/alcohol/features/excessive-alcohol-deaths.html#print

Cioarca-Nedelcu, R., Atanasiu, V., & Stoian, I. (2021). Alcoholic liver disease-from steatosis to cirrhosis - a biochemistry approach. Journal of Medicine and Life, 14(5), 594-599.

Cottle, J. (2021, March 17). What Alcohol Does to Your Body. Salt Lake City, Utah. Retrieved from https://www.youtube.com/watch?v=6q1RH8A3O3c

Feng, S., Roayaie, K., & . (2023). Liver Transplant. Retrieved from UCSF Transplant Surgery and Department of surgery: https://transplantsurgery.ucsf.edu/conditions--procedures/liver-transplant.aspx

Galicia-Moreno, M., & Gutiérrez-Reyes, G. (2014). The role of oxidative stress in the development of alcoholic liver disease. Revista de Gastroenterología de México, 135-144.

Kumar, K. (2002, April 7). What Are the 4 Stages of Cirrhosis of the Liver? Retrieved from Medicine Net: https://www.medicinenet.com/what_are_the_4_stages_of_cirrhosis_of_the_liver/article.htm

Rehm, J. (2011). The Risks Associated With Alcohol Use and Alcoholism. Alcohol Research & Health : The Journal of the National Institute on Alcohol Abuse and Alcoholism, 135-143.

Tuma, D. J., & Casey, C. A. (2003). Dangerous Byproducts of Alcohol Breakdown—Focus on Adducts. Alcohol Research & Health, 27(4), 285-290.

Valenzuela , F. C. (1997). Alcohol and Neurotransmitter Interactions. Alcohol Health and Research World, 144-148. Retrieved from Alcohol Health and Research World.

Wade, J. M. (2020, December). Is it Race, Sex, Gender or All Three? Predicting Risk for Alcohol Consumption in Emerging Adulthood. Journal of Child & Family Studies, 3481-3492.

Witkiewitz, K., Litten, R. Z., & Leggio, L. (2019, September 25). Advances in the Science and Treatment of Alcohol Use Disorder. Science Advances, 5, 1-11.

Wu, D., & Cederbaum, A. I. (2003). Alcohol, Oxidative Stress, and Free Radical Damage. Alcohol Research & Health, 27(4), 277-284.

Yerby, N. (2022, September 21). Retrieved from Alcohol Rehab Guide: https://www.alcoholrehabguide.org/resources/medical-conditions/alcohol-related-death/

Zakhari, S. (2006). Overview: How is Alcohol Metabolized by the Body? Alcohol Research and Health, 245-253.