Ethanol Intoxication Sensing Technologies and Techniques

Subjects: Engineering, Biomedical

Contributor: Szymon Paprocki, Meha Qassem, Panicos A Kyriacou

Ranging from casual drinking or as a part of celebration to more extreme binge drinking or alcohol dependence/alcoholism, often referred to as alcohol use disorder (AUD), alcohol consumption has also been associated with the development of several types of cancer. The field of alcohol intoxication sensing is over 100 years old, spanning the fields of medicine, chemistry, and computer science, aiming to produce the most effective and accurate methods of quantifying intoxication levels.

Keywords: ethanol ; intoxication ; sensors ; devices

1. Introduction

Ethanol consumption is a major component of social life in the Western world. Ranging from casual drinking or as a part of celebration to more extreme binge drinking or alcohol dependence/alcoholism, often referred to as alcohol use disorder (AUD) [1], alcohol consumption has also been associated with the development of several types of cancer [2]. With high frequency of consumption of alcoholic beverages and the corresponding effects of alcohol intoxication on the body and behavior of individuals, a necessity for quantification of intoxication has become an important part in assessing the state of an individual. Driving under the influence (DUI) of alcohol in the UK is related to an estimated 13% of all fatal road accidents and is a major cause of death for males between 15 and 59 years of age [3]. In an effort to prevent these tragedies, several methods have been developed to estimate intoxication levels spanning many fields, such as biochemistry, physiology, photonics, electronics, image analysis, and artificial intelligence.

Alcohol intoxication is a standardized metric denoted by blood alcohol concentration (BAC) only and not the effect it has on an individual, thus not accounting for tolerance resulting from regular exposure to ethanol. Although similar symptoms of intoxication can be seen amongst individuals, the influence of alcohol tolerance remains a poorly explored phenomenon in the context of the wider population. The BAC level corresponds to the weight of ethanol in milligrams per 100 mL of blood. The level of intoxication is positively correlated with the amount of ethanol in the bloodstream, with the high end of ethanol intoxication at 0.5% (500 mg/dL) and with levels as low as 0.35% (350 mg/dL) being linked to death or serious harm to the individual or those around them [4]. Regular consumption of excessive amounts of alcohol is also associated with the development of liver disease and increased blood pressure, making those individuals more susceptible to health complications in the future [5]. The legal drinking limit for driving in the UK is 80 mg per 100 mL of blood, equivalent to a BAC of 0.08, which can be categorized as one of the higher levels of alcohol permissible to drive, whilst many European countries and Middle Eastern countries allow for a very low level of intoxication (BAC 0.02) or prohibit driving under the influence of alcohol altogether under a “zero tolerance” policy. The territory with the highest permissible level of BAC is the Cayman Islands allowing a BAC level of 0.10. Besides DUI, alcohol consumption can also be linked to crimes, such as theft and criminal damage, and in such circumstances alcohol serves as a catalyst for antisocial behavior and violent crime [6]. Alcohol consumption puts a significant burden on public services. Combining the costs of dealing with alcohol-related crime, loss of productivity through unemployment and sickness, and the cost and burden on the National Health Service (NHS), the cost of alcohol on society is estimated to be GBP21 billion per year [7], although the real figure is thought to be even higher. Reviews on the subject of economic impacts of alcohol consumption express the cost figure as percentage of gross domestic product (GDP) ranging between 0.45% and 5.44% annually [8].

Short-term influences of alcohol intoxication, however, do not carry such damaging consequences, yet they are not without harm. Acute intoxication can have damaging effects on people diagnosed with cancer or currently taking antibiotics. The reaction of ethanol in the liver can trigger inflammation and damage the liver of the user. Other cases where acute consumption poses a risk of damage is particularly seen amongst people who are suicidal, increasing the risk of taking their life. [9]. Ethanol affects the body by influencing the central nervous system through the inhibition of

gamma-aminobutyric acid (GABA) receptors [10]. This results in reduced cognitive ability, slurred speech, loss of balance, and reduced social inhibition. Long-term consumption can lead to alcohol use disorder (AUD). Neuroscience researchers have also found a correlation between neuron activity and metabolites of ethanol, such as acetic acid [11]. This correlation may suggest that other chemical imbalances contribute to intoxication effects. The effects of acetic acid on the nervous system have not been studied in as much depth as ethanol, and could potentially prove to be an important component for quantifying intoxication influences or relating to the addictive properties of alcohol consumption. Globally, excessive consumption of alcohol leads to AUDs and addictions, with an estimated 586,780 sufferers of AUD just in the UK and only 18% receiving treatment [12].

With so many problems associated with alcohol consumption, methods of estimating alcohol intoxication were reported in medical literature as early as 1920 by Widmark [13]. With further development in technology and chemical analytics, several methods, such as gas chromatography, became available for measuring intoxication levels in a variety of bodily fluids. Similarly, this development in technology and analytical techniques gave rise to the most notable alcohol intoxication measuring device, the Breathalyzer™, a breath alcohol content (BrAC) measuring device. This method allows for remote BAC testing, particularly for traffic safety, without the need to send blood samples for laboratory analysis [14].

2. Toxicology of Intoxication

Intoxication can be defined as loss of control over actions or behavior changes under the influence of a drug. Intoxication due to ethanol can be divided into three main parts: initial take-up, the peak, and the decay stage. This can be illustrated by studies performed on human volunteers to investigate the changes of alcohol in their blood over time [15]. The initial uptake of ethanol causes the blood alcohol concentration (BAC) to raise rapidly, reaching peak intoxication between 30 to 60 min, although that number is heavily dependent on the dosage. After that, the peak BAC levels begin to decay, reaching zero between six to eight hours after initial consumption. This, however, is also dependent upon the volume of ethanol consumed. The standard unit of measurement of alcohol intoxication is not internationally agreed upon, with variation in the order of magnitude of measurement as well as the numerical systems used. In the medical literature, the consensus on measurement is to use BAC as volume of pure ethanol per 100 mL of blood, varying from 0 to 0.5, representative of concentration levels between 0 and 500 mg/dL.

Considering the uptake of ethanol, this period is characteristic of euphoric behavior, including laughter, social inhibition, and generally increased well-being due to the release of hormones, such as serotonin. At the peak of intoxication, these effects begin to slowly fade away, due to decreasing levels of ethanol in the body. The roll-off stage is associated with increased tiredness and depression [16]. The primary influence of ethanol intoxication originates in the central nervous system through the inhibition of GABA receptors. Alcohol molecules inhibit the active site of GABA receptors, resulting in reduced cognitive function and decreased spatial awareness. Alcohol also contributes to the production of serotonin, resulting in a relaxed state of the consumer [17], hence enacting on the reward system of the brain. With time, these effects wear off, depending on several factors, such as age, sex, and body weight. The literature correlates sex with an aspect of varied breakdown of ethanol, possibly explained by the lower resting metabolic rate in women [18]. Tolerance is also a factor when considering the decay of ethanol in the blood, as has been demonstrated by people with AUD that can metabolize ethanol at a faster rate than occasional drinkers [19]. In the body, alcohol is subject to many chemical reactions, specifically those involved in its breakdown. A group of enzymes responsible for ethanol breakdown are known as alcohol dehydrogenases. These enzymes are responsible for breaking down alcohol into acetaldehydes and subsequently acetic acid. These waste products are dealt with in the body by means of various other enzymes. Specifically, acetic acid is a subject in the acid cycle for neutralization. It is key to highlight that high concentration of these acids can lead to acidosis, a symptom of alcohol poisoning, requiring medical attention in severe cases [20]. Besides inhibiting GABA receptors and being broken down by enzymes, alcohol also influences the function of the cardiovascular and pulmonary systems. Primarily, the impact of ethanol on the blood vessels extends to the function of relaxation by vasodilation. It is key to note that although alcohol relaxes the blood vessels, this is only seen for small doses of alcohol. This is also a contributing factor to the beneficial health impacts of alcohol. However, act as exclusively limited to small doses of alcohol. At higher levels of BAC, it begins to take on a pressor, restricting the blood vessels [21]. This once again can be attributed to the acids produced through the metabolic breakdown of ethanol, although the true origin of this effect is not clear.

Alcohol affects a number of systems in the body, resulting in an intoxicated state. As mentioned previously, these effects manifest themselves in bodily organs, such as the heart, lungs, liver, and brain. However, these effects are short-lived and fade away after time. On the other hand, long-term consumption of excessive amounts of alcohol can contribute to a multitude of diseases, both physical and mental. Amongst them are the mental illness associated with dependence or addiction to alcohol. The root causes of these diseases are mostly unexplored in terms of explaining the susceptibility to developing an alcohol addiction [22]. Some research suggests that both genetic and environmental factors play a role in

the development of AUD [23]. AUD is often characterized by large and frequent consumption of alcohol, as well as by withdrawal symptoms, some of which include tachycardia, tremors, sweating, delirium, seizures, insomnia, and anxiety [24]. Several treatments exist to help recovering people with AUD [25][26]. Regular and uncontrolled consumption of alcohol can lead to an AUD, which, if untreated, can become a gateway for development of more serious health problems, some of which are fatal. Cardiac health is significantly impacted by excessive and regular consumption of alcohol. Amongst the long-term effects of alcohol consumption are alcoholic cardiomyopathy (change of shape of the heart), high blood pressure, myocardial infarction (heart attack), arrythmias (irregular heart rhythm), fatal cardiac arrest, and stroke [27]. The association between heavy alcohol use and cardiovascular disease (CVD) is unclear. Discussion on this topic focuses on alcohol's effect on the atherosclerotic process (hardening of blood vessels) in vessels and the toxic damage to the myocardium [28]. As the main site of alcohol metabolism, the liver experiences the most damage, although much of that is mitigated by its regenerative properties [29]. However, even that is not enough to prevent the tissue damage caused by excessive and prolonged consumption of alcohol. Chronic and excessive alcohol consumption results in the formation of hepatic lesions on the liver, including steatosis (deposition of fat in hepatocytes), hepatitis (inflammatory type of liver injury), and fibrosis (tissue scarring) [30]. Continuous damage to the tissue of the liver and the formation of scar tissue contributes to and increase the risk of developing liver cancer, a very prominent disease amongst heavy alcohol users. AUD and heart and liver damage are just a few of the many pathologies that can be attributed to excessive consumption of alcohol [31][32]. Alcohol-related disease is a big burden on the health system.

3. Technologies and Devices

The research of ethanol intoxication sensors yielded several results encompassing different aspects of alcohol intoxication, i.e., behavioral, physiological, and chemical changes in the individual's body. All the methods were categorized into six main sections: pharmacokinetic estimates, breath-sample testing, bodily fluids, physiological changes, transdermal, and optical spectroscopy. The findings and all the devices and techniques considered are summarized in **Table 1**.

Table 1. Summary of ethanol detection devices and techniques.

No.	Device/Technique	Parameter	Type	Form Factor
1	Nicloux Flask	Chemical reaction	Bodily fluid testing	Flask/blood extraction
2	Widmark Flask	Chemical reaction	Bodily fluid testing	Flask/blood extraction
3	EBAC Equation	Estimation based on physiological factors	Early estimation method	Equation
4	Photovoltaic Assay	Color change based on oxidation level	Breath alcohol	Portable device
5	Intoxilyzer	Near-infrared spectroscopy	Breath alcohol	Benchtop device
6	Fuel-Cell Analyzer	Current generated by ethanol oxidation	Breath alcohol	Portable device
7	Semiconductor Breath Analyzer	Strip color change	Breath alcohol	Portable device
8	Ignition Interlock Breath Analyzer	Alcohol oxidation reaction—fuel cell	Breath alcohol	Portable device
9	Gas Chromatography	Evaporation and separation of components	Bodily fluid testing	Benchtop device

No.	Device/Technique	Parameter	Type	Form Factor
10	Headspace Gas Chromatography	Evaporation and separation of components	Bodily fluid testing	Benchtop device
11	Enzymatic Blood Testing	Strip color change	Modern estimation method	Strip test
12	EtG Test	Strip color change	Modern estimation method	Strip test
13	PPG Datum Line	Changes in PPG signal—systolic and diastolic	Physiological factor analysis	PPG analysis/modern estimation method
14	Face Heat-Map Distribution	IR image analysis of the forehead and nose	Physiological factor analysis	IR in-vehicle cameras
15	Volvo SPA2 Platform	Head position	Physiological factor analysis	In-vehicle cameras
16	Bioimpedance Spectroscopy	Impedance across the body, legs, and arms	Transdermal sensor	Experimental device/benchtop
17	SCRAM CAM	Alcohol in sweat	Transdermal sensor	Wristband
18	GinerWrist TAS	Alcohol in sweat	Transdermal sensor	Wristband
19	BACtrack Skyn	Alcohol in sweat	Transdermal sensor	Wristband
20	Proof	Alcohol in sweat	Transdermal sensor	Wristband
21	Quantic Tally	Alcohol in sweat	Transdermal sensor	Wristband
22	Iontophoretic Biosensing System	Stimulated emittance of ethanol from the skin	Transdermal sensor	Tattoo sticker
23	Enzymatic Biosensors	Enzymatic redox reaction	Transdermal sensors	Transdermal sensors
24	Biosniffer	Inert gas and fluorescence	Transdermal sensors	Benchtop device
25	EtG Sensor	By-product of ethanol metabolism	Transdermal sensor	Wristband

No.	Device/Technique	Parameter	Type	Form Factor
26	ISF Sensor	Extraction of ISF	Transdermal sensor	Wristband
27	ISF Microneedle Sensor	Sensing of ethanol in the ISF	Transdermal sensors	Skin-attachable patch
28	TTT1100	Spectroscopic measurement of tissue	Optical tissue spectroscopy	Benchtop
29	TTT2500	Spectroscopic measurement of tissue	Optical tissue spectroscopy	Benchtop
30	NIR Dynamic Spectrum	Spectroscopic measurement of tissue/physiological parameter	Optical tissue spectroscopy	Algorithm
31	Autoliv	Spectroscopic measurement of exhaled air	Optical breath spectroscopy	In-vehicle module
32	WD-DPTR	Spectroscopic measurement of tissue	Optical tissue spectroscopy	Benchtop device
33	Pulse Alcometry	Absorption of light at specific wavelengths and pulse variation	Optical tissue spectroscopy	PPG adaptation
34	THC and Alcohol Saliva Sensor	Saliva content reaction with electrodes	Bodily fluid testing	Ring
35	Breast-Milk Sensing	Strip color change	Bodily fluid testing	Strip test
36	Rockley Photonics VitaSpex Pro	Spectroscopic measurement of tissue	Optical tissue spectroscopy	Wristband
37	Hair Analysis	Detection of EtG and EtPA	Modern estimation method	Laboratory test
38	Nail Analysis	Detection of EtG and EtPA	Modern estimation method	Laboratory test

As seen from **Table 1**, the field of alcohol intoxication sensing is filled with innovative methods of analyzing factors of intoxication, not exclusively changes in the concentration of ethanol biomarkers but also tracking physiological changes occurring during an intoxication episode. A great deal of attention in the literature is given to laboratory methodologies of detecting ethanol and its biomarkers through forensic analysis. These methods focus on establishing not only the intoxication level itself but also the exposure level, such as that seen in hair or nail samples, as opposed to gas chromatography blood testing. Several publications showcase the latest developments and ideas, for which the trial and experimental data are publicly available. **Table 2** and **Table 3** summarize these findings.

Table 2. Performance of the most notable experimental devices and techniques.

Author	Device/Technique	Year	Performance Summary	Reference
Widmark E.M.P.	Widmark flask	1918	First direct measure of ethanol blood concentrations	Early BrAC methods
Widmark E.M.P. et al.	EBAC equation	1924	Largely inaccurate by modern standards, error in the ranges of ±20% from true value	Widmark Flask and early BrAC methods
Brokenstein R.F. et al.	Breathalyzer (photovoltaic assay)	1961	Revolutionary device in the field of portable testing devices for intoxication, susceptible to environmental error and variance in lung volume across the population	Analysis of blood and bodily fluids
Mishra et al.	THC and ethanol saliva sensing ring	2020	Detection range: 0.1 to 1 mM (0.1 mM increments RSD of 1.5% (n = 5) Stable multianalyte sensing (THC)	Commercial BrAC device
Chen et al.	PPG datum line analysis	2018	85% identification rate 18 ms processing and identification time	Commercial BrAC device
Wang et al.	ECG and PPG analysis	2017	95% identification rate Only identifies if a subject is above 0.15 mg/dL	Commercial BrAC device
Rachakonda et al.	Multisensory steering wheel	2020	Detection between sober and intoxicated at 0.08 mg/dL Accuracy of 93%	No reference stated
Kubieck et al.	IR facial imaging	2019	No specific correlation number states Results indicate a very strong correlation between alcohol consumption and facial temperature distribution in all cases	No reference stated
Chaplik et al.	Bioimpedance spectroscopy	2019	Noticeable changes between intoxication and reference group Weak correlation with absolute impedance (r = 0.47) Sensitivity 92% Specificity 76%	Commercial BrAC device Blood-sample analysis (method unknown)

Author	Device/Technique	Year	Performance Summary	Reference
Wen-fei et al.	NIR dynamic spectrum	2011	Calibration set: R = 0.9672 Prediction set: R = 0.9384 Relative error between 0.6 and 9%, average error 3.26%	Hospital biochemical analysis
Yamakoshi et al.	Integrated sphere finger-PPG	2015	Lower SNR compared to traditional PPG acquisition method Sensitivity of 0.43 ± 0.29	No reference (Pilot Study)
Kim et al.	Iontophoretic biosensing system	2016	Correlation recorded = 0.912 High specificity for ethanol Increased accuracy of the system at higher ethanol concentrations	FDA-approved commercial BrAC device
X. Guo et al.	Wavelength-modulated differential photometry	2018	High ethanol resolution: 5–6 mg/dL Lag of 10–15 between ISF and blood ethanol Correlation between 0.96 and 0.98	Commercially available BrAC device
Lansborp et al.	Wearable enzymatic alcohol biosensor	2019	Linear sensor response between 0 and 0.05 mol/L Results of the sensor closely resemble those predicted by Widmark equation, however fall short during the decay stage, and generally underestimate ethanol readings	Widmark equation (BrAC device deemed impractical for application)
Arakawa et al.	Skin ethanol gas	2020	Strong correlation of 0.995 Range of estimation 73.9–112.1 ppb/cm^2 Results demonstrate superiority over an ordinary biosniffer Results indicate strong correlation for at least 3 distinct levels of ethanol	No reference for intoxication measure stated

Author	Device/Technique	Year	Performance Summary	Reference
Selvam et al.	EtG biochemical sensor	2016	Ethanol detection in the range of 0.001–100 ug/L Lower sensitivity at 1 ug/L with gold electrodes compared to ZnO (sensitivity of 0.001ug/L) Three distinct levels of EtG identified Correlation of 0.97	
Venugopal et al.	ISF sensor for remote continuous alcohol monitoring	2008	Generally strong correlation between 0.7203 to 0.866 Correlation between BrAc = 0.879	BrAC device and blood testing
Tehrani et al.	Microneedle ISF Lactate/Ethanol and Glucose Sensor	2022	Low cross-talk between sensing elements Correlation of 0.94	Commercially available BrAC device

Table 3. Commercially available devices for ethanol intoxication sensing.

Product	Stage in Development	Cost	Applications
Intoxilyzer (near-infrared spectroscopy)	Well established	High ($3.5k)	Forensic testing
Ljungblad et al. (Autoliv)	Prototypes in testing	—	Roadside safety
Urine alcohol test (strip)	Available to the general public	Low ($10–25)	Workstation monitoring
Gas chromatography	Gold standard	High ($50k)	Forensic analysis
Saliva alcohol sensing (strip)	Available to the general public	Low ($10–25)	Workstation monitoring
Headspace chromatography	Gold standard	High ($70k)	Forensic analysis
Breast-milk testing kits	Available to the general public	Low ($10–25)	Home and child well-being
Volvo SPA2	In testing	—	Roadside safety
SCRAM CAM	Generally available	Medium ($450 monthly)	High-risk individual monitoring
TT1100	Discontinued	—	Workstation monitoring

Product	Stage in Development	Cost	Applications
TTT2500	Commercially available	High ($300 per week)	Workstation monitoring
TT Mark III	In testing	—	Roadside safety
Rockley PhotonicsVitalSpex	First prototype release expected in 2023	—	Personal monitoring

References

1. Tavolacci, M.-P.; Berthon, Q.; Cerasuolo, D.; Dechelotte, P.; Ladner, J.; Baguet, A. Does binge drinking between the age of 18 and 25 years predict alcohol dependence in adulthood? A retrospective case–control study in France. BMJ Open 2019, 9, e026375.
2. Connor, J. Alcohol consumption as a cause of cancer. Addiction 2017, 112, 222–228.
3. Murphy, A. Reported Road Casualties in Great Britain: 2019 Annual Report; HM Department for Transport: London, UK, 2020. Available online: https://www.gov.uk/government/ (accessed on 13 March 2022).
4. Heatley, M.K.; Crane, J. The blood alcohol concentration at post-mortem in 175 fatal cases of alcohol intoxication. Med. Sci. Law 1990, 30, 101–105.
5. Rehm, J. The risks associated with alcohol use and alcoholism. Alcohol. Res. Health 2011, 34, 135–143.
6. Evans, I.; Heron, J.; Murray, J.; Hickman, M.; Hammerton, G. The Influence of Alcohol Consumption on Fighting, Shoplifting and Vandalism in Young Adults. Int. J. Environ. Res. Public Health 2021, 18, 3509.
7. The Costs of Alcohol to Society. Institute of Alcohol Studies. 2020. Available online: www.ias.org.uk|@InstAlcStud (accessed on 13 March 2022).
8. Thavorncharoensap, M.; Teerawattananon, Y.; Yothasamut, J.; Lertpitakpong, C.; Chaikledkaew, U. The economic impact of alcohol consumption: A systematic review. Subst. Abus. Treat. Prev. Policy 2009, 4, 20.
9. Borges, G.; Bagge, C.; Cherpitel, C.J.; Conner, K.; Orozco, R.; Rossow, I. A meta-analysis of acute use of alcohol and the risk of suicide attempt. Psychol. Med. 2017, 47, 949–957.
10. Olsen, R.W.; Liang, J. Role of GABAA receptors in alcohol use disorders suggested by chronic intermittent ethanol (CIE) rodent model. Mol. Brain 2017, 10, 45.
11. Chapp, A.D.; Mermelstein, P.G.; Thomas, M.J. The ethanol metabolite acetic acid activates mouse nucleus accumbens shell medium spiny neurons. J. Neurophysiol. 2021, 125, 620–627.
12. National Statistics. Adult Substance Misuse Treatment Statistics 2020 to 2021: Report; HM Office for Health Improvement & Disparities, Department of Health and Social Care: London, UK, 2021.
13. Widmark, E. Eine Mikromethode zur Bestimmung von Athylalkohol im Blut. Biochem. Z. 1922, 131, 473–484.
14. Borkenstein, R.F.; Smith, H.W. The Breathalyzer and its Applications. Med. Sci. Law 1961, 2, 13–22.
15. Dilley, J.; Nicholson, E.R.; Fischer, S.M.; Zimmer, R.; Froehlich, J.C. Alcohol Drinking and Blood Alcohol Concentration Revisited. Alcohol. Clin. Exp. Res. 2017, 42, 260–269.
16. Vonghia, L.; Leggio, L.; Ferrulli, A.; Bertini, M.; Gasbarrini, G.; Addolorato, G. Acute alcohol intoxication. Eur. J. Intern. Med. 2008, 19, 561–567.
17. Abrahao, K.P.; Salinas, A.G.; Lovinger, D.M. Alcohol and the Brain: Neuronal Molecular Targets, Synapses, and Circuits. Neuron 2017, 96, 1223–1238.
18. Thomasson, H.R. Gender Differences in Alcohol Metabolism Physiological Responses to Ethanol. In Recent Developments in Alcoholism; Springer: Berlin/Heidelberg, Germany, 2002; pp. 163–179.
19. Cederbaum, A.I. Alcohol Metabolism. Clin. Liver Dis. 2012, 16, 667–685.
20. McGuire, L.C.; Cruickshank, A.M.; Munro, P.T. Alcoholic ketoacidosis. Emerg. Med. J. 2006, 23, 417–420.

21. Sasaki, S.; Yoshioka, E.; Saijo, Y.; Kita, T.; Okada, E.; Tamakoshi, A.; Kishi, R. Relation between alcohol consumption and arterial stiffness: A cross-sectional study of middle-aged Japanese women and men. Alcohol 2013, 47, 643–649.
22. Chartier, K.G.; Karriker-Jaffe, K.J.; Cummings, C.R.; Kendler, K.S. Review: Environmental influences on alcohol use: Informing research on the joint effects of genes and the environment in diverse U.S. populations. Am. J. Addict. 2017, 26, 446–460.
23. Edenberg, H.J.; Foroud, T. Genetics and alcoholism. Nat. Rev. Gastroenterol. Hepatol. 2013, 10, 487–494.
24. Bayard, M.; McIntyre, J.; Hill, K.R.; Woodside, J., Jr. Alcohol Withdrawal Syndrome. Am. Fam. Physician 2004, 69, 1443–1450. Available online: www.aafp.org/afp (accessed on 8 August 2022).
25. Witkiewitz, K.; Litten, R.Z.; Leggio, L. Advances in the science and treatment of alcohol use disorder. Sci. Adv. 2019, 5, eaax4043.
26. Huebner, R.B.; Kantor, L.W. Advances in Alcoholism Treatment. Alcohol Res. Health 2011, 33, 295–299.
27. Piano, M.R.; Mazzuco, A.; Kang, M.; Phillips, S.A. Cardiovascular Consequences of Binge Drinking: An Integrative Review with Implications for Advocacy, Policy, and Research. Alcohol. Clin. Exp. Res. 2017, 41, 487–496.
28. Iakunchykova, O.; Averina, M.; Kudryavtsev, A.; Wilsgaard, T.; Soloviev, A.; Schirmer, H.; Cook, S.; Leon, D.A. Evidence for a Direct Harmful Effect of Alcohol on Myocardial Health: A Large Cross-Sectional Study of Consumption Patterns and Cardiovascular Disease Risk Biomarkers From Northwest Russia, 2015 to 2017. J. Am. Heart Assoc. 2020, 9, e014491.
29. Michalopoulos, G.K.; Bhushan, B. Liver regeneration: Biological and pathological mechanisms and implications. Nat. Rev. Gastroenterol. Hepatol. 2021, 18, 40–55.
30. Donohue, T.M.; Kharbanda, K.K.; Osna, N.A. Alcoholic Liver Disease: Pathogenesis and Current Management. Alcohol. Res. Curr. Rev. 2017, 38, 147–161.
31. Loconte, N.K.; Brewster, A.M.; Kaur, J.S.; Merrill, J.K.; Alberg, A.J. Alcohol and cancer: A statement of the American Society of Clinical Oncology. J. Clin. Oncol. 2017, 36, 83–93.
32. Rumgay, H.; Shield, K.; Charvat, H.; Ferrari, P.; Sornpaisarn, B.; Obot, I.; Islami, F.; Lemmens, V.E.P.P.; Rehm, J.; Soerjomataram, I. Global burden of cancer in 2020 attributable to alcohol consumption: A population-based study. Lancet Oncol. 2021, 22, 1071–1080.
