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Ethanol and its metabolites: update on toxicity, benefits and focus on
immunomodulatory effects

Running head : Toxicity, benefits and immunomodulatory effects of
ethanol

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Abstract

This article summarizes recent experimental and epidemiological data on the toxic and beneficial effects of ethanol and its metabolites (acetaldehyde), and focuses on their immunomodulatory effects. The section dealing with the toxic effects of alcohol focuses on its chronic toxicity (liver disorders, carcinogenic effects, cardiovascular disorders, neuropsychic disorders, addiction and withdrawal syndrome, hematologic disorders, reprotoxicity, osteoporosis) although acute toxicity is considered. The role of oxidative metabolism of ethanol by alcohol dehydrogenase, cytochrome P450 2E1, and aldehyde dehydrogenase, as well as the impact of genetic polymorphism in its physiopathology are also highlighted. The section dealing with the beneficial effects of low to moderate alcohol consumption (on cardiovascular system, diabetes, the nervous system and sensory organs, autoimmune diseases, and rheumatology) highlights the importance of anti-inflammatory and immunomodulatory effects in these observations. This knowledge, enriched by a focus on the immunomodulatory effects of ethanol and its metabolites, in particular on the NLRP3 inflammasome pathway, might facilitate the development of treatments that can reduce ethanol's harmful effects or accentuate its beneficial effects.

Keywords: Ethanol, alcohol, acetaldehyde, metabolism, toxicity, immunomodulation

1. The origin of alcoholic beverages

It is not known when humans discovered alcohol and its effects. One can nevertheless assume that as is often the case for the evolution of lifestyle factors, this was not a chance discovery. Given that ethanol can be produced by the fermentation of sugars contained in fruits, our ancestors may have consumed alcohol involuntarily by eating rotten (and thus fermented) fruits. In Neolithic times, the simultaneous appearance of agriculture and pottery may have markedly facilitated the exploitation of this natural phenomenon. Thus, the first traces of fermented beverages based on rice, honey and fruits (discovered in Henan Province, China) date back to the seventh millennium BC (McGovern et al. 2004).

In the 18th century, the development of new agricultural and distillation techniques led to the wide availability of spirits as consumer products. During the industrial revolution, the poor increasingly resorted to alcohol as a means of enduring their harsh working or living conditions. It was not until the end of the 18th century that alcohol addiction and alcohol abuse began to be perceived as physical and mental health problems. In his 1849 book *Alcoholismus Chronicus*, the Swedish physician Magnus Huss introduced the term “alcoholism” and described a number of alcohol-related visceral or mental illnesses. The first temperance societies were founded in the following decades, on the basis of scientific publications and literary depictions of alcoholism (such as those by the novelists Zola in France and Dickens in the UK). The first centers for treating and recovering from alcoholism were also founded at around this time (Porter 1987).

Specialist in-hospital care of alcoholic patients appeared in the 1920s; for example, Sainte-Anne psychiatric hospital (Paris, France) opened a ward in 1922. The first pharmacologic

treatment (apomorphine, with its emetic effects) was introduced in the 1930s. Disulfiram (discovered in 1948) is still prescribed today in out-patient treatment (Porter 1987). A large body of scientific research has now shed light on the pathophysiological mechanisms underlying acute and chronic alcoholism. However, there is also a growing body of evidences in favor of ethanol's beneficial effects in general and its anti-inflammatory and immunomodulatory effects in particular. These diverging characteristics mean that ethanol has a "Jekyll and Hyde" profile. Here, we review the current state of knowledge about ethanol and its harmful and beneficial effects (notably its immunomodulatory properties).

2. Search strategy

MEDLINE and PubMed databases were searched for relevant papers published in English in peer-reviewed journals between 1979 and 2019. Studies providing information about association between drinking and selected diseases or benefits, or mechanic explanation for the association were included for review.

3. The metabolism of ethanol

Given that ethanol's biological effects are closely related to its metabolism, knowledge of the latter is essential for understanding the associated pathophysiological mechanisms (Figure 1). In the first part of this section, we consider the metabolism of ethanol to acetaldehyde. In the second part, we look at the production of acetate from acetaldehyde.

Cytosolic alcohol dehydrogenase (ADH) is the major enzyme responsible for the phase I oxidative metabolism of ethanol, producing acetaldehyde and reduced nicotinamide adenine

1 dinucleotide (NADH) (Cederbaum 2012). The enzyme is predominantly expressed by
2 hepatocytes but is also found in the gastrointestinal tract, lung and kidneys (Crabb 1995;
3 Edenberg 2000). In humans, seven genes (*ADH1* to *ADH7*) code respectively for ADH's
4 different subunits (α , $\beta 1$, $\beta 2$, $\beta 3$, $\gamma 1$, $\gamma 2$, π , χ , σ , and μ) (Cederbaum 2012). These subunits
5 bind together in pairs to form isoenzymes classified into five classes (ADH class I to ADH
6 class V), depending on their enzymatic proprieties (Crabb 1995). Class I ADH (formed from
7 subunits encoded by *ADH1*, *ADH2* and *ADH3*) has a crucial role in alcohol metabolism. Even
8 though polymorphisms in ADH isoenzyme have been described, they do not appear to be
9 linked to a particular alcohol-related disease or change in alcohol metabolism. However, some
10 researchers have reported that alcohol is eliminated more slowly in the fasted state than in the
11 fed state because of decreased ADH levels (Cederbaum 2012).

12
13 The microsomal pathway (involving the cytochrome P450 (CYP) family) is responsible for
14 about 10% of the body's ethanol metabolism (Hamitouche et al. 2006). Even though CYP1A2
15 and CYP3A4 are known to be involved, CYP2E1 is considered to be the main CYP in the
16 first phase of ethanol metabolism (Kunitoh et al. 1996; Cederbaum 2012). This oxidative
17 metabolic pathway takes place in the endoplasmic reticulum of hepatocytes. Using NADPH
18 and oxygen, CYP2E1 converts ethanol into acetaldehyde and then acetaldehyde into acetate.
19 The conversion of ethanol into acetaldehyde produces reactive oxygen species (ROS), which
20 notably contribute to alcohol's toxicity (Ekström and Ingelman-Sundberg 1989). Furthermore,
21 ethanol upregulates its own metabolism by protecting CYP2E1 from ubiquitination and
22 degradation by the proteasome complex (Zhukov and Ingelman-Sundberg 1999; Lu and
23 Cederbaum 2008). This mechanism results in an elevated levels of CYP2E1 in hepatocytes,
24 and is considered to have a major role in the ethanol tolerance seen in chronic alcohol users
25 (Cederbaum 2012).

Catalase (an enzyme found in peroxisomes) is also known to metabolize alcohol. However, hepatic catalase does not have a significant role in ethanol metabolism. In contrast, brain catalase appears to be involved in alcohol tolerance and positive reinforcement (Cederbaum 2012).

Figure 1 near here

Other minor phase II non-oxidative metabolic pathways for ethanol include glucuronidation (giving rise to ethylglucuronide) and sulfation (giving rise to ethylsulfate). Phosphatidylethanol and fatty acid ethyl esters (respectively produced by phospholipase D and fatty acid ethyl ester synthase) also contribute to the non-oxidative metabolism of ethanol (Pichini et al. 2009; Cederbaum 2012; Schröck et al. 2018).

The acetaldehyde generated by these metabolic pathways is then oxidized by aldehyde dehydrogenase (ALDH) to form acetate. In humans, the ALDH superfamily of NAD⁺-dependent enzymes is encoded by 16 genes. The cytosolic ALDH1 and mitochondrial ALDH2 isoenzymes are those primarily involved in ethanol metabolism (Vasiliou and Pappa 2000). In contrast to ADH, polymorphisms appears to have a greater influence on ALDH activity. The *ALDH2*1* allele (known to code for a highly active variant) is considered to protect against liver disease in alcoholism, whereas the enzyme encoded by *ALDH2*2* allele is an inactive enzyme (Cederbaum 2012). Furthermore, chronic ethanol consumption lowers ALDH and increases the acetaldehyde level (Lin et al. 1984). Acetate is not the final metabolite in this pathway because it be converted into CO₂, fatty acids, ketones, cholesterol or steroids (Cederbaum 2012).

The activity of the various isoforms of ADH and ALDH regulates acetaldehyde concentrations, and constitutes a risk factor in the development of alcoholism (Agarwal and Goedde 1989). Indeed, the effects of ethanol intolerance (such as nausea, dysphagia, headache, and the vasodilation responsible for facial flush in particular) have been attributed to the concentration of acetaldehyde. The accumulation of this metabolite in individuals with inactive or poorly active ALDH isoenzymes may explain the cultural barriers to drinking large amounts of alcohol seen in some societies, which thus protect against alcoholism. This is particularly the case in eastern Asia, where 15-40% of the population have inactive ALDH2 isoenzymes and thus acetaldehyde levels that are 5 to 20 times higher than in individuals with active isoenzyme (Cederbaum 2012).

4. The toxicity of ethanol

According to the World Health Organization, alcohol consumption is a causal factor in more than 60 major types of diseases and injuries, and results in approximately 2.5 million deaths each year (World Health Organization 2011). Thus, approximately 4.5% of the global burden of disease and injury is attributable to alcohol. Furthermore, this morbidity and mortality caused by alcohol consumption has socioeconomic impacts, including the medical costs borne by governments, and the financial and psychological burden to families (World Health Organization 2011). By convention, ethanol's toxicity is subdivided into acute toxicity and chronic toxicity. Here, we review the main acute and chronic outcomes of ethanol consumption, and describe the relationship between dose and overall mortality.

3.1 Overall mortality as a function of dose

Many researchers have reported that low levels of alcohol intake are associated with a lower risk of mortality (Keller 2016). Jayasekara et al.'s (2014) meta-analysis of 62,950 study participants found that ethanol's protective effect is observed for intakes of 1 to 29 g/day (corresponding to zero to three standard units of alcohol per day), with a relative risk (RR) [95% confidence interval (CI)] of 0.90 [0.81, 0.99]. Conversely, alcohol consumptions of between 30 to 59 g/day and over 60 g/day were associated with an RR [95%CI] of mortality of 1.19 [0.89, 1.58] and 1.52 [0.78, 2.98], respectively (Jayasekara et al. 2014). In a study of 380,395 people, Bergmann et al. (2013) found that limiting alcohol consumption to below five alcoholic units per day was associated with a lower risk of death (mainly due to less cardiovascular disease), whereas the consumption of five or more alcoholic drinks per day was associated with a 2- to 5-fold greater risk of death (mainly due to alcohol-related cancer) (Bergmann et al. 2013). A meta-analysis linking moderate ethanol consumption to lower all-cause mortality was consistent with these results (Gmel et al. 2003; Di Castelnuovo 2006).

Despite the growing body of evidence for a protective effect of low to moderate alcohol consumption, the results are subject to debate. For example, Goulden et al.'s (2016) study of 24,029 individuals over the age of 50 years did not reveal an association between all-cause mortality and moderate alcohol consumption (Goulden 2016). Likewise, a recent study of 28 million individuals found that all-cause mortality rose with increasing levels of consumption; the researchers concluded that the level of alcohol consumption minimizing health loss is zero (Griswold et al. 2018).

1 Thus, the evidence is inconclusive as to whether moderate alcohol consumption has a
2 protective effect. However, all researchers agree that excessive alcohol consumption increases
3 all-cause mortality. The dose at which excess mortality is observed varies from one study to
4 another but ranges from 30 to 40 g/day - corresponding to three to four standard units of
5 alcohol (Bergmann et al. 2013; Jayasekara et al. 2014).

7 **3.2 Acute toxicity**

8
9 The clinical manifestations of acute alcohol intoxication are well known, and are closely
10 related to those of alcoholism. The initial neuropsychic symptoms (intellectual and psychic
11 excitation) are followed by a cerebellar syndrome accompanying marked drunkenness, and
12 then by a variably deep coma that may be life-threatening (through paralysis of the respiratory
13 centers) (Wimer et al. 1983; Girre et al. 1995).

14
15 In humans, the first symptoms (decreased motor coordination, longer reaction time, and
16 impaired judgment) can be observed at a blood alcohol concentration of 0.2 g/L. These effects
17 disappear quickly after the end of the exposure (Bismuth et al. 2000). Curiously, the acute
18 intoxicant effects of a given blood alcohol concentration are more intense when the level is
19 rising than when it is falling (the so-called “Mellanby effect”). By extension, this term is used
20 to refer to the phenomenon of rapid ethanol tolerance because the neuropsychic effects are
21 less intense when the concentration is falling (Wang et al. 1993; Holland and Ferner 2017).

22
23 Ethanol’s depressant neuropsychic effects have been well documented, and are related to the
24 compound’s interaction with gamma-aminobutyric acid (GABA)-A receptors (Davies 2003).
25 These receptors belong to a family of ligand-dependent transmembrane ion channels that

enable rapid neuronal responses within the mammalian central nervous system. Most GABA-A receptors are postsynaptic, although some subtypes are located outside the synapses (Davies 2003).

In addition to these effects on GABA-A receptors, ethanol antagonizes N-methyl-D-aspartate receptors, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, and kainate receptors (Valenzuela et al. 1998; Läck et al. 2008). Since glutamate is an excitatory neurotransmitter, blockade of these receptors heightens ethanol's depressant action on the central nervous system (Hoffman et al. 1989). Lastly, ethanol has also been shown to interact with glycine receptors, neuronal nicotinic receptors, and serotonin type 3 receptors (Davies 2003; Ding et al. 2015).

3.3 Chronic toxicity

Chronic ethanol exposure is toxic for many different organs, and notably affects the digestive tract (steatosis, hepatic cirrhosis, chronic gastritis, and pancreatitis), the nervous system (polyneuritis, cerebellar atrophy, and memory disorders) and the cardiovascular system. Ethanol also has chronic hematologic, carcinogenic and reprotoxic effects. In the following section, we review the pathophysiological effects of ethanol and its metabolites on these various organ systems.

3.3.1 Liver disorders

In the early stages of ethanol-related liver disease, the ROS generated by ethanol metabolism are responsible for a rapid increase in the fluidity of the hepatocyte cell membrane. In turn,

1 this leads to elevated cytoplasmic levels of low-molecular-weight iron and thus even greater
2 ROS production. This phenomenon can then induce lipid peroxidation and apoptosis (Sergent
3 et al. 2005).

4
5 Liver injury due to ethanol can be divided into three phases. The first phase (hepatic steatosis)
6 involves the accumulation of lipids in hepatocytes. It is relatively benign, and usually
7 reversible. The pathophysiology of steatosis is closely related to the oxidative metabolism of
8 ethanol. By inducing lipolysis in adipocytes, chronic alcohol consumption increases the
9 fraction of free fatty acids captured by the liver (Wei et al. 2013; Osna et al. 2017).
10 Furthermore, acetaldehyde increases the expression of sterol regulatory element-binding
11 protein transcription factor which upregulates lipogenesis genes (Osna et al. 2017).

12
13 In the second phase, steatohepatitis follows steatosis. The lipids accumulated in the
14 hepatocytes undergo peroxidation and oxidative damage. Complex interactions involving the
15 effects of acetaldehyde, ROS, intestinal lipopolysaccharide-mediated lesions and endoplasmic
16 reticulum stress are responsible for infiltration of the liver by immune system cells (such as
17 neutrophils) and activation of Kupffer cells (the liver's resident macrophages) (Osna et al.
18 2017). The resulting massive release of pro-inflammatory cytokines is directly responsible for
19 hepatocyte death and the maintenance of alcoholic hepatitis (Duddempudi 2012).

20
21 The third phase reflects the fibrotic progression of inflammatory steatohepatitis. The
22 regeneration of hepatocytes is severely compromised, and hepatic lesions lead to the
23 activation of hepatic stellate cells - the main sources of extracellular matrix deposition that
24 characterizes fibrosis. The progression of fibrosis during ethanol-induced chronic
25 inflammation leads to the progressive replacement of the hepatic parenchyma by scar tissue,

1 which compromises the liver's metabolic and homeostatic functions (Osna et al. 2017).
2 Ultimately, severe complications develop, such as hepatocellular carcinoma - the second
3 leading cause of cancer death – and portal hypertension (Grewal and Viswanathen 2012; Zhou
4 et al. 2016).

5 6 3.3.2 Carcinogenic effects

7
8 According to Seitz and Stickel (2007), 3.6% of cancers worldwide are due to chronic alcohol
9 consumption. This causal relationship is particularly strong for tumors of the upper digestive
10 tract (such as cancers of the mouth, pharynx, larynx and esophagus), liver tumors, colonic
11 tumors, and breast tumors (Seitz and Stickel 2007; Zhou et al. 2016).

12
13 Once again, acetaldehyde has been incriminated in the pathophysiology of these cancers.
14 Indeed, this initial metabolite of ethanol can bind to proteins and alter their structures and
15 functions - particularly for enzymes involved in DNA repair and glutathione (Garro et al.
16 1986). Furthermore, acetaldehyde can bind to DNA and form adducts (Wang et al. 2000).
17 Lastly, carriers of an allele coding for inactive ALDH2 * 2 have an increased risk of
18 esophageal cancer, due to overexposure to this metabolite (Seitz and Stickel 2007).

19
20 Thus, the mechanisms of ethanol-induced hepatocarcinogenesis are closely related to
21 ethanol's metabolic pathways; they involve the induction of hepatic cirrhosis, increased
22 oxidative stress, and alterations in methylation. Lastly, retinoic acid (which is essential for
23 proliferation and cell differentiation) is metabolized abnormally after CYP2E1 expression has
24 been upregulated by ethanol (Seitz and Stickel 2007).

1 In chronic alcohol users, a meta-analysis found that the risk of breast cancer increase with a
2 dose-response relation giving a relative risk of 1.11 (CI = 1.07-1.16), 1.24 (CI = 1.15-1.34),
3 and 1.38 (CI = 1.23-1.55) with the consumption of one, two or three drinks a day respectively
4 (Longnecker 1994). This risk is linked to the ethanol-induced increase in estradiol levels.
5 Since steroid hormones, including estrogens are metabolized by ADH (McEvily et al. 1988),
6 the effect might be due to competition between estrogen and ethanol, resulting in impaired
7 metabolism of estrogens (Seitz and Stickel 2007; Al-Sader et al. 2009). These data are
8 supported by Hines et al. (2000) findings, showing a positive correlation between alcohol
9 consumption and bioavailable estradiol in a prospective study involving 1086 individuals
10 (Hines et al. 2000). In addition, ethanol can stimulate the transcriptional activity of estrogen
11 receptor in human breast cancer cells which is related to increased breast cancer risk (Fan et
12 al. 2000).

13
14 Furthermore, ethanol alters methyl group transfers. Gene methylation is crucial in the
15 regulation of gene expression: hypermethylation tends to decrease gene expression, whereas
16 hypomethylation increases it. Thus, the induction of oncogenes or the repression of tumor
17 suppressor genes appear to be key steps in ethanol-induced cancer. These mechanisms would
18 be associated with frequent malnutrition of alcoholics, leading to vitamins deficiencies (folate,
19 vitamin B6), which are co-factors of methyl group transfer. Conversely, an excess of vitamin
20 A has been associated with an increased risk of alcohol-associated tumours (Seitz and Stickel
21 2007).

22
23 Lastly, the results of animal experiments have shown that a large amount of acetaldehyde is
24 produced by colonic bacteria after alcohol consumption (Jokelainen et al. 1996). Furthermore,

elevated colonic acetaldehyde concentrations (due to the inhibition of ALDH) have been linked to the induction of colonic carcinogenesis (Seitz et al. 1990).

3.3.3 Cardiovascular disorders

High-dose ethanol consumption has been linked to various cardiovascular disorders, such as hypertension, atrial fibrillation, atherosclerosis, and alcoholic cardiomyopathies (Girre et al. 1995; Bismuth et al. 2000; Zhou et al. 2016; Obad et al. 2018).

Although the mechanisms underlying this toxicity are not fully understood, the metabolites of ethanol seem to be intricately involved. Indeed, myocardial damage appears to be associated with acetaldehyde accumulation (Guo et al. 2012). The stress imposed on myocytes by the increase in pro-inflammatory cytokines, ROS, mitochondrial dysfunctions and endoplasmic reticulum stress are known to be involved in myocyte hypertrophy, which in turn is responsible for altering the heart's contractile performance (Machackova et al. 2006). The cardiovascular events associated with excessive alcohol consumption can therefore lead to cardiac arrest (Haddad et al. 2008). The pathophysiological mechanisms potentially involved in cardiovascular disease are summarized in Table 1.

Table 1 near here

3.3.4 Neuropsychic disorders

The toxic effects of ethanol and its metabolites on brain tissue vary according to the region of the brain, age, the dose, and the duration of exposure. Both neurons and glial cells are

1 affected. The major complications include alteration of astrocyte and oligodendrocyte
2 functions, resulting in reduced synaptogenesis and cell survival.

3
4 The diencephalon, cerebral cortex, hippocampus, and white matter corresponding to myelin,
5 are also targets for the toxicity of ethanol and its metabolites. This toxicity results in atrophy
6 of the brain, although the underlying mechanism is not yet fully understood (de la Monte
7 1988; Bühler and Mann 2011; Konrad et al. 2012). These various neurotoxic consequences
8 are aggravated by the thiamine (vitamin B1) deficiency caused by ethanol's inhibition of its
9 absorption and physiological action (Vetreno et al. 2011).

10
11 Furthermore, there is growing evidence of a link between the alcohol-induced loss of liver
12 function and neurotoxicity. Firstly, reduced ethanol metabolism in the liver is responsible for
13 overexposure of the brain to this toxic compound. Secondly, liver damage leads to the
14 production of metabolic and inflammatory mediators that damage the brain. This relationship
15 is most notable in the context of hepatic encephalopathy (De la Monte et al. 2009; Chen et al.
16 2012). Lastly, by jeopardizing the tight junctions of the intestinal mucosa, ethanol allows
17 lipopolysaccharide (a gram-negative bacterial endotoxin) to enter systemic circulation. As a
18 result, lipopolysaccharide binds to TLR4 receptors on liver macrophages and promotes pro-
19 inflammatory response via cytokines, chemokines, proteases and ROS production. These
20 cytokines are known to cross the blood brain barrier and activate the brain's resident
21 macrophages (microglia), increasing neurotoxicity (Mayfield et al. 2013).

22
23 In light of these effects, it is not surprising that chronic alcohol consumption is responsible for
24 severe cognitive impairment, including dementia. The most common types of alcohol-related
25 dementia are Wernicke-Korsakoff syndrome and Marchiafava-Bignami disease (Charness

1993; Victor 1994). Today, the frontal, cerebellar and/or temporal brain atrophy induced by ethanol consumption can be readily detected by medical imaging techniques (Matsui et al. 2012).

3.3.5 Addiction and withdrawal syndrome

In the field of addiction, "conventional" products act on a specific target: opiate receptors for heroin, cannabinoid CB1 receptors for cannabis, nicotinic receptors for tobacco, and monoamine transporters for cocaine (Hamon 2014). In contrast, ethanol acts on many levels. As mentioned above, ethanol facilitates GABAergic transmission via GABA-A receptors and decreases glutaminergic neurotransmission (Hoffman et al. 1989; Valenzuela et al. 1998; Läck et al. 2008; Uusi-Oukari and Korpi 2010).

Like other addictogenic compounds, alcohol activates the reward circuit and thus the release of dopamine into the mesocorticolimbic system. This system consists of dopaminergic neurons whose cell bodies are located in the ventral tegmental area and whose axons project into the nucleus accumbens, amygdala, and frontal cortex (Inserm 2012). Although dopamine has a key role in the mechanism of dependence, other neurotransmitters (such as GABA, glutamate, serotonin, norepinephrine, and opioid peptides) are also involved (Inserm 2012).

The repeated intake of alcohol leads to tolerance and adaptive processes that decrease the effectiveness of GABAergic neurotransmission and facilitate glutaminergic neurotransmission. In turn, these processes lead to neuronal hyperexcitability - a characteristic of alcohol dependence (Hamon 2014).

1 The respective roles of ethanol and its metabolites in the mechanism of alcohol addiction are
2 still unclear but acetaldehyde has its own psychoactive effects and rewarding proprieties
3 (Brancato et al. 2017).

4 Chronic exposure to ethanol results in higher membrane levels of saturated fatty acids and
5 cholesterol, which decrease the membrane's fluidity (i.e. the opposite of the fluidifying effects
6 of acute ethanol consumption on the hepatocyte membrane described above). As a result, a
7 sharp decrease in alcohol consumption causes temporary membrane hyper-rigidity and
8 disrupts cellular homeostasis (Littleton 1998). In cases of sudden alcohol withdrawal, clinical
9 alcohol withdrawal syndrome is characterized by hypertension, tachycardia, hallucinations,
10 agitation, fever, tremor, seizures, and hyperexcitation, and may progress to delirium tremens
11 (Tetrault and O'Connor 2008).

13 *3.3.6 Hematologic disorders*

15 Several hematological disorders are promoted or accentuated by alcohol consumption:
16 leukopenia, anemia, thrombocytopenia, myelodysplasia, and acute leukemia (Girre et al.
17 1995; Bismuth et al. 2000). Recently, Smith et al. (2015) hypothesized that an ALDH
18 polymorphism predisposes to these hematological disorders. Since the ALDH1A1 isoform
19 protein is present in hematopoietic stem cells, overexposure to acetaldehyde may explain the
20 increased risk of impaired hematopoiesis associated with the inhibition of DNA repair (Smith
21 et al. 2015).

3.3.7 Reprotoxicity

Ethanol consumption disrupts the menstrual cycle in women and decreases male fertility, including testicular atrophy, reduced libido, and decreased testosterone. Furthermore, a decrease in the likelihood of a clinical pregnancy per cycle was observed from five units per week upwards (Council of the Netherlands 2000; ANSES 2010).

During pregnancy, ethanol consumption is responsible in a dose-dependent manner for multiple congenital anomalies, such as growth restriction, central nervous system impairments, and malformations. These manifestations are referred to collectively as fetal alcohol syndrome (FAS), and give rise to a particular facies with narrow palpebral fissures, a flat mid-face, a short nose, a smooth philtrum, a thin upper lip, epicanthus, a flat nasal bridge, minor ear abnormalities, and micrognathia (Wattendorf and Muenke 2005).

The pathogenesis of FAS is related to the pharmacokinetics and metabolism of ethanol. It is well known that ethanol crosses the placenta, and distributes into the fetal compartment. Furthermore, ethanol is eliminated slowly by the fetus, leading to greater exposure (Heller and Burd 2014). Furthermore, several characteristics make the fetus more fragile to alterations in oxidative metabolism. CYP2E1 protein is produced earlier than ADH during gestation (Hines and McCarver 2002; Arfsten et al. 2004), and the induction of placental CYP2E1 by ethanol (Rasheed et al. 1997) means that CYP becomes the major metabolic pathway for ethanol. Ethanol's teratogenic effects are thought to be due to ROS production (leading to mitochondrial damage, brain lipid peroxidation, and a decrease in endogenous antioxidant levels), apoptosis (leading to disrupted neuron-neuron adhesion), placenta vasoconstriction, and inhibition of cofactors required for fetal growth and development (Gupta et al. 2016).

1
2 Acetaldehyde is also directly involved in the induction of FAS. It is now known that retinoic
3 acid regulates various embryonic and differentiation processes (Shabtai and Fainsod 2018).
4 However, retinoic acid is obtained from retinaldehyde, which itself is obtained from vitamin
5 A. Through competition with retinaldehyde dehydrogenase, acetaldehyde inhibits the
6 production of retinoic acid and leads to characteristics developmental malformations (Shabtai
7 and Fainsod 2018; Shabtai et al. 2018). Furthermore, the administration of acetaldehyde to
8 pregnant mice had teratogenic effects – suggesting that this metabolite of ethanol has a direct
9 role (O'Shea and Kaufman 1979).

10
11 Maternal consumption of 10 to 20 g of alcohol per day (corresponding to one to two standard
12 units) has been shown to induce intellectual and behavioral delays – especially if the infant is
13 breastfed (Bonnard et al. 2011).

14 15 3.3.8 Osteoporosis

16
17 It is well known that chronic high-level ethanol consumption is associated with osteoporosis
18 and osteoporotic fractures (Diamond et al. 1989; Schapira 1990). The underlying mechanism
19 has been linked to elevated p21 expression, which suppresses osteoblast differentiation and
20 mineralization and disturbs remodeling (Maurel et al. 2012; Mikosch 2014). Furthermore, the
21 observation that protein-disrupting ALDH2 polymorphisms accentuate this toxicity suggests
22 that acetaldehyde has a direct role (Shimizu et al. 2011; Tsuchiya et al. 2013).

23
24 Figure 2 near here

1 It is now clear than acetaldehyde and oxidative stress generated by ethanol metabolism have
2 key roles in the pathophysiology underlying alcohol's various toxic effects. The molecular
3 and pathophysiological effects of acetaldehyde are summarized in Figure 2. Thus,
4 acetaldehyde appears to have only harmful effects, whereas ethanol's effects are both
5 beneficial and harmful.

6 7 **5. Benefits of ethanol**

8
9 Despite Burton et al.'s (2018) statement that "no level of alcohol consumption improves
10 health" (Burton and Sheron 2018) and the many harmful effects of ethanol consumption, it
11 nevertheless appears that light to moderate alcohol consumption does have beneficial effects.

12 ***4.1 The cardiovascular system***

13
14 There is evidence of an inverse correlation between low to moderate alcohol consumption
15 (corresponding to one to two units per day) and mortality from cardiovascular disease; this
16 gives rise to the "French paradox" (Albert et al. 1999; Belleville 2002; Ronksley et al. 2011).
17 However, high alcohol consumption increases the risk of mortality from other causes and
18 wipes out the beneficial effects - giving results in a "J" shaped curve for the relationship
19 between mortality and alcohol consumption (Klatsky et al. 1992). At present, there is no
20 consensus on whether the protective cardiovascular effects of ethanol are restricted to one or
21 more types of alcoholic beverage drink (i.e. wine, beer or spirits) (Bau et al. 2007). However,
22 many studies have found that wine had a greater beneficial effect on cardiovascular events.
23 Rodrigues et al. (Rodrigues et al. 2018) found that wine consumption was associated with less
24 harmful findings in cardiac structure. Wine's particular protective effect is linked to the anti-
25 inflammatory, antioxidant and hypotensive properties of polyphenols (Das et al. 2007; Arranz

et al. 2012). In parallel, ethanol *per se* has been linked to elevated high-density lipoprotein (HDL) cholesterol levels, reduced low-density lipoprotein (LDL) cholesterol levels, and reduced blood coagulation (Agarwal 2002). Moderate long-term alcohol consumption was also found to be associated with low blood triglyceride levels and elevated lipoprotein lipase activity (Kovář and Zemánková 2015). A review of wine's metabolic effects has been published (Markoski et al. 2016).

Gil-Bernabe et al. (Gil-Bernabe et al. 2011) found that moderate alcohol consumption reduces atherosclerosis by regulating fibroblasts' production of CXCL12 (stromal cell-derived factor-1). Furthermore, Nurmi et al.'s (2013) work on the underlying pathophysiological mechanisms prompted the suggestion that the NLRP3 inflammasome is a key player in the protective cardiovascular effect of moderate alcohol consumption. Indeed, acute exposure to ethanol was found to inhibit the NLRP3 inflammasome in macrophages, leading to an anti-inflammatory effect (Nurmi et al. 2013). These results were confirmed by Hoyt et al. (2016) (Hoyt et al. 2016).

The procyanidin compounds in wine have also been found to inhibit the NLRP3 inflammasome; this suggests that wine has a stronger anti-inflammatory effect than other beverages. Given the presence of many pharmacologically active compounds other than ethanol in alcoholic beverages, it is hard to predict the effects of these mixtures (Liu et al. 2017).

4.2 Diabetes

The positive impact of moderate alcohol consumption on the cardiovascular system appears to be coupled with beneficial effects on diabetes mellitus. In Knott et al.'s (2015) meta-analysis

of 1,902,605 participants, consumption of less than 63 grams of alcohol per day in women and in non-Asian populations was associated with a decrease in the risk of developing type 2 diabetes mellitus (Knott et al. 2015). The risk of diabetes increased for alcohol consumption levels above this threshold. In mechanistic terms, some researchers have attributed these observations to a decrease in fasting insulin concentrations, an increase in the insulin sensitivity in moderate alcohol consumers (Kawamoto et al. 2009; Schrieks et al. 2015; Zhou et al. 2016) and an increase of estradiol in women (Rohwer et al. 2015). Furthermore, alcohol consumption appears to have beneficial effects on lipid metabolism by raising levels of HDL and apolipoproteins A1 and A2 (Fragopoulou et al. 2018). However, these findings must be considered with caution since detailed mechanisms are still poorly understood (Polsky and Akturk 2017). Moreover, alcohol consumption, even moderate, is associated with impaired self-care behavior including glucose self-monitoring and exercise (Howard et al. 2004; Engler et al. 2013). Lastly, interactions are well known between alcohol and diabetes medications such as sulphonylureas for which the risk of hypoglycemia is increased (Shai et al. 2004).

4.3 The nervous system and sensory organs

4.3.1 Neuroprotection and dementia

Interestingly, ethanol appears to have a neuroprotective effect. For example, Tizabi et al.'s (2017) studies in *in vitro* models of Parkinson's and Alzheimer disease evidenced a protective effect of low ethanol consumption (Tizabi et al. 2018). The underlying mechanisms were related to low levels of pro-inflammatory cytokines (TNF- α and IL-1 β) and elevated levels of brain-derived neurotrophic factor and the anti-inflammatory cytokine IL-10 - resulting in greater neuroplasticity and neuroprotection. Furthermore, preclinical studies in an animal

model have shown that a low blood ethanol concentration has an antidepressant effect (Müller et al. 2017).

In a broader context, a recent prospective study of 9,087 participants aged between 35 and 55 at baseline found that moderate alcohol consumption was associated with a lower risk of dementia. Over the 23-year study, teetotalers and those who consumed more than 14 units of alcohol per week had a higher risk of dementia (hazard ratio [95%CI] = 1.47 [1.15; 1.89]). People consuming between one and 14 units of alcohol per week were therefore protected against this risk (Yasar 2018). These results were supported by those of Perters et al. (Peters et al. 2008).

Consistently, Paganini-Hill et al. (2016) found that moderate drinkers participating in the 90+ Study presented a decreased risk of dementia (Paganini-Hill et al. 2016).

4.3.2 Chronic pain

On the same lines, Scott et al.'s study (2018) of 2583 patients with chronic pain found that moderate alcohol consumption was associated with lower pain levels, fewer painful body areas, and less intense somatic and mood symptoms (Scott et al. 2018). Physical function also appeared to be improved by moderate alcohol consumption (Scott et al. 2018).

4.3.3 Anxiolytic effects

As mentioned above, ethanol depresses the central nervous system by interacting with GABA and N-methyl-D-aspartate receptors. This depressant effect triggers an anxiolytic effect and

behavioral disinhibition at ethanol blood concentrations between 5 to 10 mM, with an effect on the hippocampus and the amygdala in particular (Harrison et al. 2017). Interestingly, ethanol's anxiolytic effects (i.e. making people more likely to start a conversation) have been linked to language abilities. Indeed, consumption of a small amount of ethanol was found to have beneficial effects on the pronunciation of a recently learned foreign language (Renner et al. 2018).

4.4 Autoimmune diseases

Of all ethanol's beneficial effects, those affecting the immune system are the least well understood, and there is no consensus on the pathophysiologic mechanisms. The following section summarizes the literature data in this field.

4.4.1 Rheumatoid arthritis

In Di Giuseppe et al.'s 2012 study of 34,141 women (197 of whom presented with rheumatoid arthritis), the consumption of at least three units of alcohol per week halved the incidence of the disease (relative to teetotalers) (Di Giuseppe et al. 2012). Consistently, a 2014 meta-analysis found that low to moderate alcohol consumption in women prevents the onset of rheumatoid arthritis in a time-, dose- and sex-dependent manner (Jin et al. 2014). Even after the development of rheumatoid arthritis, the effects of alcohol consumption should still be considered - especially for the avoidance of drug interactions. According to the results of a study published in 2008, alcohol consumption does not increase the hepatic toxicity of methotrexate and leflunomide - both of which are widely prescribed to patients with rheumatoid arthritis. Hence, the British Society for Rheumatology guidelines suggests that alcohol consumption well within national limits is appropriate (Rajakulendran et al. 2008).

Furthermore, the frequent consumption of low amounts of alcohol was found to interact with the innate immune response by delaying the onset and stopping the progression of collagen-induced arthritis (Jonsson et al. 2007).

4.4.2 Systemic lupus erythematosus

Two studies have reported that alcohol has beneficial effects in patients with systemic lupus erythematosus; the consumption of no more than 30 units per week was inversely correlated with the development of this disease (Nagata et al. 1995; Hardy et al. 1998).

4.4.3 Thyroid disorders

Alcohol consumption was found to protect against the development of autoimmune hypothyroidism, independently of sex or the type of alcoholic beverage (Carle et al. 2012). Interestingly, Carlé et al. (2013) also reported that moderate alcohol consumption is associated with a dose-dependent reduction in the risk of developing of Grave's hyperthyroidism (Carlé et al. 2013).

Ethanol's beneficial action on the symptoms of these autoimmune diseases highlights an interesting spectrum of immune effects. However, alcohol does not appears to be of value in all immune diseases, for example, Skaaby et al. (2018) did not observe a causal relationship between alcohol consumption and the prevalence of asthma or allergic disease (Skaaby et al. 2018).

4.5 Rheumatology

Over the last few decades, several studies have described beneficial effects of ethanol on bone mineral density in general and in the trochanteric region of the proximal femur in particular (Angus et al. 1988; Holbrook and Barrett-Connor 1993). Furthermore, Felson *et al.* found that at least 7 oz/week (approximately 200 mL/week) of alcohol was associated with high bone density in postmenopausal women. The researchers concluded that these results might be related to the elevated endogenous estrogen levels induced by ethanol, and ruled out a direct effect of alcohol (Felson et al. 1995). Consistent with these results, Ganry et al.'s analysis of the "Epidémiologie de l'Ostéoporose" (EPIDOS) study found that trochanteric bone mineral density was higher in elderly women with moderate alcohol consumption (one to three glasses of wine per day) than in teetotalers (Ganry et al. 2000).

4.6 Cancer

Although alcohol is known to be a carcinogenic agent in humans (see above), moderate wine consumption may decrease the risk of several cancers (including colon, lung, ovarian and prostate cancer, basal cell carcinoma, and esophageal adenocarcinoma) (Bianchini and Vainio 2003; Schoonen et al. 2005; Anderson et al. 2009; Klarich et al. 2015; Zhou et al. 2016). These properties are mostly related to resveratrol, an antioxidant agent that inhibits the metabolic activation of carcinogens, decreases cell proliferation, induces apoptosis and exerts anti-inflammatory effects. The mechanisms underlying the beneficial effects of ethanol are summarized in Table 2.

Table 2 near here

6. The immunomodulatory effects of ethanol

Alcohol has contrasting effects on the body. Most of alcohol's toxic effects are linked to acetaldehyde (the first oxidative metabolite of ethanol), whereas most of its beneficial effects appear to be related to the properties of ethanol *per se*. Thus, ethanol can be likened to Robert Louis Stevenson's literary character Dr Jekyll, with acetaldehyde as Mister Hyde.

Of all ethanol's effects on the body, those on the immune system are particularly contrasting: the adverse effects are associated with pro-inflammatory activities, whereas the beneficial effects are associated with anti-inflammatory activities (in cardiovascular disease, cancer, and neuroprotection) and immune system modulation (in rheumatoid arthritis, systemic lupus erythematosus, hyperthyroidism, and hypothyroidism).

The immune system is conventionally divided into innate and adaptive mechanisms, and alcohol is known to influence both. Barr et al.'s (2016) reviews of the effects of ethanol on the immune system found that ethanol had dose-dependent effects on adaptive immune responses; moderate alcohol consumption increased T and B lymphocyte counts, whereas chronic heavy consumption was associated with a falls in cell counts (Barr et al. 2016). In addition, McClintick et al. (2019) showed that ethanol exposure on lymphoblastoid cells induces a robust immune response after 24 hours exposure (including neuroinflammation and K κ B pathway, IL-6, IL-2 and IL-8 activation), but decreased in intensity after 48 hours exposure (partially explained by a reversal of interferon signaling) (McClintick et al. 2019). Furthermore, some researchers have reported that moderate alcohol consumption is associated with lower levels of immunoglobulins G, M and A (Gonzalez-Quintela et al. 2007; Romeo et al. 2007). These findings may explain the above-mentioned beneficial effect of low to

1 moderate alcohol consumption on autoimmune diseases such as rheumatoid arthritis, systemic
2 lupus erythematosus, hyperthyroidism, and hypothyroidism.

3
4 In contrast, ethanol's harmful and beneficial effects on the cardiovascular system, nervous
5 system, rheumatism and cancer do not appear to interact with the adaptive immune response.

6 One can therefore hypothesize that the duality of ethanol's effects (leading to anti-
7 inflammatory and pro-inflammatory responses) particularly involves the innate immune
8 response. In the literature, a brief exposure to ethanol was found to modulate the function of
9 innate immune cells (including monocytes) via the inhibition of NF- κ B and then a reduction

10 in TNF- α , IL-6 and IL-1 β production (Muralidharan et al. 2014). Conversely, Sureshchandra
11 et al. (2019) showed that chronic alcohol drinking, regardless of dose alters resting
12 transcriptomes of peripheral blood mononuclear cells, with the largest impact seen in innate
13 immune cells. Interestingly, the pro-inflammatory impact of drinking was significant only
14 with chronic heavy alcohol drinking. These transcriptional changes are being claimed to be
15 partially explained by alterations in microRNA profiles (Sureshchandra et al. 2019a).

16 Furthermore, expansion of granulocytic-myeloid-derived suppressor cells (one of the major
17 components in the immune suppressive network in both innate and adaptive immune
18 responses) in response to ethanol consumption has been highlighted to play a protective role
19 in acute alcoholic liver damage (Li et al. 2018). Conversely, prolonged exposure to alcohol in
20 humans was associated with elevated blood levels of IL-6 and IL-1 β (Pang et al. 2011).

21 Lastly, it has been reported that splenic macrophages from chronic heavy alcohol drinking
22 animals generated a larger inflammatory response to lipopolysaccharide, both at protein and
23 gene expression levels. By increasing levels of H3K4me3 (a histone mark of active
24 promoters), as well as chromatin accessibility at promoters and intergenic regions that
25 regulate inflammatory responses, alcohol is thought to alter the immune fitness of tissue-

1 resident macrophages *via* epigenetic mechanisms (Sureshchandra et al. 2019b). Recent studies
2 have highlighted the NLRP3 inflammasome (a cytosolic complex of the innate immune
3 system mainly expressed by myeloid cells like monocytes and macrophages) as an important
4 inhibitory target of ethanol (Nurmi et al. 2013). This inflammasome is a potent means of
5 immune defense, and triggers the production of IL-1 β and IL-18 in response to danger and
6 pathogen signals. Activation of NLRP3 inflammasome requires the assembly of three
7 effectors: (i) NLRP3, (ii) the apoptosis-associated speck-like protein containing a caspase
8 recruitment domain (ASC, an adaptor protein), and (iii) procaspase 1 (Keyel 2014).
9 Interestingly, ethanol was found to interact with the NLRP3 inflammasome by activating the
10 phosphorylation and thus inhibition of the ASC adaptor protein (Hoyt et al. 2016). Hence,
11 acute ethanol exposure has an anti-inflammatory effect.

12
13 As described above, high levels of alcohol consumption are responsible for many toxic
14 effects. The oxidative metabolic production of acetaldehyde is the cornerstone of this toxicity.
15 Remarkably, oxidative stress and acetaldehyde were found to activate the NLRP3
16 inflammasome, which has a key role in the pro-inflammatory effect of chronic ethanol
17 consumption (Hoyt et al. 2017). This sterile inflammation mechanism may override ethanol's
18 beneficial effects on the immune system and accentuate its toxicity. Furthermore, purinergic
19 receptors (which are also able to activate the NLRP3 inflammasome (Gicquel et al. 2017)) are
20 affected by ethanol treatment. It was recently reported that 24 hours of ethanol exposure was
21 enough to modulate purinergic receptor levels (including P2X7R upregulation in human
22 macrophages) and thus interleukin production - highlighting a new target for ethanol (Le Daré
23 et al. 2018). Taken as a whole, these results suggest that purinergic receptor and NLRP3
24 inflammasome antagonists may be of value in the treatment of ethanol-related disease.

7. Conclusion

Alcohol consumption has both toxic and beneficial effects; ethanol can be likened to Doctor Jekyll, whereas acetaldehyde is Mister Hyde. The detrimental effects associated with high ethanol consumption are probably due to the high resulting concentrations of acetaldehyde. Taken as a whole, the risk-benefit ratio of ethanol remains negative in terms of public health, particularly in view of the carcinogenic effects.

Although a variety of mechanisms underlie the pathologic and beneficial effects of alcohol consumption, it appears that most of ethanol's effects on the body relate to the immune system. Both innate and adaptive immune responses are affected by ethanol, leading to a spectrum of clinical presentations. Modulation of adaptive immunity might be associated with reductions in the incidence and severity of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, hyperthyroidism, and hypothyroidism. The inhibition of innate immunity by low to moderate alcohol consumption has been linked to beneficial effects, whereas high consumption is associated with detrimental effects (through pro-inflammatory activities). Although the specific mechanisms have yet to be characterized, the modulation of cytokine production via the NF- κ B or NLRP3 pathways appears to be the cornerstone of ethanol's immunomodulatory effects.

Further investigations are thus required in order to clarify the biological effects attributable to ethanol and acetaldehyde, and thus characterize the complex interactions between alcohol and the immune system. This knowledge might facilitate the development of treatments that can reduce ethanol's harmful effects or accentuate its beneficial effects.

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Declaration of interest

The authors declare that they have no conflict of interest.

Bibliography

Agarwal DP. Cardioprotective effects of light-moderate consumption of alcohol: a review of putative mechanisms. *Alcohol Alcohol*. 2002 Oct;37(5):409–15.

Agarwal DP, Goedde HW. Human aldehyde dehydrogenases: their role in alcoholism. *Alcohol*. 1989 Dec;6(6):517–23.

Albert CM, Manson JE, Cook NR, Ajani UA, Gaziano JM, Hennekens CH. Moderate alcohol consumption and the risk of sudden cardiac death among US male physicians. *Circulation*. 1999 Aug 31;100(9):944–50.

Al-Sader H, Abdul-Jabar H, Allawi Z, Haba Y. Alcohol and breast cancer: the mechanisms explained. *J Clin Med Res*. 2009 Aug;1(3):125–31.

Anderson LA, Cantwell MM, Watson RGP, Johnston BT, Murphy SJ, Ferguson HR, et al. The Association Between Alcohol and Reflux Esophagitis, Barrett's Esophagus, and Esophageal Adenocarcinoma. *Gastroenterology*. 2009 Mar;136(3):799–805.

Angus RM, Sambrook PN, Pocock NA, Eisman JA. Dietary intake and bone mineral density. *Bone Miner*. 1988 Jul;4(3):265–77.

ANSES. L'éthanol en population professionnelle. Evaluation des risques de l'éthanol en population professionnelle ; avis et rapport d'expertise collective. 2010.

Arfsten DP, Silbergeld EK, Loffredo CA. Fetal *ADH2*3*, Maternal Alcohol Consumption, and Fetal Growth. *International Journal of Toxicology*. 2004 Jan;23(1):47–54.

Arranz S, Chiva-Blanch G, Valderas-Martínez P, Medina-Remón A, Lamuela-Raventós RM, Estruch R. Wine, beer, alcohol and polyphenols on cardiovascular disease and cancer. *Nutrients*. 2012;4(7):759–81.

Barr T, Helms C, Grant K, Messaoudi I. Opposing effects of alcohol on the immune system. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2016 Feb;65:242–51.

- 1 Bau PFD, Bau CHD, Rosito GA, Manfroï WC, Fuchs FD. Alcohol consumption,
2 cardiovascular health, and endothelial function markers. *Alcohol*. 2007
3 Nov;41(7):479–88.
- 4 Belleville J. The French paradox: possible involvement of ethanol in the protective effect
5 against cardiovascular diseases. *Nutrition*. 2002 Feb;18(2):173–7.
- 6 Bergmann MM, Rehm J, Klipstein-Grobusch K, Boeing H, Schutze M, Drogan D, et al. The
7 association of pattern of lifetime alcohol use and cause of death in the European
8 Prospective Investigation into Cancer and Nutrition (EPIC) study. *International*
9 *Journal of Epidemiology*. 2013 Dec 1;42(6):1772–90.
- 10 Bianchini F, Vainio H. Wine and resveratrol: mechanisms of cancer prevention? *Eur J Cancer*
11 *Prev*. 2003 Oct;12(5):417–25.
- 12 Bismuth C, Baud F, Conso F, Dally S, Frejaville JP, Garnier R. *Toxicologie clinique.*
13 *Médecine-Sciences Flammarion, Paris; 2000.*
- 14 Bonnard N, Falcy M, Jargot D, Pasquier E. Ethanol – Fiche toxicologique n°48 [Internet].
15 Institut National de Recherche et de Sécurité; 2011 [cited 2018 Jul 3]. Available from:
16 [http://www.inrs.fr/publications/bdd/fichetox/fiche.html?refINRS=FICHETOX_48&se](http://www.inrs.fr/publications/bdd/fichetox/fiche.html?refINRS=FICHETOX_48§ion=bibliographieAuteurs)
17 [ction=bibliographieAuteurs](http://www.inrs.fr/publications/bdd/fichetox/fiche.html?refINRS=FICHETOX_48§ion=bibliographieAuteurs)
- 18 Brancato A, Lavanço G, Cavallaro A, Plescia F, Cannizzaro C. Acetaldehyde, Motivation and
19 Stress: Behavioral Evidence of an Addictive ménage à trois. *Front Behav Neurosci*.
20 2017;11:23.
- 21 Bühler M, Mann K. Alcohol and the Human Brain: A Systematic Review of Different
22 Neuroimaging Methods: ALCOHOL AND THE HUMAN BRAIN. *Alcoholism:*
23 *Clinical and Experimental Research*. 2011 Oct;35(10):1771–93.
- 24 Burton R, Sheron N. No level of alcohol consumption improves health. *The Lancet*. 2018
25 Sep;392(10152):987–8.
- 26 Carlé A, Bülow Pedersen I, Knudsen N, Perrild H, Ovesen L, Rasmussen LB, et al. Graves'
27 hyperthyroidism and moderate alcohol consumption: evidence for disease prevention.
28 *Clinical Endocrinology*. 2013 Jul;79(1):111–9.
- 29 Carle A, Pedersen IB, Knudsen N, Perrild H, Ovesen L, Rasmussen LB, et al. Moderate
30 alcohol consumption may protect against overt autoimmune hypothyroidism: a
31 population-based case-control study. *European Journal of Endocrinology*. 2012 Oct
32 1;167(4):483–90.
- 33 Cederbaum AI. Alcohol Metabolism. *Clinics in Liver Disease*. 2012 Nov;16(4):667–85.
- 34 Charness ME. Brain lesions in alcoholics. *Alcohol Clin Exp Res*. 1993 Feb;17(1):2–11.
- 35 Chen C-H, Walker J, Momenan R, Rawlings R, Heilig M, Hommer DW. Relationship
36 Between Liver Function and Brain Shrinkage in Patients with Alcohol Dependence:
37 RELATIONSHIP BETWEEN LIVER FUNCTION AND BRAIN SHRINKAGE.
38 *Alcoholism: Clinical and Experimental Research*. 2012 Apr;36(4):625–32.

- 1 Council of the Netherlands TH. Ethanol, evaluation of the effects on reproduction,
2 recommendation for classification. Committee for Compounds toxic to reproduction, a
3 committee of the Health. 2000.
- 4 Crabb DW. Ethanol oxidizing enzymes: roles in alcohol metabolism and alcoholic liver
5 disease. *Prog Liver Dis.* 1995;13:151–72.
- 6 Das S, Santani DD, Dhalla NS. Experimental evidence for the cardioprotective effects of red
7 wine. *Exp Clin Cardiol.* 2007;12(1):5–10.
- 8 Davies M. The role of GABAA receptors in mediating the effects of alcohol in the central
9 nervous system. *J Psychiatry Neurosci.* 2003 Jul;28(4):263–74.
- 10 De la Monte S, Longato L, Tong M, DeNucci S, Wands J. The Liver-Brain Axis of Alcohol-
11 Mediated Neurodegeneration: Role of Toxic Lipids. *International Journal of*
12 *Environmental Research and Public Health.* 2009 Jul 23;6(7):2055–75.
- 13 Di Castelnuovo A. Alcohol Dosing and Total Mortality in Men and Women: An Updated
14 Meta-analysis of 34 Prospective Studies. *Archives of Internal Medicine.* 2006 Dec
15 11;166(22):2437.
- 16 Di Giuseppe D, Alfredsson L, Bottai M, Askling J, Wolk A. Long term alcohol intake and
17 risk of rheumatoid arthritis in women: a population based cohort study. *BMJ.* 2012 Jul
18 10;345:e4230.
- 19 Diamond T, Stiel D, Lunzer M, Wilkinson M, Posen S. Ethanol reduces bone formation and
20 may cause osteoporosis. *Am J Med.* 1989 Mar;86(3):282–8.
- 21 Ding Z-M, Ingraham CM, Rodd ZA, McBride WJ. The reinforcing effects of ethanol within
22 the nucleus accumbens shell involve activation of local GABA and serotonin
23 receptors. *Journal of Psychopharmacology.* 2015 Jun;29(6):725–33.
- 24 Duddempudi AT. Immunology in Alcoholic Liver Disease. *Clinics in Liver Disease.* 2012
25 Nov;16(4):687–98.
- 26 Edenberg HJ. Regulation of the mammalian alcohol dehydrogenase genes. *Prog Nucleic Acid*
27 *Res Mol Biol.* 2000;64:295–341.
- 28 Ekström G, Ingelman-Sundberg M. Rat liver microsomal NADPH-supported oxidase activity
29 and lipid peroxidation dependent on ethanol-inducible cytochrome P-450 (P-450IIE1).
30 *Biochem Pharmacol.* 1989 Apr 15;38(8):1313–9.
- 31 Engler PA, Ramsey SE, Smith RJ. Alcohol use of diabetes patients: the need for assessment
32 and intervention. *Acta Diabetologica.* 2013 Apr;50(2):93–9.
- 33 Fan S, Meng Q, Gao B, Grossman J, Yadegari M, Goldberg ID, et al. Alcohol stimulates
34 estrogen receptor signaling in human breast cancer cell lines. *Cancer Res.* 2000 Oct
35 15;60(20):5635–9.
- 36 Faris RF, Henein MY, Coats AJS. Influence of Gender and Reported Alcohol Intake on
37 Mortality in Nonischemic Dilated Cardiomyopathy: *Heart Disease.* 2003 Mar;5(2):89–
38 94.

- 1 Felson DT, Zhang Y, Hannan MT, Kannel WB, Kiel DP. Alcohol intake and bone mineral
2 density in elderly men and women. The Framingham Study. *Am J Epidemiol*. 1995
3 Sep 1;142(5):485–92.
- 4 Fernandezsola J, Fatjo F, Sacanella E, Estruch R, Bosch X, Urbanomarquez A, et al. Evidence
5 of apoptosis in alcoholic cardiomyopathy☆. *Human Pathology*. 2006
6 Aug;37(8):1100–10.
- 7 Fragopoulou E, Choleva M, Antonopoulou S, Demopoulos CA. Wine and its metabolic
8 effects. A comprehensive review of clinical trials. *Metabolism*. 2018 Jun;83:102–19.
- 9 Ganry O, Baudoin C, Fardellone P. Effect of alcohol intake on bone mineral density in elderly
10 women: The EPIDOS Study. *Epidémiologie de l’Ostéoporose. Am J Epidemiol*. 2000
11 Apr 15;151(8):773–80.
- 12 Garro AJ, Espina N, Farinati F, Salvagnini M. The effects of chronic ethanol consumption on
13 carcinogen metabolism and on O6-methylguanine transferase-mediated repair of
14 alkylated DNA. *Alcohol Clin Exp Res*. 1986;10(6 Suppl):73S-77S.
- 15 Gicquel T, Le Daré B, Boichot E, Lagente V. Purinergic receptors: new targets for the
16 treatment of gout and fibrosis. *Fundamental & Clinical Pharmacology*. 2017
17 Apr;31(2):136–46.
- 18 Gil-Bernabe P, Boveda-Ruiz D, D’Alessandro-Gabazza C, Toda M, Miyake Y, Mifuji-
19 Moroka R, et al. Atherosclerosis amelioration by moderate alcohol consumption is
20 associated with increased circulating levels of stromal cell-derived factor-1. *Circ J*.
21 2011;75(9):2269–79.
- 22 Girre C, Hispard E, Tuszynski T. Toxicité de l’éthanol. *Encyclopédie Médico-Chirurgicale*
23 *Toxicologie-Pathologie professionnelle*. Elsevier, Paris; 1995.
- 24 Gmel G, Gutjahr E, Rehm J. How stable is the risk curve between alcohol and all-cause
25 mortality and what factors influence the shape? A precision-weighted hierarchical
26 meta-analysis. *Eur J Epidemiol*. 2003;18(7):631–42.
- 27 Gonzalez-Quintela A, Alende R, Gude F, Campos J, Rey J, Meijide LM, et al. Serum levels of
28 immunoglobulins (IgG, IgA, IgM) in a general adult population and their relationship
29 with alcohol consumption, smoking and common metabolic abnormalities: Serum
30 immunoglobulin levels in adults. *Clinical & Experimental Immunology*. 2007 Nov
31 15;151(1):42–50.
- 32 Goulden R. Moderate Alcohol Consumption Is Not Associated with Reduced All-cause
33 Mortality. *The American Journal of Medicine*. 2016 Feb;129(2):180-186.e4.
- 34 Grewal P, Viswanathen VA. Liver Cancer and Alcohol. *Clinics in Liver Disease*. 2012
35 Nov;16(4):839–50.
- 36 Griswold MG, Fullman N, Hawley C, Arian N, Zimsen SRM, Tymeson HD, et al. Alcohol
37 use and burden for 195 countries and territories, 1990–2016: a systematic analysis for
38 the Global Burden of Disease Study 2016. *The Lancet*. 2018 Sep;392(10152):1015–
39 35.

- 1 Guo R, Hu N, Kandadi MR, Ren J. Facilitated ethanol metabolism promotes cardiomyocyte
2 contractile dysfunction through autophagy in murine hearts. *Autophagy*. 2012
3 Apr;8(4):593–608.
- 4 Gupta KK, Gupta VK, Shirasaka T. An Update on Fetal Alcohol Syndrome-Pathogenesis,
5 Risks, and Treatment. *Alcoholism: Clinical and Experimental Research*. 2016
6 Aug;40(8):1594–602.
- 7 Gürtl B, Kratky D, Guelly C, Zhang L, Gorkiewicz G, Das SK, et al. Apoptosis and fibrosis
8 are early features of heart failure in an animal model of metabolic cardiomyopathy:
9 Animal model of metabolic cardiomyopathy. *International Journal of Experimental*
10 *Pathology*. 2009 May 11;90(3):338–46.
- 11 Haddad GE, Saunders L, Carles M, Crosby SD, del Monte F, Macgillivray TE, et al.
12 Fingerprint Profile of Alcohol-Associated Heart Failure in Human Hearts.
13 *Alcoholism: Clinical and Experimental Research*. 2008 May;32(5):814–21.
- 14 Hamitouche S, Poupon J, Dreano Y, Amet Y, Lucas D. Ethanol oxidation into acetaldehyde
15 by 16 recombinant human cytochrome P450 isoforms: Role of CYP2C isoforms in
16 human liver microsomes. *Toxicology Letters*. 2006 Dec;167(3):221–30.
- 17 Hamon M. Bases neurobiologiques des traitements de l'alcool-dépendance – Quelles
18 perspectives ? *European Psychiatry*. 2014 Nov;29(8):539.
- 19 Hansson GK, Libby P, Schönbeck U, Yan Z-Q. Innate and Adaptive Immunity in the
20 Pathogenesis of Atherosclerosis. *Circulation Research*. 2002 Aug 23;91(4):281–91.
- 21 Hardy CJ, Palmer BP, Muir KR, Sutton AJ, Powell RJ. Smoking history, alcohol
22 consumption, and systemic lupus erythematosus: a case-control study. *Ann Rheum*
23 *Dis*. 1998 Aug;57(8):451–5.
- 24 Harrison NL, Skelly MJ, Grosserode EK, Lowes DC, Zeric T, Phister S, et al. Effects of acute
25 alcohol on excitability in the CNS. *Neuropharmacology*. 2017 Aug;122:36–45.
- 26 Heller M, Burd L. Review of ethanol dispersion, distribution, and elimination from the fetal
27 compartment: Fetal Alcohol Exposure. *Birth Defects Research Part A: Clinical and*
28 *Molecular Teratology*. 2014 Apr;100(4):277–83.
- 29 Hines LM, Hankinson SE, Smith-Warner SA, Spiegelman D, Kelsey KT, Colditz GA, et al. A
30 prospective study of the effect of alcohol consumption and ADH3 genotype on plasma
31 steroid hormone levels and breast cancer risk. *Cancer Epidemiol Biomarkers Prev*.
32 2000 Oct;9(10):1099–105.
- 33 Hines RN, McCarver DG. The ontogeny of human drug-metabolizing enzymes: phase I
34 oxidative enzymes. *J Pharmacol Exp Ther*. 2002 Feb;300(2):355–60.
- 35 Hoffman PL, Rabe CS, Moses F, Tabakoff B. N-methyl-D-aspartate receptors and ethanol:
36 inhibition of calcium flux and cyclic GMP production. *J Neurochem*. 1989
37 Jun;52(6):1937–40.
- 38 Holbrook TL, Barrett-Connor E. A prospective study of alcohol consumption and bone
39 mineral density. *BMJ*. 1993 Jun 5;306(6891):1506–9.

- 1 Holland MG, Ferner RE. A systematic review of the evidence for acute tolerance to alcohol –
2 the “Mellanby effect.” *Clinical Toxicology*. 2017 Jul 3;55(6):545–56.
- 3 Howard AA, Arnsten JH, Gourevitch MN. Effect of Alcohol Consumption on Diabetes
4 Mellitus: A Systematic Review. *Annals of Internal Medicine*. 2004 Feb 3;140(3):211.
- 5 Hoyt LR, Ather JL, Randall MJ, DePuccio DP, Landry CC, Wewers MD, et al. Ethanol and
6 Other Short-Chain Alcohols Inhibit NLRP3 Inflammasome Activation through Protein
7 Tyrosine Phosphatase Stimulation. *The Journal of Immunology*. 2016 Aug
8 15;197(4):1322–34.
- 9 Hoyt LR, Randall MJ, Ather JL, DePuccio DP, Landry CC, Qian X, et al. Mitochondrial ROS
10 induced by chronic ethanol exposure promote hyper-activation of the NLRP3
11 inflammasome. *Redox Biology*. 2017 Aug;12:883–96.
- 12 Inserm. Médicaments psychotropes : Consommations et pharmacodépendances [Internet].
13 Paris : Les éditions Inserm; 2012 [cited 2018 Aug 9]. Available from:
14 [http://www.ipubli.inserm.fr/bitstream/handle/10608/2072/?sequence=30&wb4861727](http://www.ipubli.inserm.fr/bitstream/handle/10608/2072/?sequence=30&wb48617274=5B7365DD)
15 [4=5B7365DD](http://www.ipubli.inserm.fr/bitstream/handle/10608/2072/?sequence=30&wb48617274=5B7365DD)
- 16 Jayasekara H, English DR, Room R, MacInnis RJ. Alcohol Consumption Over Time and Risk
17 of Death: A Systematic Review and Meta-Analysis. *American Journal of*
18 *Epidemiology*. 2014 May 1;179(9):1049–59.
- 19 Ji C. Mechanisms of Alcohol-Induced Endoplasmic Reticulum Stress and Organ Injuries.
20 *Biochemistry Research International*. 2012;2012:1–12.
- 21 Jin Z, Xiang C, Cai Q, Wei X, He J. Alcohol consumption as a preventive factor for
22 developing rheumatoid arthritis: a dose-response meta-analysis of prospective studies.
23 *Annals of the Rheumatic Diseases*. 2014 Nov;73(11):1962–7.
- 24 Jokelainen K, Matysiak-Budnik T, Mäkisalo H, Höckerstedt K, Salaspuro M. High
25 intracolonic acetaldehyde values produced by a bacteriocolonial pathway for ethanol
26 oxidation in piglets. *Gut*. 1996 Jul;39(1):100–4.
- 27 Jonsson I-M, Verdrengh M, Brisslert M, Lindblad S, Bokarewa M, Islander U, et al. Ethanol
28 prevents development of destructive arthritis. *Proceedings of the National Academy of*
29 *Sciences*. 2007 Jan 2;104(1):258–63.
- 30 Kawamoto R, Kohara K, Tabara Y, Miki T, Ohtsuka N, Kusunoki T, et al. Alcohol
31 Consumption Is Associated with Decreased Insulin Resistance Independent of Body
32 Mass Index in Japanese Community-Dwelling Men. *The Tohoku Journal of*
33 *Experimental Medicine*. 2009;218(4):331–7.
- 34 Keller DL. Benefits of Moderate Alcohol Consumption Not Disproven. *The American Journal*
35 *of Medicine*. 2016 Aug;129(8):e149.
- 36 Keyel PA. How is inflammation initiated? Individual influences of IL-1, IL-18 and HMGB1.
37 *Cytokine*. 2014 Sep;69(1):136–45.
- 38 Klarich DS, Brasser SM, Hong MY. Moderate Alcohol Consumption and Colorectal Cancer
39 Risk. *Alcoholism: Clinical and Experimental Research*. 2015 Aug;39(8):1280–91.

- 1 Klatsky AL, Armstrong MA, Friedman GD. Alcohol and mortality. *Ann Intern Med.* 1992
2 Oct 15;117(8):646–54.
- 3 Knott C, Bell S, Britton A. Alcohol Consumption and the Risk of Type 2 Diabetes: A
4 Systematic Review and Dose-Response Meta-analysis of More Than 1.9 Million
5 Individuals From 38 Observational Studies. *Diabetes Care.* 2015 Sep;38(9):1804–12.
- 6 Konrad A, Vucurevic G, Lorscheider M, Bernow N, Thümmel M, Chai C, et al. Broad
7 Disruption of Brain White Matter Microstructure and Relationship with
8 Neuropsychological Performance in Male Patients with Severe Alcohol Dependence.
9 *Alcohol and Alcoholism.* 2012 Mar 1;47(2):118–26.
- 10 Kovář J, Zemánková K. Moderate alcohol consumption and triglyceridemia. *Physiol Res.*
11 2015;64 Suppl 3:S371-375.
- 12 Kunitoh S, Asai H, Imaoka S, Funae Y, Monna T. Metabolism of acetaldehyde to acetate by
13 rat hepatic P-450s: presence of different metabolic pathway from acetaldehyde
14 dehydrogenase system. *Alcohol Clin Exp Res.* 1996 Feb;20(1 Suppl):22A-24A.
- 15 Läck AK, Ariwodola OJ, Chappell AM, Weiner JL, McCool BA. Ethanol inhibition of
16 kainate receptor-mediated excitatory neurotransmission in the rat basolateral nucleus
17 of the amygdala. *Neuropharmacology.* 2008 Oct;55(5):661–8.
- 18 Laonigro I, Correale M, Di Biase M, Altomare E. Alcohol abuse and heart failure. *European*
19 *Journal of Heart Failure.* 2009 May;11(5):453–62.
- 20 Le Daré B, Victoni T, Bodin A, Vlach M, Vene E, Loyer P, et al. Ethanol upregulates the
21 P2X7 purinergic receptor in human macrophages. *Fundamental & Clinical*
22 *Pharmacology* [Internet]. 2018 Nov 17 [cited 2018 Nov 27]; Available from:
23 <http://doi.wiley.com/10.1111/fcp.12433>
- 24 Li S, Wang N, Tan H-Y, Hong M, Yuen M-F, Li H, et al. Expansion of Granulocytic,
25 Myeloid-Derived Suppressor Cells in Response to Ethanol-Induced Acute Liver
26 Damage. *Frontiers in Immunology.* 2018 Jul 19;9:1524.
- 27 Lin CC, Potter JJ, Mezey E. Erythrocyte aldehyde dehydrogenase activity in alcoholism.
28 *Alcohol Clin Exp Res.* 1984 Dec;8(6):539–41.
- 29 Littleton J. Neurochemical mechanisms underlying alcohol withdrawal. *Alcohol Health Res*
30 *World.* 1998;22(1):13–24.
- 31 Liu H-J, Pan X-X, Liu B-Q, Gui X, Hu L, Jiang C-Y, et al. Grape seed-derived procyanidins
32 alleviate gout pain via NLRP3 inflammasome suppression. *Journal of*
33 *Neuroinflammation* [Internet]. 2017 Dec [cited 2018 Aug 13];14(1). Available from:
34 <http://jneuroinflammation.biomedcentral.com/articles/10.1186/s12974-017-0849-y>
- 35 Longnecker MP. Alcoholic beverage consumption in relation to risk of breast cancer: meta-
36 analysis and review. *Cancer Causes Control.* 1994 Jan;5(1):73–82.
- 37 Lopes da Silva A, Ruginsk SG, Uchoa ET, Crestani CC, Scopinho AA, Correa FMA, et al.
38 Time-Course of Neuroendocrine Changes and Its Correlation with Hypertension

1 Induced by Ethanol Consumption. *Alcohol and Alcoholism*. 2013 Jul 1;48(4):495–
2 504.

3 Lu Y, Cederbaum AI. CYP2E1 and oxidative liver injury by alcohol. *Free Radical Biology*
4 *and Medicine*. 2008 Mar;44(5):723–38.

5 Machackova J, Barta J, Dhalla NS. Myofibrillar remodeling in cardiac hypertrophy, heart
6 failure and cardiomyopathies. *Can J Cardiol*. 2006 Sep;22(11):953–68.

7 Markoski MM, Garavaglia J, Oliveira A, Olivaes J, Marcadenti A. Molecular Properties of
8 Red Wine Compounds and Cardiometabolic Benefits. *Nutrition and Metabolic*
9 *Insights*. 2016 Jan;9:NMI.S32909.

10 Matsui T, Sakurai H, Toyama T, Yoshimura A, Matsushita S, Higuchi S. [Clinical application
11 of neuroimaging to alcohol-related dementia]. *Nihon Arukoru Yakubutsu Igakkai*
12 *Zasshi*. 2012 Jun;47(3):125–34.

13 Maurel DB, Boisseau N, Benhamou CL, Jaffre C. Alcohol and bone: review of dose effects
14 and mechanisms. *Osteoporosis International*. 2012 Jan;23(1):1–16.

15 Mayfield J, Ferguson L, Harris RA. Neuroimmune signaling: a key component of alcohol
16 abuse. *Current Opinion in Neurobiology*. 2013 Aug;23(4):513–20.

17 McClintick JN, Tischfield JA, Deng L, Kapoor M, Xuei X, Edenberg HJ. Ethanol activates
18 immune response in lymphoblastoid cells. *Alcohol*. 2019 Sep;79:81–91.

19 McEvily AJ, Holmquist B, Auld DS, Vallee BL. 3.beta.-Hydroxy-5.beta.-steroid
20 dehydrogenase activity of human liver alcohol dehydrogenase is specific to .gamma.-
21 subunits. *Biochemistry*. 1988 Jun;27(12):4284–8.

22 McGovern PE, Zhang J, Tang J, Zhang Z, Hall GR, Moreau RA, et al. Fermented beverages
23 of pre- and proto-historic China. *Proceedings of the National Academy of Sciences*.
24 2004 Dec 21;101(51):17593–8.

25 Mikosch P. Alcohol and bone. *Wiener Medizinische Wochenschrift*. 2014 Jan;164(1–2):15–
26 24.

27 de la Monte SM. Disproportionate atrophy of cerebral white matter in chronic alcoholics.
28 *Arch Neurol*. 1988 Sep;45(9):990–2.

29 Müller CP, Kalinichenko LS, Tiesel J, Witt M, Stöckl T, Sprenger E, et al. Paradoxical
30 antidepressant effects of alcohol are related to acid sphingomyelinase and its control
31 of sphingolipid homeostasis. *Acta Neuropathologica*. 2017 Mar;133(3):463–83.

32 Muralidharan S, Ambade A, Fulham MA, Deshpande J, Catalano D, Mandrekar P. Moderate
33 Alcohol Induces Stress Proteins HSF1 and hsp70 and Inhibits Proinflammatory
34 Cytokines Resulting in Endotoxin Tolerance. *The Journal of Immunology*. 2014 Aug
35 15;193(4):1975–87.

36 Nagata C, Fujita S, Iwata H, Kurosawa Y, Kobayashi K, Kobayashi M, et al. Systemic lupus
37 erythematosus: a case-control epidemiologic study in Japan. *Int J Dermatol*. 1995
38 May;34(5):333–7.

- 1 Nurmi K, Virkanen J, Rajamäki K, Niemi K, Kovanen PT, Eklund KK. Ethanol Inhibits
2 Activation of NLRP3 and AIM2 Inflammasomes in Human Macrophages—A Novel
3 Anti-Inflammatory Action of Alcohol. Catapano A, editor. PLoS ONE. 2013 Nov
4 11;8(11):e78537.
- 5 Obad A, Peeran A, Little JJ, Haddad GE, Tarzami ST. Alcohol-Mediated Organ Damages:
6 Heart and Brain. *Frontiers in Pharmacology* [Internet]. 2018 Feb 13 [cited 2018 Jul
7 25];9. Available from:
8 <http://journal.frontiersin.org/article/10.3389/fphar.2018.00081/full>
- 9 O'Shea KS, Kaufman MH. The teratogenic effect of acetaldehyde: implications for the study
10 of the fetal alcohol syndrome. *J Anat.* 1979 Jan;128(Pt 1):65–76.
- 11 Osna NA, Donohue TM, Kharbanda KK. Alcoholic Liver Disease: Pathogenesis and Current
12 Management. *Alcohol Res.* 2017;38(2):147–61.
- 13 Paganini-Hill A, Kawas CH, Corrada MM. Lifestyle Factors and Dementia in the Oldest-old:
14 The 90+ Study. *Alzheimer Disease & Associated Disorders.* 2016;30(1):21–6.
- 15 Panchenko LF, Moiseev VS, Pirozhkov SV, Terebilina NN, Naumova TA, Baronets VI, et al.
16 [Blood Content of Markers of Inflammation and Cytokines in Patients With Alcoholic
17 Cardiomyopathy and Ischemic Heart Disease at Various Stages of Heart Failure].
18 *Kardiologiia.* 2015;55(3):41–8.
- 19 Pang M, Bala S, Kodys K, Catalano D, Szabo G. Inhibition of TLR8- and TLR4-induced
20 Type I IFN induction by alcohol is different from its effects on inflammatory cytokine
21 production in monocytes. *BMC Immunology.* 2011;12(1):55.
- 22 Peters R, Peters J, Warner J, Beckett N, Bulpitt C. Alcohol, dementia and cognitive decline in
23 the elderly: a systematic review. *Age and Ageing.* 2008 May 16;37(5):505–12.
- 24 Pichini S, Morini L, Marchei E, Palmi I, Rotolo MC, Vagnarelli F, et al. Ethylglucuronide and
25 ethylsulfate in meconium to assess gestational ethanol exposure: preliminary results in
26 two Mediterranean cohorts. *Can J Clin Pharmacol.* 2009;16(2):e370-375.
- 27 Polsky S, Akturk HK. Alcohol Consumption, Diabetes Risk, and Cardiovascular Disease
28 Within Diabetes. *Current Diabetes Reports* [Internet]. 2017 Dec [cited 2019 Oct
29 1];17(12). Available from: <http://link.springer.com/10.1007/s11892-017-0950-8>
- 30 Porter R. Jean-Charles Sournia, *Histoire de l'alcoolisme*, Paris, Flammarion, 1986, 8vo, pp.
31 323, Fr. 125.00 (paperback). *Medical History.* 1987 Jul;31(03):372–3.
- 32 Rajakulendran S, Gadsby K, Deighton C. Rheumatoid arthritis, alcohol, leflunomide and
33 methotrexate. Can changes to the BSR guidelines for leflunomide and methotrexate on
34 alcohol consumption be justified? *Musculoskeletal Care.* 2008 Dec;6(4):233–46.
- 35 Rasheed A, Hines RN, McCarver-May DG. Variation in Induction of Human Placental
36 CYP2E1: Possible Role in Susceptibility to Fetal Alcohol Syndrome? *Toxicology and
37 Applied Pharmacology.* 1997 Jun;144(2):396–400.

- 1 Renner F, Kersbergen I, Field M, Werthmann J. Dutch courage? Effects of acute alcohol
2 consumption on self-ratings and observer ratings of foreign language skills. *Journal of*
3 *Psychopharmacology*. 2018 Jan;32(1):116–22.
- 4 Rodrigues P, Santos-Ribeiro S, Teodoro T, Gomes FV, Leal I, Reis JP, et al. Association
5 Between Alcohol Intake and Cardiac Remodeling. *Journal of the American College of*
6 *Cardiology*. 2018 Sep;72(13):1452–62.
- 7 Rohwer RD, Liu S, You N-C, Buring JE, Manson JE, Song Y. Interrelationship Between
8 Alcohol Intake and Endogenous Sex-Steroid Hormones on Diabetes Risk in
9 Postmenopausal Women. *Journal of the American College of Nutrition*. 2015 Jul
10 4;34(4):273–80.
- 11 Romeo J, Wärnberg J, Díaz LE, González-Gross M, Marcos A. Effects of moderate beer
12 consumption on first-line immunity of healthy adults. *J Physiol Biochem*. 2007
13 Jun;63(2):153–9.
- 14 Ronksley PE, Brien SE, Turner BJ, Mukamal KJ, Ghali WA. Association of alcohol
15 consumption with selected cardiovascular disease outcomes: a systematic review and
16 meta-analysis. *BMJ*. 2011 Feb 22;342:d671.
- 17 Sánchez-Sellero I, San-Román-Rodríguez E, Santos-Pérez S, Rossi-Izquierdo M, Soto-Varela
18 A. Alcohol consumption in Menière's disease patients. *Nutritional Neuroscience*. 2018
19 May 7;1–7.
- 20 Schapira D. Alcohol abuse and osteoporosis. *Semin Arthritis Rheum*. 1990 Jun;19(6):371–6.
- 21 Schoonen WM, Salinas CA, Kiemeny LALM, Stanford JL. Alcohol consumption and risk of
22 prostate cancer in middle-aged men. *International Journal of Cancer*. 2005 Jan
23 1;113(1):133–40.
- 24 Schrieks IC, Heil ALJ, Hendriks HFJ, Mukamal KJ, Beulens JWW. The effect of alcohol
25 consumption on insulin sensitivity and glycemic status: a systematic review and meta-
26 analysis of intervention studies. *Diabetes Care*. 2015 Apr;38(4):723–32.
- 27 Schröck A, Henzi A, Bütikofer P, König S, Weinmann W. Determination of the formation
28 rate of phosphatidylethanol by phospholipase D (PLD) in blood and test of two
29 selective PLD inhibitors. *Alcohol*. 2018 Dec;73:1–7.
- 30 Scott JR, Hassett AL, Schrepf AD, Brummett CM, Harris RE, Clauw DJ, et al. Moderate
31 Alcohol Consumption Is Associated with Reduced Pain and Fibromyalgia Symptoms
32 in Chronic Pain Patients. *Pain Medicine* [Internet]. 2018 Mar 13 [cited 2018 Aug 16];
33 Available from: [https://academic.oup.com/painmedicine/advance-](https://academic.oup.com/painmedicine/advance-article/doi/10.1093/pm/pny032/4931682)
34 [article/doi/10.1093/pm/pny032/4931682](https://academic.oup.com/painmedicine/advance-article/doi/10.1093/pm/pny032/4931682)
- 35 Seitz HK, Simanowski UA, Garzon FT, Rideout JM, Peters TJ, Koch A, et al. Possible role of
36 acetaldehyde in ethanol-related rectal cocarcinogenesis in the rat. *Gastroenterology*.
37 1990 Feb;98(2):406–13.
- 38 Seitz HK, Stickel F. Molecular mechanisms of alcohol-mediated carcinogenesis. *Nature*
39 *Reviews Cancer*. 2007 Aug;7(8):599–612.

- 1 Sergeant O, Pereira M, Belhomme C, Chevanne M, Huc L, Lagadic-Gossmann D. Role for
2 Membrane Fluidity in Ethanol-Induced Oxidative Stress of Primary Rat Hepatocytes.
3 Journal of Pharmacology and Experimental Therapeutics. 2005 Apr;313(1):104–11.
- 4 Shabtai Y, Bendelac L, Jubran H, Hirschberg J, Fainsod A. Acetaldehyde inhibits retinoic
5 acid biosynthesis to mediate alcohol teratogenicity. Scientific Reports [Internet]. 2018
6 Dec [cited 2018 Nov 24];8(1). Available from:
7 <http://www.nature.com/articles/s41598-017-18719-7>
- 8 Shabtai Y, Fainsod A. Competition between ethanol clearance and retinoic acid biosynthesis
9 in the induction of fetal alcohol syndrome. Biochemistry and Cell Biology. 2018
10 Apr;96(2):148–60.
- 11 Shai I, Rimm EB, Schulze MB, Rifai N, Stampfer MJ, Hu FB. Moderate alcohol intake and
12 markers of inflammation and endothelial dysfunction among diabetic men.
13 Diabetologia. 2004 Oct;47(10):1760–7.
- 14 Shimizu Y, Sakai A, Menuki K, Mori T, Isse T, Oyama T, et al. Reduced bone formation in
15 alcohol-induced osteopenia is associated with elevated p21 expression in bone marrow
16 cells in aldehyde dehydrogenase 2-disrupted mice. Bone. 2011 May;48(5):1075–86.
- 17 Silva SM, Silva S, Meireles M, Leal S. nNOS is involved in cardiac remodeling induced by
18 chronic ethanol consumption. Toxicology. 2015 Mar;329:98–105.
- 19 Skaaby T, Kilpeläinen TO, Taylor AE, Mahendran Y, Wong A, Ahluwalia TS, et al.
20 Association of alcohol consumption with allergic disease and asthma: a multicenter
21 Mendelian Randomization analysis. Addiction [Internet]. 2018 Sep 12 [cited 2018 Sep
22 22]; Available from: <http://doi.wiley.com/10.1111/add.14438>
- 23 Smith C, Gasparetto M, Jordan C, Pollyea DA, Vasiliou V. The Effects of Alcohol and
24 Aldehyde Dehydrogenases on Disorders of Hematopoiesis. In: Vasiliou V, Zakhari S,
25 Seitz HK, Hoek JB, editors. Biological Basis of Alcohol-Induced Cancer [Internet].
26 Cham: Springer International Publishing; 2015 [cited 2018 Jul 25]. p. 349–59.
27 Available from: http://link.springer.com/10.1007/978-3-319-09614-8_20
- 28 Steinbigler P, Haberl R, König B, Steinbeck G. P-wave signal averaging identifies patients
29 prone to alcohol-induced paroxysmal atrial fibrillation. The American Journal of
30 Cardiology. 2003 Feb;91(4):491–4.
- 31 Sureshchandra S, Raus A, Jankeel A, Ligh BJK, Walter NAR, Newman N, et al. Dose-
32 dependent effects of chronic alcohol drinking on peripheral immune responses.
33 Scientific Reports [Internet]. 2019a Dec [cited 2019 Oct 1];9(1). Available from:
34 <http://www.nature.com/articles/s41598-019-44302-3>
- 35 Sureshchandra S, Stull C, Ligh BJK, Nguyen SB, Grant KA, Messaoudi I. Chronic heavy
36 drinking drives distinct transcriptional and epigenetic changes in splenic macrophages.
37 EBioMedicine. 2019b May;43:594–606.
- 38 Tetrault JM, O'Connor PG. Substance Abuse and Withdrawal in the Critical Care Setting.
39 Critical Care Clinics. 2008 Oct;24(4):767–88.

- 1 Tizabi Y, Getachew B, Ferguson CL, Csoka AB, Thompson KM, Gomez-Paz A, et al. Low
2 Vs. High Alcohol: Central Benefits Vs. Detriments. *Neurotoxicity Research* [Internet].
3 2018 Jan 4 [cited 2018 Sep 22]; Available from:
4 <http://link.springer.com/10.1007/s12640-017-9859-x>
- 5 Tsuchiya T, Sakai A, Menuki K, Mori T, Takeuchi Y, Kanoh S, et al. Disruption of aldehyde
6 dehydrogenase 2 gene results in altered cortical bone structure and increased cortical
7 bone mineral density in the femoral diaphysis of mice. *Bone*. 2013 Apr;53(2):358–68.
- 8 Urbano-Márquez A, Fernández-Solà J. Effects of alcohol on skeletal and cardiac muscle:
9 Alcoholic Myopathy. *Muscle & Nerve*. 2004 Dec;30(6):689–707.
- 10 Uusi-Oukari M, Korpi ER. Regulation of GABAA Receptor Subunit Expression by
11 Pharmacological Agents. *Pharmacological Reviews*. 2010 Mar 1;62(1):97–135.
- 12 Valenzuela CF, Bhawe S, Hoffman P, Harris RA. Acute effects of ethanol on
13 pharmacologically isolated kainate receptors in cerebellar granule neurons:
14 comparison with NMDA and AMPA receptors. *J Neurochem*. 1998 Oct;71(4):1777–
15 80.
- 16 Vasiliou V, Pappa A. Polymorphisms of Human Aldehyde Dehydrogenases. *Pharmacology*.
17 2000;61(3):192–8.
- 18 Vetreno RP, Hall JM, Savage LM. Alcohol-related amnesia and dementia: Animal models
19 have revealed the contributions of different etiological factors on neuropathology,
20 neurochemical dysfunction and cognitive impairment. *Neurobiology of Learning and*
21 *Memory*. 2011 Nov;96(4):596–608.
- 22 Victor M. Alcoholic dementia. *Can J Neurol Sci*. 1994 May;21(2):88–99.
- 23 Wang M, McIntee EJ, Cheng G, Shi Y, Villalta PW, Hecht SS. Identification of DNA adducts
24 of acetaldehyde. *Chem Res Toxicol*. 2000 Nov;13(11):1149–57.
- 25 Wang MQ, Nicholson ME, Mahoney BS, Li Y, Perko MA. Proprioceptive Responses under
26 Rising and Falling BACs: A Test of the Mellanby Effect. *Perceptual and Motor Skills*.
27 1993 Aug;77(1):83–8.
- 28 Wattendorf DJ, Muenke M. Fetal alcohol spectrum disorders. *Am Fam Physician*. 2005 Jul
29 15;72(2):279–82, 285.
- 30 Wei X, Shi X, Zhong W, Zhao Y, Tang Y, Sun W, et al. Chronic Alcohol Exposure Disturbs
31 Lipid Homeostasis at the Adipose Tissue-Liver Axis in Mice: Analysis of
32 Triacylglycerols Using High-Resolution Mass Spectrometry in Combination with In
33 Vivo Metabolite Deuterium Labeling. Mukhopadhyay P, editor. *PLoS ONE*. 2013 Feb
34 6;8(2):e55382.
- 35 Wimer W, Russel J, Kaplan H. *Alcohols toxicology*. Park Ridg : Noyes Data Corp; 1983.
- 36 World Health Organization. Global status report on alcohol and health [Internet]. 2011 [cited
37 2018 Sep 22]. Available from:
38 [http://www.who.int/substance_abuse/publications/global_alcohol_report/msbgsruprofi](http://www.who.int/substance_abuse/publications/global_alcohol_report/msbgsruprofiles.pdf)
39 [les.pdf](http://www.who.int/substance_abuse/publications/global_alcohol_report/msbgsruprofiles.pdf)

- 1 Yasar S. Relation between alcohol consumption in midlife and dementia in late life. BMJ.
2 2018 Aug 1;k3164.
- 3 Zhou Y, Zheng J, Li S, Zhou T, Zhang P, Li H-B. Alcoholic Beverage Consumption and
4 Chronic Diseases. International Journal of Environmental Research and Public Health.
5 2016 May 24;13(6):522.
- 6 Zhukov A, Ingelman-Sundberg M. Relationship between cytochrome P450 catalytic cycling
7 and stability: fast degradation of ethanol-inducible cytochrome P450 2E1 (CYP2E1)
8 in hepatoma cells is abolished by inactivation of its electron donor NADPH-
9 cytochrome P450 reductase. Biochem J. 1999 Jun 1;340 (Pt 2):453–8.

1 Tables

Cardiovascular diseases	Potential mechanisms	References
Heart failure	Cardiac fibrosis Vitamin deficiency and malnutrition Decrease in contractile proteins, and myocyte loss Mitochondrial dysfunction Impaired calcium homeostasis Oxidative stress Activation of neurohormonal systems Coronary heart disease	(Faris et al. 2003; Urbano-Márquez and Fernández-Solà 2004; Fernandezsola et al. 2006; Gürtl et al. 2009; Laonigro et al. 2009)
Alcoholic cardiomyopathy	Decrease in nNOS expression Increased pro-inflammatory effects Neurohormonal activation Metabolic changes Acetaldehyde accumulation Altered protein synthesis Elevated of brain natriuretic peptide Genetically related factors.	(Machackova et al. 2006; Guo et al. 2012; Ji 2012; Panchenko et al. 2015; Silva et al. 2015)
Atrial fibrillation	Increase in ROS	(Steinbigler et al. 2003)
Atherosclerosis	Activation of the innate and adaptive immune systems Presence of mediators of inflammation (TNF, IFN γ)	(Hansson et al. 2002)
Hypertension	Increased secretion of catecholamines Decrease in nNOS expression	(Lopes da Silva et al. 2013; Silva et al. 2015)

2 **Table 1: Mechanisms potentially linking alcohol consumption with cardiovascular**
3 **pathologies.**

4

Disease	Potential mechanisms	References
Cardiovascular mortality	Antioxidant and hypotensive responses Elevated HDL cholesterol Low LDL cholesterol and reduced blood coagulation Inhibition of the NLRP3 inflammasome	(Agarwal 2002; Das et al. 2007; Gil-Bernabe et al. 2011; Arranz et al. 2012; Nurmi et al. 2013; Kovář and Zemánková 2015; Hoyt et al. 2016; Markoski et al. 2016; Liu et al. 2017; Rodrigues et al. 2018)
Type 2 diabetes	Decrease in fasting insulin concentrations and lower insulin sensitivity	(Knott et al. 2015; Schrieks et al. 2015; Fragopoulou et al. 2018)
Neuroprotection	Decrease in pro-inflammatory cytokine levels (TNF- α ; IL-1 β) Elevated neurotrophic factors (BDNF) Elevated anti-inflammatory cytokine levels (IL-10)	(Müller et al. 2017)
Dementia	Mechanism unknown	(Peters et al. 2008; Paganini-Hill et al. 2016; Yasar 2018)
Chronic pain	Central nervous system depressant effect	(Scott et al. 2018)
Meniere's disease	Mechanism unknown	(Sánchez-Sellero et al. 2018)
Rheumatoid arthritis	Interaction with the innate immune response, delaying the onset of collagen-induced arthritis and stopping its progression	(Jonsson et al. 2007; Rajakulendran et al. 2008; Di Giuseppe et al. 2012; Jin et al. 2014)
Systemic lupus erythematosus	Mechanism unknown	(Nagata et al. 1995; Hardy et al. 1998)
Hyperthyroidism	Mechanism unknown	(Carlé et al. 2013)
Hypothyroidism	Mechanism unknown	(Carle et al. 2012)
Osteoporosis	Elevated endogenous estrogen levels induced by ethanol	(Angus et al. 1988; Holbrook and Barrett-Connor 1993; Felson et al. 1995; Ganry et al. 2000)
Cancers	Resveratrol inhibits the metabolic activation of carcinogens, decreases cell proliferation, induces apoptosis and exerts anti-inflammatory activities	(Bianchini and Vainio 2003; Schoonen et al. 2005; Anderson et al. 2009; Klarich et al. 2015)

Table 2: Diseases in which moderate alcohol consumption appears to have beneficial effects.

Figures

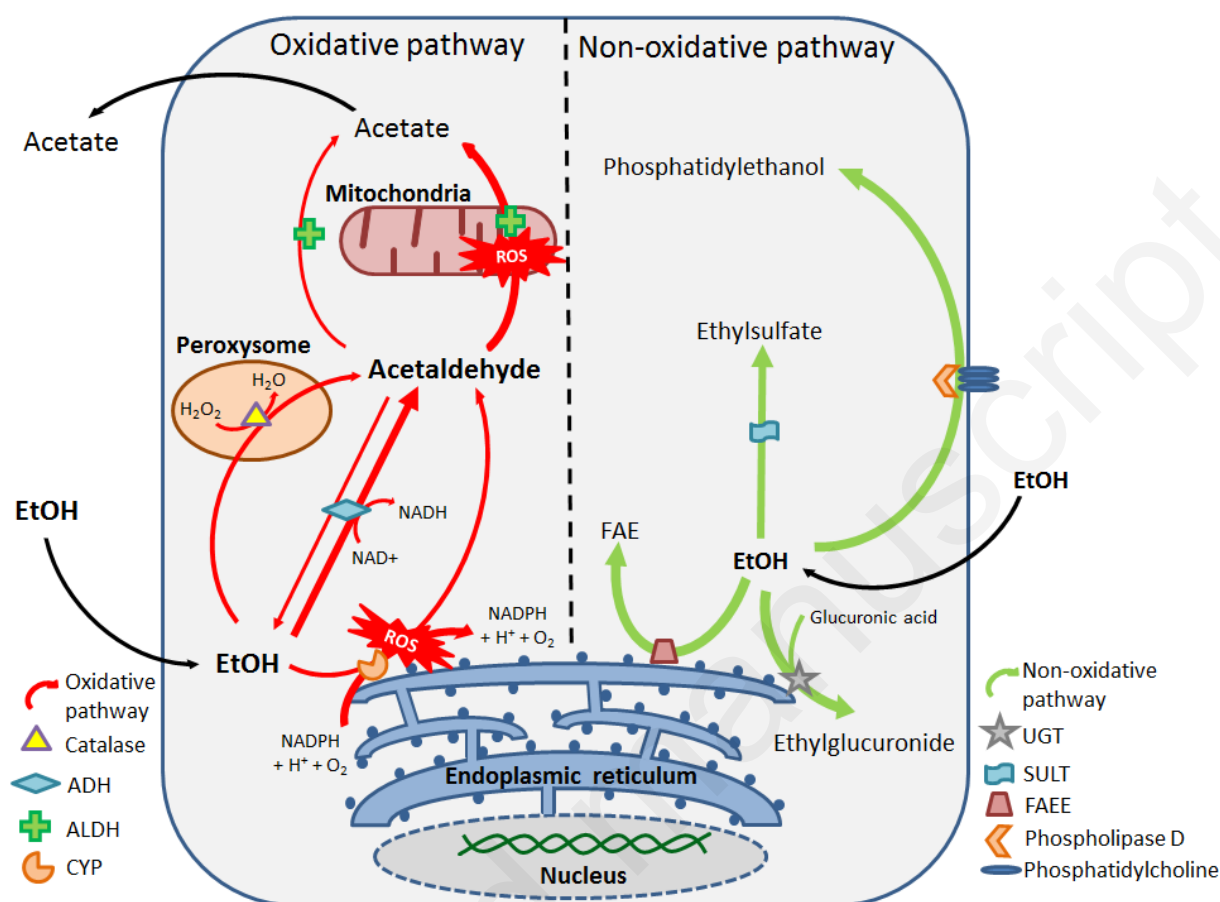


Figure 1: Oxidative and non-oxidative ethanol metabolic pathways in the hepatocyte. ADH: alcohol dehydrogenase; ALDH: aldehyde dehydrogenase; CYP: cytochrome P450; EtOH: ethanol; FAE: fatty acid ester; FAEE: fatty acid ethyl ester; SULT: sulfotransferase; UGT: uridine diphosphate glucuronyltransferase

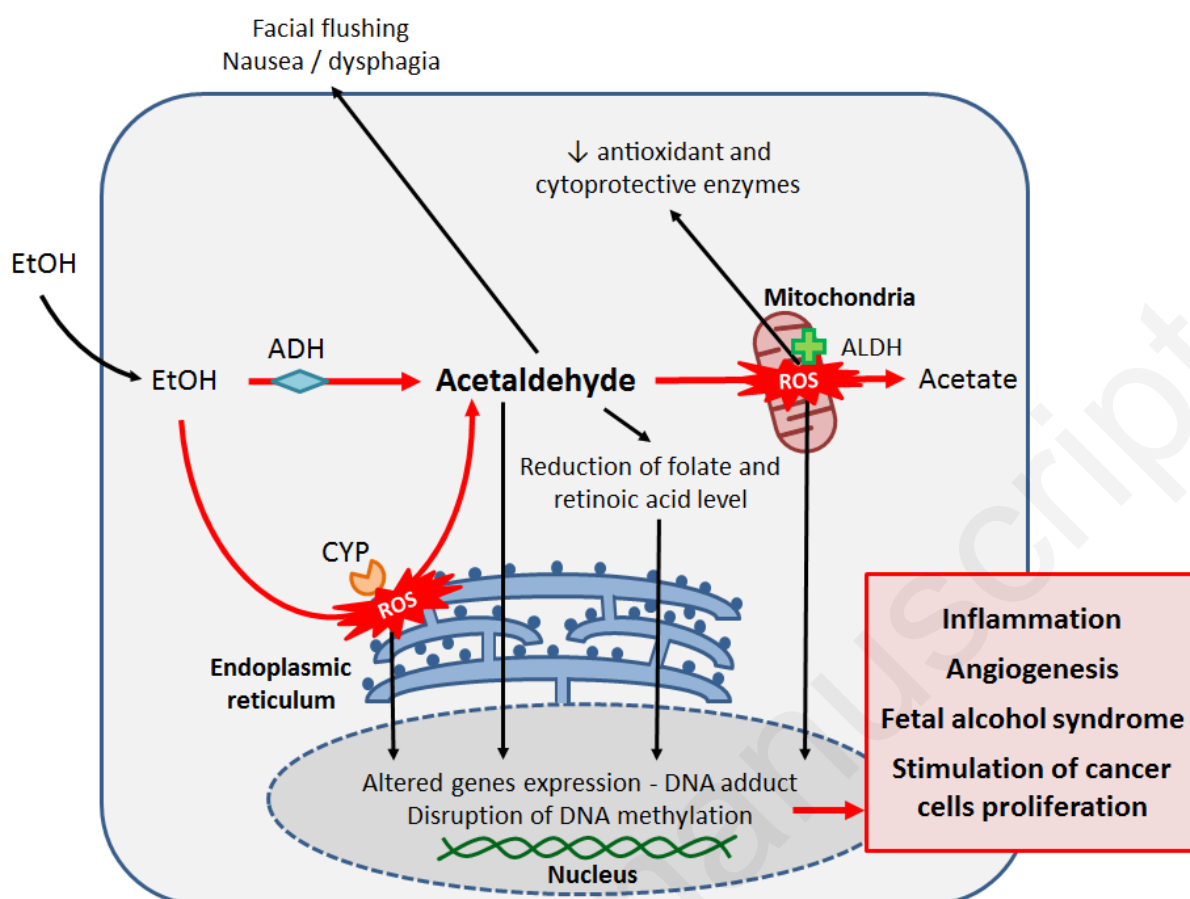


Figure 2: Molecular and pathophysiological effects of acetaldehyde