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

3 Running head : Toxicity, benefits and immunomodulatory effects of
4 ethanol

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1 **Abstract**

2

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

18

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

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1. The origin of alcoholic beverages

2

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

11

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

23

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

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

9

10 **2. Search strategy**

11

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

16

17 **3. The metabolism of ethanol**

18

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

23

24 Cytosolic alcohol dehydrogenase (ADH) is the major enzyme responsible for the phase I
25 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 , β_1 , β_2 , β_3 , γ_1 , γ_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).

1

2 Catalase (an enzyme found in peroxisomes) is also known to metabolize alcohol. However,
3 hepatic catalase does not have a significant role in ethanol metabolism. In contrast, brain
4 catalase appears to be involved in alcohol tolerance and positive reinforcement (Cederbaum
5 2012).

6

7 Figure 1 near here

8

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

14

15 The acetaldehyde generated by these metabolic pathways is then oxidized by aldehyde
16 dehydrogenase (ALDH) to form acetate. In humans, the ALDH superfamily of NAD⁺-
17 dependent enzymes is encoded by 16 genes. The cytosolic ALDH1 and mitochondrial
18 ALDH2 isoenzymes are those primarily involved in ethanol metabolism (Vasiliou and Pappa
19 2000). In contrast to ADH, polymorphisms appears to have a greater influence on ALDH
20 activity. The *ALDH2*1* allele (known to code for a highly active variant) is considered to
21 protect against liver disease in alcoholism, whereas the enzyme encoded by *ALDH2*2* allele
22 is an inactive enzyme (Cederbaum 2012). Furthermore, chronic ethanol consumption lowers
23 ALDH and increases the acetaldehyde level (Lin et al. 1984). Acetate is not the final
24 metabolite in this pathway because it be converted into CO₂, fatty acids, ketones, cholesterol
25 or steroids (Cederbaum 2012).

1

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

12

13 **4. The toxicity of ethanol**

14

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

24

25

1 *3.1 Overall mortality as a function of dose*

2

3 Many researchers have reported that low levels of alcohol intake are associated with a lower
4 risk of mortality (Keller 2016). Jayasekara et al.'s (2014) meta-analysis of 62,950 study
5 participants found that ethanol's protective effect is observed for intakes of 1 to 29 g/day
6 (corresponding to zero to three standard units of alcohol per day), with a relative risk (RR)
7 [95% confidence interval (CI)] of 0.90 [0.81, 0.99]. Conversely, alcohol consumptions of
8 between 30 to 59 g/day and over 60 g/day were associated with an RR [95%CI] of mortality
9 of 1.19 [0.89, 1.58] and 1.52 [0.78, 2.98], respectively (Jayasekara et al. 2014). In a study of
10 380,395 people, Bergmann et al. (2013) found that limiting alcohol consumption to below
11 five alcoholic units per day was associated with a lower risk of death (mainly due to less
12 cardiovascular disease), whereas the consumption of five or more alcoholic drinks per day
13 was associated with a 2- to 5-fold greater risk of death (mainly due to alcohol-related cancer)
14 (Bergmann et al. 2013). A meta-analysis linking moderate ethanol consumption to lower all-
15 cause mortality was consistent with these results (Gmel et al. 2003; Di Castelnuovo 2006).

16

17 Despite the growing body of evidence for a protective effect of low to moderate alcohol
18 consumption, the results are subject to debate. For example, Goulden et al.'s (2016) study of
19 24,029 individuals over the age of 50 years did not reveal an association between all-cause
20 mortality and moderate alcohol consumption (Goulden 2016). Likewise, a recent study of 28
21 million individuals found that all-cause mortality rose with increasing levels of consumption;
22 the researchers concluded that the level of alcohol consumption minimizing health loss is zero
23 (Griswold et al. 2018).

24

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).

6

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

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

4

5 In addition to these effects on GABA-A receptors, ethanol antagonizes N-methyl-D-aspartate
6 receptors, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, and kainate
7 receptors (Valenzuela et al. 1998; Läck et al. 2008). Since glutamate is an excitatory
8 neurotransmitter, blockade of these receptors heightens ethanol's depressant action on the
9 central nervous system (Hoffman et al. 1989). Lastly, ethanol has also been shown to interact
10 with glycine receptors, neuronal nicotinic receptors, and serotonin type 3 receptors (Davies
11 2003; Ding et al. 2015).

12

13 ***3.3 Chronic toxicity***

14

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

21

22 ***3.3.1 Liver disorders***

23

24 In the early stages of ethanol-related liver disease, the ROS generated by ethanol metabolism
25 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 Seits 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).

25

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,

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

3

4 *3.3.3 Cardiovascular disorders*

5

6 High-dose ethanol consumption has been linked to various cardiovascular disorders, such as
7 hypertension, atrial fibrillation, atherosclerosis, and alcoholic cardiomyopathies (Girre et al.
8 1995; Bismuth et al. 2000; Zhou et al. 2016; Obad et al. 2018).

9

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

19

20 Table 1 near here

21

22 *3.3.4 Neuropsychic disorders*

23

24 The toxic effects of ethanol and its metabolites on brain tissue vary according to the region of
25 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

1 1993; Victor 1994). Today, the frontal, cerebellar and/or temporal brain atrophy induced by
2 ethanol consumption can be readily detected by medical imaging techniques (Matsui et al.
3 2012).

4

5 *3.3.5 Addiction and withdrawal syndrome*

6

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

13

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

20

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

25

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 properties
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).

12

13 *3.3.6 Hematologic disorders*

14

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).

22

23

24

25

1 3.3.7 Reprotoxicity

2

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

7

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

14

15 The pathogenesis of FAS is related to the pharmacokinetics and metabolism of ethanol. It is
16 well known that ethanol crosses the placenta, and distributes into the fetal compartment.
17 Furthermore, ethanol is eliminated slowly by the fetus, leading to greater exposure (Heller and
18 Burd 2014). Furthermore, several characteristics make the fetus more fragile to alterations in
19 oxidative metabolism. CYP2E1 protein is produced earlier than ADH during gestation (Hines
20 and McCarver 2002; Arfsten et al. 2004), and the induction of placental CYP2E1 by ethanol
21 (Rasheed et al. 1997) means that CYP becomes the major metabolic pathway for ethanol.
22 Ethanol's teratogenic effects are thought to be due to ROS production (leading to
23 mitochondrial damage, brain lipid peroxidation, and a decrease in endogenous antioxidant
24 levels), apoptosis (leading to disrupted neuron-neuron adhesion), placenta vasoconstriction,
25 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

25

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

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

7
8 Gil-Bernabe et al. (Gil-Bernabe et al. 2011) found that moderate alcohol consumption reduces
9 atherosclerosis by regulating fibroblasts' production of CXCL12 (stromal cell-derived factor-
10 1). Furthermore, Nurmi et al.'s (2013) work on the underlying pathophysiological
11 mechanisms prompted the suggestion that the NLRP3 inflammasome is a key player in the
12 protective cardiovascular effect of moderate alcohol consumption. Indeed, acute exposure to
13 ethanol was found to inhibit the NLRP3 inflammasome in macrophages, leading to an anti-
14 inflammatory effect (Nurmi et al. 2013). These results were confirmed by Hoyt et al. (2016)
15 (Hoyt et al. 2016).

16
17 The procyanidin compounds in wine have also been found to inhibit the NLRP3
18 inflammasome; this suggests that wine has a stronger anti-inflammatory effect than other
19 beverages. Given the presence of many pharmacologically active compounds other than
20 ethanol in alcoholic beverages, it is hard to predict the effects of these mixtures (Liu et al.
21 2017).

22 23 **4.2 Diabetes**

24
25 The positive impact of moderate alcohol consumption on the cardiovascular system appears to
26 be coupled with beneficial effects on diabetes mellitus. In Knott et al.'s (2015) meta-analysis

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

15

16 ***4.3 The nervous system and sensory organs***

17

18 *4.3.1 Neuroprotection and dementia*

19

20 Interestingly, ethanol appears to have a neuroprotective effect. For example, Tizabi et al.'s
21 (2017) studies in *in vitro* models of Parkinson's and Alzheimer disease evidenced a protective
22 effect of low ethanol consumption (Tizabi et al. 2018). The underlying mechanisms were
23 related to low levels of pro-inflammatory cytokines (TNF- α and IL-1 β) and elevated levels of
24 brain-derived neurotrophic factor and the anti-inflammatory cytokine IL-10 - resulting in
25 greater neuroplasticity and neuroprotection. Furthermore, preclinical studies in an animal

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

3

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

11

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

14

15 *4.3.2 Chronic pain*

16

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

21

22 *4.3.3 Anxiolytic effects*

23

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

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

7 *4.4 Autoimmune diseases*

8

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

12

13 *4.4.1 Rheumatoid arthritis*

14

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

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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).

1 **4.5 Rheumatology**

2

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

13

14 **4.6 Cancer**

15

16 Although alcohol is known to be a carcinogenic agent in humans (see above), moderate wine
17 consumption may decrease the risk of several cancers (including colon, lung, ovarian and
18 prostate cancer, basal cell carcinoma, and esophageal adenocarcinoma) (Bianchini and Vainio
19 2003; Schoonen et al. 2005; Anderson et al. 2009; Klarich et al. 2015; Zhou et al. 2016).
20 These properties are mostly related to resveratrol, an antioxidant agent that inhibits the
21 metabolic activation of carcinogens, decreases cell proliferation, induces apoptosis and exerts
22 anti-inflammatory effects. The mechanisms underlying the beneficial effects of ethanol are
23 summarized in Table 2.

24

25 Table 2 near here

26

1 **6. The immunomodulatory effects of ethanol**

2

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

7

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

13

14 The immune system is conventionally divided into innate and adaptive mechanisms, and
15 alcohol is known to influence both. Barr et al.'s (2016) reviews of the effects of ethanol on the
16 immune system found that ethanol had dose-dependent effects on adaptive immune responses;
17 moderate alcohol consumption increased T and B lymphocyte counts, whereas chronic heavy
18 consumption was associated with a falls in cell counts (Barr et al. 2016). In addition,
19 McClintick et al. (2019) showed that ethanol exposure on lymphoblastoid cells induces a
20 robust immune response after 24 hours exposure (including neuroinflammation and K $\text{F}\kappa\text{B}$
21 pathway, IL-6, IL-2 and IL-8 activation), but decreased in intensity after 48 hours exposure
22 (partially explained by a reversal of interferon signaling) (McClintick et al. 2019).
23 Furthermore, some researchers have reported that moderate alcohol consumption is associated
24 with lower levels of immunoglobulins G, M and A (Gonzalez-Quintela et al. 2007; Romeo et
25 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.

25

1 **7. Conclusion**

2

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

8

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

20

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

25

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4

5 **Declaration of interest**

6 The authors declare that they have no conflict of interest.

7

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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.**

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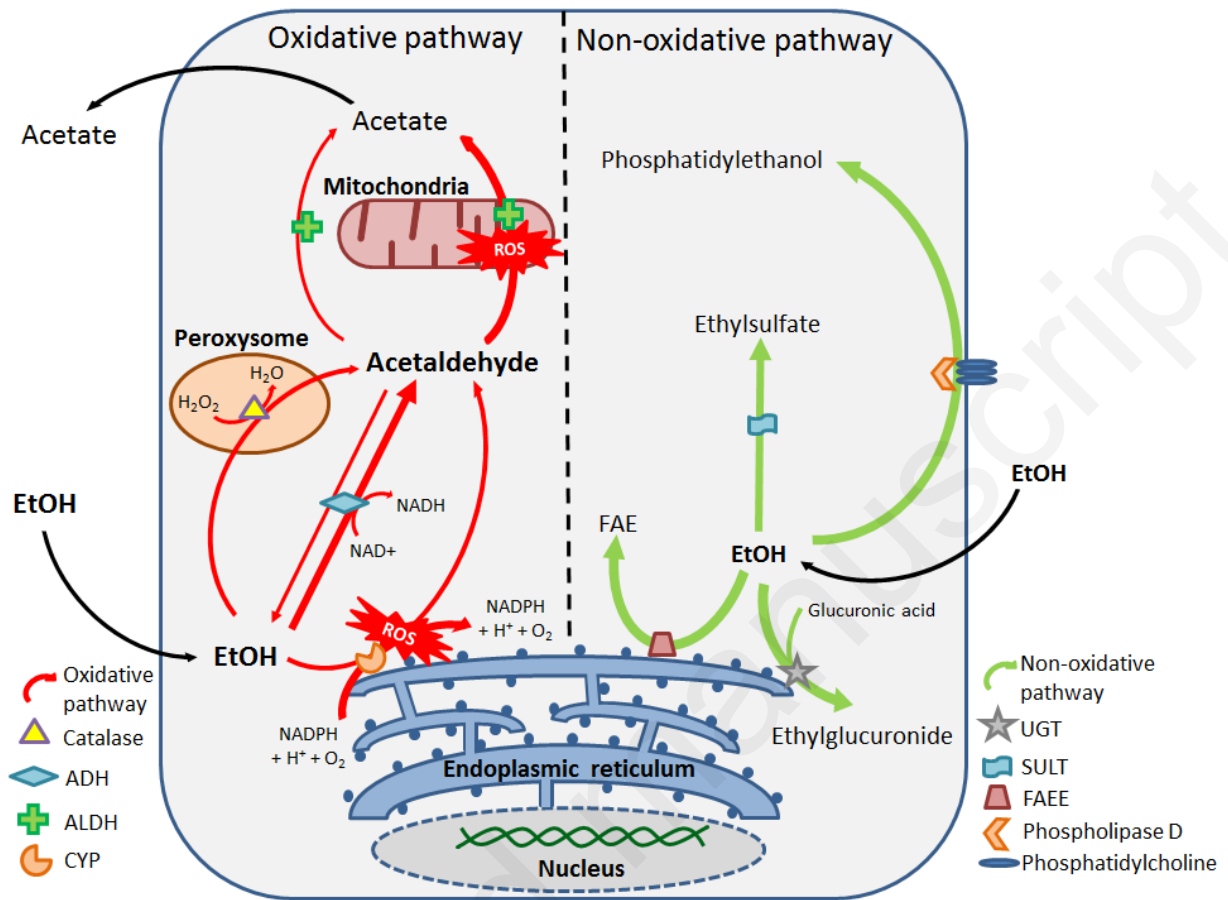
Disease	Potential mechanisms	References
Cardiovascular mortality	Antioxidant and hypotensive responses Elevated HDL cholesterol Low LDL cholesterol and reduced blood coagulation Inhibition of the NLRP3 inflammasome	(Agarwal 2002; Das et al. 2007; Gil-Bernabe et al. 2011; Arranz et al. 2012; Nurmi et 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.

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1 **Figures**

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5 **Figure 1: Oxidative and non-oxidative ethanol metabolic pathways in the hepatocyte. ADH:**

6 **alcohol dehydrogenase; ALDH: aldehyde dehydrogenase; CYP: cytochrome P450; EtOH:**

7 **ethanol; FAE: fatty acid ester; FAEE: fatty acid ethyl ester; SULT: sulfotransferase; UGT:**

8 **uridine diphosphate glucuronyltransferase**

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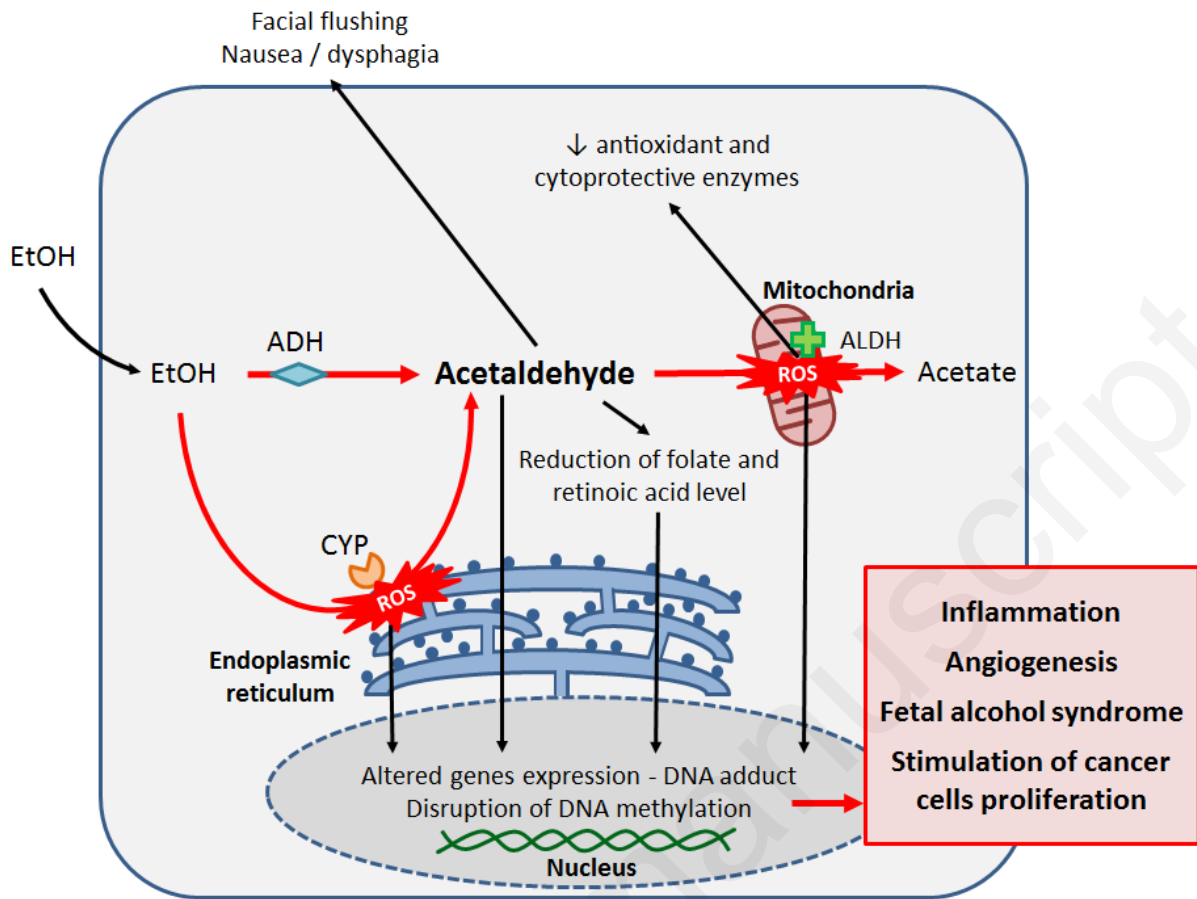
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Figure 2: Molecular and pathophysiological effects of acetaldehyde