Binge drinking during the adolescence period causes oxidative damage-induced cardiometabolic disorders: a possible ameliorative approach with selenium supplementation.

María Luisa Ojeda [1], Fátima Nogales [1,*], María del Carmen Gallego-López[1], and Olimpia Carreras [1]

[1]Department of Physiology, Faculty of Pharmacy, Seville University, 41012 Seville, Spain.

*Correspondence: fnogales@us.es

*Address: Dra. Fátima Nogales Bueno.

Department of Physiology.

Faculty of Pharmacy, Seville University.

C/ Profesor García González, nº 2.

41012. Seville. Spain.

Tel: +34 954556518

Fax: +34 954233765

E-mail: fnogales@us.es

Abstract:

Binge drinking (BD) is the most common alcohol consumption model among adolescents. BD exposure during adolescence disrupts the nervous system function, being involved in the major mortality causes at this age: motor vehicle accidents, homicides and suicides. Recent studies have also shown that BD consumption during adolescence affects liver, renal and cardiovascular physiology, predisposing adolescents to future adult cardiometabolic damage. BD is a particularly pro-oxidant alcohol consumption pattern, because it leads to the production of a great source of reactive oxygen species (ROS) via the microsomal ethanol oxidizing system, also decreasing the antioxidant activity of glutathione peroxidase (GPx). Selenium (Se) is a mineral which plays a pivotal role against oxidation; it forms part of the catalytic center of different antioxidant selenoproteins such as GPxs (GPx1, GPx4, GPx3) and selenoprotein P (SelP). Specifically, GPx4 has an essential role in mitochondria, preventing their oxidation, apoptosis and NFkB-inflamative response, being this function even more relevant in heart's tissue. Se serum levels are decreased in acute and chronic alcoholic adult patients, being correlated to the severity of oxidation, liver damage and metabolic profile. Experimental studies have described that Se supplementation to alcohol exposed mice clearly decreases oxidative and liver damage. However, clinical BD effects on Se homeostasis and selenoproteins' tissue distribution related to oxidation during adolescence are not yet studied. In this narrative review we will describe the use of sodium selenite supplementation as an antioxidant therapy in adolescent BD rats in order to analyze Se homeostasis implication during BD exposure, oxidative balance, apoptosis and inflammation, mainly in liver, kidney, and heart. These biomolecular changes and the cardiovascular function will be analyzed. Se supplementation therapies could be a good strategy to prevent the oxidation, inflammation and apoptosis generated in tissues by BD during adolescence, such as liver, kidney and heart, improving cardiovascular functioning.

Keywords: selenium, antioxidant, binge drinking, apoptosis, NFkB, alcohol metabolism.

1. Introduction:

Ethanol (EtOH) is a major contributor to global disease, being a causal factor in more than 200 diseases and a leading cause of preventable death [1]. According to the World Health Organization (WHO), in 2018 EtOH consumption led to the 5.3 % of all deaths, increasing this value to 13.5 % in the 20–39 years age group. Moreover, EtOH consumption causes death and disability relatively early in life and during adolescence; during both periods, EtOH consumption could lead to disease later in life, including metabolic and cardiovascular diseases [2–4].

Relative to the adolescent period, Fagundes et al. reported that those individuals over 15 years of age consume on average 6.2 liters of pure alcohol per year [5]. Besides, their pattern of EtOH consumption is particularly dangerous, since adolescents consume high doses of EtOH for a short period of time. According to the National Institute on Alcohol Abuse and Alcoholism (NIAAA), binge drinking (BD) is an acute EtOH consumption model, which brings blood alcohol concentration (BAC) to 0.08 % or higher within 2 hours. Before and during the COVID-19 pandemic, this pattern of EtOH consumption has been the most widespread among teenagers [6,7], being a public health concern. Adolescence is a stage especially vulnerable to the toxic neural effects of EtOH; to engage in risk-taking behavior, such as initial drug consumption; and to increase a person´s propensity for later EtOH problems [8,9]. Finally, hormonal changes during puberty may also affect sensitivity to alcohol, making adolescents less sensitive to the effects of intoxication and increasing its consumption [10]. The BD alcohol consumption model in adolescents has been associated with numerous injuries and is involved in all of the major causes of mortality at this age: motor vehicle accidents, homicides, and suicides [11]**.** Moreover, recently the adolescent BD exposure has not only been associated with nervous harms [12], but also with long term systemic harms related to hepatic [13], metabolic [14], renal [15] and cardiovascular damage [16].

Acute EtOH consumption leads to different biological effects than chronic (Chr-EtOH), since in its metabolism, it produces higher amounts of reactive oxygen species (ROS) by increasing hepatic CYP2E1 activity [17]; and also because EtOH arrives in a higher amount to the extrahepatic tissues. Therefore, BD exposure is an especially potent pro-oxidant that could damage different tissues, compromising future adolescent health later in life. Clinically, it is well documented that Chr-EtOH consumption during adulthood decreases the antioxidant activity of glutathione peroxidase (GPx), a selenoprotein which needs selenium (Se) in its catalytic center; presenting these patients lower serum Se levels [18,19]. Moreover, serum Se levels showed a direct correlation with GPx activity and lipid oxidation, suggesting that serum Se/lipid oxidation ratio could be an indicator of hepatic damage caused by Chr-EtOH consumption; this points to Se as a

possible antioxidant therapy to alcoholic patients with liver disease [20]. Recently, Isobe et al. have found in adult patients that the alcohol intake is associated with serum Se levels and Selenoprotein P [21], a hepatokine related to insulin resistance, lipid profile and cardiovascular function. Clinical acute-EtOH studies in adults exposed to chronic heavy alcohol consumption also found lower serum and erythrocyte Se levels in these patients, which were independent of malnutrition, and returned to normal levels by cessation of EtOH ingestion; these data indicate a clear inverse correlation among acute EtOH intake and serum Se levels [22–25].

However, there are no clinical studies related to BD EtOH consumption and serum Se levels during adolescence. These data should be interesting since this depletion could be compromising the oxidative balance in the adolescence even more. Moreover, since plasma levels of metabolites are not a simple reflection of changes in tissue levels of the same metabolites [26], Se tissue deposits should be analyzed. In this context, preclinical animal research strategies are needed to enhance our understanding of the effects of BD consumption during adolescence on oxidative balance, Se and selenoproteins' tissue balance; and its relationship to metabolic and cardiovascular physiology. Considering the fact that there are few studies in adult acute-EtOH exposed mice showing that hepatic Se and SelP deposits are related to EtOH consumption [27], and that Se supplementation by modulating these deposits is effective avoiding oxidative, apoptotic, inflammatory and metabolic hepatic damage [27,28], only our research group has studied these effects in BD exposed adolescent rats [14,15,29–31]. This narrative review will try to summarize these findings.

2. BD and Oxidative Stress

Among the pathophysiological mechanisms that have been identified as causative factors in tissue and organ injuries as a consequence of excessive EtOH consumption, such as BD, are: acetaldehyde generation, adduct formation, mitochondrial injury, cell membrane perturbations, immune modulation, and oxidative stress (OS). Some of these mechanisms can appear as a result of direct alcohol-induced cell perturbations, while the others are the consequence of tissue alcohol metabolism [11]. Moreover, the consumption pattern, amount, frequency, and type of alcoholic beverages all contribute to provoking alcohol-induced tissue injury. For this reason, it is important to analyze EtOH metabolism and OS generation during BD exposition.

EtOH intake damages cells and organs in part due to the OS generated while this drug is being metabolized by the oxidative pathway. OS is an imbalance between the production of free radicals and the body's ability to detoxify or fight against their harmful effects by neutralizing them with antioxidants [32]. Studies with animals and humans indicate that BD can specifically increase, even more than other EtOH consumption patterns, the development of reactive oxygen

species (ROS) and decrease the antioxidant body activity [30,33–38]. The main ROS molecules generated by the organisms and by the BD-exposition include the superoxide anion (O_2^-), hydroxyl radical (•OH) and hydrogen peroxide (H_2O_2), these reactive species could lead to lipid, protein and DNA damage, which would compromise cell functioning [11,39]. Therefore, OS causes serious damage in different tissues, including liver and heart, since disturbances in the redox-equilibrium also trigger intracellular inflammatory and apoptotic signaling, which may further progress to different health issues related to cardiovascular function [40–42].

The oxidative metabolism of alcohol uses the enzymes alcohol dehydrogenase (ADH), cytochrome P450 2E1 (CYP2E1), and catalase (CAT), all of which generate acetaldehyde [43]. In mitochondria, the enzyme alcetaldehyde dehydrogenase (ALDH) subsequently coverts acetaldehyde into acetate which is then released from the liver into blood and thence exported to other tissues where it enters the Krebs cycle (KC) to be broken down into CO_2 and H_2O [44]. During this metabolism, both ADH and ALDH enzymes reduce NAD^+ to NADH, shifting the cellular redox ratio [45]. High NADH levels lead to an increase in ROS formation and a decrease in eNOS activity [38,46]. The liver is the main organ for metabolizing ingested alcohol – more than 90%; however, when BACs are high, EtOH can arrive to more tissues, where it is also metabolized leading to OS.

ADH is located in the cellular cytosol and plays a significant role in alcohol metabolism, however due to its low Km, it is saturated once the BACs exceed 15-20 mg/dL (2 × Km), as happens during BD [45,47]. Therefore during BD, alcohol is then oxidized by the CYP2E1 located in the endoplasmic reticulum, which has a significantly higher Km. CYP2E1 requires reduced nicotinamide adenine dinucleotide phosphate (NADPH) or NADPH-regenerating systems to act [48,49]. This results in the production of a high amount of ROS [11,50]. Induced CYP2E1 is described as a major contributor of the OS that causes a predisposition to experimental and clinical liver injury [51].

There is another pathway by which EtOH-exposure leads to OS. It has a direct action on the biological membranes of cells and organelles. In high amount, such as BD exposure, it damages the mitochondrial membrane and provokes a dysfunction of these organelles, causing ROS overproduction and reducing ATP production, displaying apoptosis [35,52,53].

In addition, alcohol consumption also affects the enzymatic and non-enzymatic antioxidant systems. BD-exposure decreases reduced glutathione (GSH), which plays an important pathogenic role in alcoholic liver disease [46,48,54]. Moreover, BD exposure disturbs the hepatic activity of the endogenous antioxidant system: Superoxide Dismutase (SOD), CAT, Glutathione Peroxidase (GPx), and Glutathione Reductase (GR) [15,29,33,55,56]. The SOD enzyme acts as

the first line of defense against free radicals, since it catalyzes the dismutation of O_2- to H_2O_2 and oxygen. Then, the H_2O_2 generated or lipid hydroperoxides are reduced by CAT and GPx enzymes to water and oxygen, and to water and alcohol respectively. GPx uses the GSH to reduce its substrate, working together with GR, an enzyme NADPH-dependent that regenerates GSH from its oxidized form, the glutathione disulfide (GSSG). This antioxidant system is unbalanced in adolescent rats exposed to BD, being the selenoprotein GPx the most affected enzyme [15,29,33,55].

BD exposure during adolescence generates not only hepatic oxidative damage, but also systemic and cardiac OS [55,57]. ROS generation alters the redox-homeostasis leading to systemic damage and increasing vascular endothelial growth factor (VEGF), which provokes microvascular proliferation-related cellular damage [42]. Besides, increased lipid peroxidation and nitric oxide promotes reduced cell viability, deoxyribonucleic acid damage and apoptosis via activation of caspase 3 in liver and heart [40,42]. In this context, the use of exogenous antioxidants in pro-oxidative situations significantly ameliorates the induced hyperlipidemia, the metabolic disturbances, the inflammatory response (via regulating the NFkB expression), and it avoids the loss of mitochondrial membrane potential decreasing the apoptosis [41].

3. **Selenium and Selenoproteins**

Selenium (Se^{34}_{79}) is a metalloid member of the group XVI of the periodic table, closely allied in chemical and physical properties with the elements sulfur and tellurium. It was discovered in 1817 by the Swedish chemist Jöns Jacob Berzelius. Se is a micronutrient, which plays an essential role in human health since, as part of the catalytic center of different selenoproteins, it is involved in a variety of physiological processes; the best known is its antioxidant capacity.

The Recommended Dietary Allowance (RDA) for Se intake is 20–30 μg/d for children, from 40 to 70 μg/d for adult males and, 45–60 μg/d for adult females, rising to 65 μg/day for pregnant women and 75 μg/day for lactating mothers [58,59]. No data is available regarding Se requirements for adolescents; this reference values are based on the values compiled for adults and are calculated taking into account body weights and growth factors. The resulting estimated values for Se intake are: for 10 to under 13 years old 45 μg/d, for 13 to under 15 years old 60 μg/d, and for 15 years old and more, like adults, the gender is taken into account [60]. Se intake is, however, considered a mixed blessing because it has been associated with negative health effects and it is characterized by a U-shaped relationship [61,62]. An increased risk of mortality, a depressed immune system (a decrease in T lymphocytes and in the activity of Natural killer cells), and cognitive decline (related with depression, anxiety, mental confusion, and hostility, epileptic seizures, and Alzheimer's) have all been associated with low Se levels. Meanwhile, moderate Se levels has antiviral effects, reduces the risk of autoimmune thyroid disease (Hashimoto's thyroiditis) and it is crucial for reproduction, reducing the risk of miscarriage

and improving sperm motility [61]. However, high Se levels are toxic (66 mg Se/Kg b/w) provoking diarrhea, abdominal pain, hypotension, poor perfusion, prolonged electrocardiogram QT intervals, hypokalemia, and death six hours after ingestion [63–65]. Urine is the dominant route of excretion of Se in monogastric. It depends on the amount of Se ingested, the chemical form, the composition of the food, the Se status of the animal and the percentage of the glomerular filtration. Se is also excreted by feces [66].

Se is present in grain, meat, seafood, and nuts, as well as dairy products. It is also used as a dietary supplement. In Spain, the Se content in food is low, in agreement with the low levels of Se in serum [67]. Rural areas of China, Siberia and parts of Europe are also Se-poor regions [68,69]. Severe and endemic Se deficiency is linked to Keshan disease, a myocardiopathy located in China and Kaschin-Beck disease, an endemic osteoarthritis in adolescents [70,71].

Se is present in a pivotal group of proteins called selenoproteins, so called because Se is incorporated in the form of selenocysteine (SeCys), a selenium-containing amino acid. Se in the form of SeCys is specified in the genetic code and is now recognized as proteinogenic amino acid 21 [72,73]. Moreover, it also has its own codon (UGA) which is normally the signal for protein synthesis completion [74]. To date, 25 selenoproteins have been identified in the human proteome [75]. Most selenoproteins have antioxidant effects and cell signaling and redox homeostasis functions like GPx family [76]. There are other selenoproteins which participate in different processes. The thioredoxin reductase (TrxRs), and iodothyronine deiodinase (DIOs) families participate in thyroid hormones regulation; selenoprotein W (SelW), selenoprotein H (SelH), selenoprotein T (SelT), selenoprotein V (SelV) in redox regulation processes; selenoprotein P15 (SeP15) in apoptosis regulation. Selenoprotein P (SelP) is the only selenoprotein that contains 10 SeCys residues. It is synthesized mainly in liver, regulates Se transport, storage, OS, immunomodulation and is related to the insulin resistance process.

In mammals, the GPx family (GPx1-GPx8) participates in the defense against OS. They reduce lipid hydroperoxides to their corresponding alcohols and free H_2O_2 to water [77]. GPx1 is pervasive in cytosol and participates in the reduction of H_2O_2 and lipid hydroperoxides [78]. GPx1 is the most sensitive to changes in both oxidative balance and Se status: low Se levels can cause a decrease in its mRNA and protein levels [79]. GPx2 is mainly expressed in the intestinal epithelium, acting as an antioxidant against ingested oxidants. GPx3 is found in the extracellular space and in plasma with a 10-fold lower activity than GPx1 [80,81]. GPx1, GPx2 and GPx3 operate in the aqueous phase, while GPx4 protects the membranes from oxidative damage, therefore reducing hydroperoxides to lipoproteins and complex lipids [77]. GPx4 function is also related to the transcriptional factor NFkB and apoptosis. Recently, Ojeda et al. have published that GPx4,

198 specifically, has an indispensable role in mitochondria, preventing their oxidation, apoptosis, and NFkB dysregulation,
199 being crucial in heart function [30]. In summary, GPx4 plays an antioxidant and anti-inflammatory role, reducing
200 peroxided complex lipids integrated in biomembranes from cells and organelles, and could avoid ferroptotic cell death in
201 cardiomyocytes upon metabolic stress [82]. GPx5, containing a cysteine (Cys) instead of SeCys in the active center, is
202 characterized as a protein secreted in the epididymis. GPx6 is a selenoprotein, whose function as yet remains unknown, is
203 found in humans, but not in rats or mice, and is expressed in the olfactory epithelium and embryonic tissues. GPx7 and
204 GPx8 are CysGPxs with low GPx activity, although they are the only selenoproteins that contribute to oxidative protein
205 folding in the endoplasmic reticulum [77,80–82]. The function of fifty percent of the selenoproteome still remains
206 undefined.
207 Depending on the amount of selenium, the tissue and physiological conditions, the synthesis of this Se is altered in
208 different ways [83]. As they are produced according to a certain hierarchy, the production of some selenoproteins
209 terminates when there is a scarcity of Se [84]. An example of this concept was provided by comparing the activities of
210 GPxs: GPx1 and GPx4 in rat liver, kidney, and heart. In a Se-deficient status, GPx1 activity falls dramatically, while
211 GPx4 activity is better maintained. This hierarchy is a tissue phenomenon, since each tissue synthetizes its own
212 selenoproteins; for instance, GPx1, GPx4, and SelP are specifically found in a rodent's hepatic tissue [85], yet GPx4 is
213 found mainly in heart and GPx3 in kidney and serum [86]. The regulation of selenoprotein's synthesis in each tissue,
214 therefore, needs to be researched.

215 **4. Se homeostasis and BD during adolescence**

216 It has recently been found that in rats BD exposure during adolescence profoundly affects Se homeostasis, leading to
217 severe Se depletion in serum, liver, kidney, and heart, accompanied by an imbalance in antioxidant selenoproteins'
218 expressions [30]. In this context, to demonstrate the role of Se and selenoproteins during BD exposure, the homeostasis of
219 Se has been studied in adolescent rats with BD exposure administered orally and intraperitoneally (i.p.) [29]. It was
220 demonstrated that BD during adolescence alters Se homeostasis regardless of the administration route employed. Despite
221 the fact that the BD oral group ingested less Se in diet than the i.p. group, leading to a lower Se apparent balance, the
222 changes in Se body distribution were similar in both BD models. BD rats exposed via i.p. intake a higher amount of Se in
223 diet, but this route of administration leads to higher oxidation by increasing cortisol levels, NOX activity and decreasing
224 GSH hepatic levels [33]. Consequently, more Se is needed in order to counteract this oxidation and, therefore, EtOH per
225 se, and not only because of the effect on dietary nutritional status, leads to a general body depletion of Se. Moreover, in
226 both BD models Se retention increased, in line with lower Se excretion via feces and urine. However, this effort was

insufficient and a decrease in serum and hepatic Se was found in both models, correlating with a descent in the activity and expression of several antioxidant selenoproteins and with an increase in lipid, protein, and DNA oxidation [29,33]. Se supplementation therapies could be a good strategy to prevent EtOH-oxidative damage. This narrative review is focused on the use of sodium selenite supplementation administered to BD adolescent rats, examining its effect in liver, kidney, heart, and systemic oxidative balance, related in part to the above organs functioning and their cardiovascular implications.

5. Selenium supplementation and BD during adolescence

5.1. Effects in liver

5.1.1. BD damage in liver function

Alcohol is one of the greatest causes of liver-related death worldwide related to its hepatotoxicity [11], leading to the alcoholic liver disease (ALD). ALD covers alcoholic fatty liver (steatosis), inflammation, fibrosis/cirrhosis, and increased risk of hepatocellular carcinoma [87]. However, despite the fact that among teenagers binge-alcohol exposition is one of the most widely-used intoxicating drug [88], and that it is specially pro-oxidant in liver [30] inducing hepatocyte apoptosis via the mitochondrial pathway [89], the effects of BD intoxication on the liver function in teenagers are not well characterized. In a recent clinical trial Binder et al. [13], it has been found that a single event of acute alcohol intoxication in adolescent increases aspartate transaminase (AST) and alanine transaminase (ALT) levels. Most liver diseases course with an increase in serum transaminases, especially ALT, except in ALD, where AST levels are twice those of ALT, with a resulting increase in the AST/ALT ratio, being this index a specific marker of ALD [90]. Similar results of this index were found in more than 90% of these teenagers, indicating damage in hepatocyte, and reflecting the fact that ALD is initiating. One difference among AST and ALT lies in the fact that AST is located within the cell, linked to mitochondria, while the ALT is free in the cytoplasm. This confirms what it was expected, that BD during adolescence affects the hepatocyte function mainly affecting mitochondria. Experimental research have confirmed these effects on transaminases serum levels after BD-exposure during adolescence and hepatocyte damage. Donohue et al. defend that acute EtOH administration during early growth contributes to steatosis development and to important metabolic disturbances related to future cardiovascular function.

In this context, it has been described that during adolescence BD affects mitochondrial functions and energy status by increasing the intramitochondrial NADH/NAD+ ratio, which produces ATP and ROS. The increase in ATP and ROS generated after BD exposure decreases AMP-dependent protein kinase (AMPK) activity (Figure 1a) [14]. AMPK is an important energy metabolism regulator. When a cell's energy state is diminished, AMPK activation restores energy

balance by stimulating catabolic processes that generate ATP and by downregulating anabolic processes that consume ATP [91]. It is also known, however, that the action of AMPK is suppressed by OS [92]. By generating ATP and ROS in liver, BD in adolescent rats decreases AMPK activity leading, among others, to higher Acetyl CoA carboxylase (ACC) activity and higher Malonyl CoA levels, increasing lipogenesis and preventing lipolysis, thus contributing to steatosis and to the development of ALD [93].

The mechanisms by which BD affects liver function are related in part to oxidation, inflammation, apoptosis and to changes in the mitochondrial energetic balance related to lipogenesis and lipolysis, which in turn leads to steatosis. Se supplementation as an antioxidant therapy with capacity to modulate lipid profile could, therefore, be a good strategy to prevent this kind of damage.

5.1.2. Se Supplementation and antioxidant effects

The descent of hepatic Se levels provoked by BD during adolescence is correlated with a decrease in the expression of hepatic GPx1 and GPx4, affecting liver oxidative balance (Figue1a). In the hepatocytes' cytoplasm the rest of the antioxidant enzymes' (GR, CAT and SOD) activities are increased, and a high lipid and protein oxidation appears. This points to GPx1 as a key factor in hepatic cytoplasm oxidative balance [30,45] GPx4 is the only selenoprotein associated with protecting biomembranes against oxidative insults, including mitochondria. GPx4 must be playing a crucial role in the hepatic damage caused by BD, since it is at the top of the selenoproteins hierarchy and should be maintained; however, it is decreased. Therefore, another stimulus apart from Se liver deposits is at work, modulating GPx4 expression. As other authors affirm, this factor could be the inflammatory modulator NFkB [94]. After BD GPx4 is related to a NFkB lower expression in the liver according to the greater clinical predisposition to develop an infection after acute EtOH exposition in adolescents and with greater apoptosis [30,95]. SelP P was, however, not affected by acute EtOH [30]. Therefore, its action delivering Se to serum and other tissues, and its relationship to AMPK inactivation seems to be unaffected. Surprisingly hepatic AMPK activation decreases after BD exposition, contributing to impair insulin signaling in the liver. In adolescent BD rats, sodium selenite supplementation repletes hepatic Se deposits, improving principally GPx1 expression and activity, preventing cytosolic lipid and protein oxidation [30]. Furthermore, CAT, SOD and GR activities were balanced (Figure 1b). Se supplementation increased hepatic GPx4 expression and decreased mitochondrial oxidation, increasing NFkB activation, and decreasing apoptosis [30].

After Se supplementation, AMPK was upregulated. This increased orchestrated by Se supplementation does not seem to be related to SelP expression, since it was unaffected. More studies are needed in order to understand SelP function in insulin resistance. This implies that OS plays a pivotal role in AMPK inactivation by BD. This link is even more

285 important, since it is increasingly clear that AMPK activation also has multiple actions on the inflammatory signaling
286 process [96].

287 *5.1.3. Physiological implications*

288 The Se supplementation used (0.4 ppm) prevents in part cytosolic and mitochondrial oxidation leading to a better
289 apoptotic and inflammatory profile and a better energetic-metabolic rate in hepatocytes. Therefore, the Se
290 supplementation used in BD-exposed rats improves hepatic function; it modifies transaminases' profile by decreasing
291 AST levels and thus compensating AST/ALT ratio [30]. This therapy also increases to normal values the hepatic
292 expression of NFkB p65, in consonance with the increase in serum pro-inflammatory cytokines and chemokines (IL-6,
293 MCP-1 and CINC-1) preventing future infections. Se supplementation avoids, in part, hepatic apoptosis since it leads to a
294 decrease in the pro-apoptotic caspase-3 activation and to an increase in the anti-apoptotic TIMP-1 which protects from
295 apoptosis modulating the Bcl-2 family of proteins and decreasing Bax expression, preventing cyt. c liberation and the
296 intrinsic apoptotic pathway [30,97]. Moreover, Se supplementation increases the hepatic activation of AMPK,
297 contributing to improving both energy and the metabolic state, probably decreasing lipogenesis and increasing lipolysis,
298 thus preventing steatosis [14].

299 ***5.2. Effects in kidney***

300 *5.2.1. BD damage in kidney function*

301 Acute EtOH exposure has deleterious structural and functional effects on kidney intimately related to hypertension (HT)
302 since EtOH consumption leads to a dysregulation of renal water and sodium excretion [98,99]. This imbalance is related
303 in part to an increase in anti-natriuretic hormones such as Aldosterone (Aldo) or Angiotensin II (AGTII) [100]. Aldo and
304 AGTII decrease the glomerular filtration rate (GFR) and constrict the peripheral vasculature, they are also related to the
305 genesis of vascular OS [101], elevating blood pressure values. In the case of repeated binge EtOH administration during
306 adolescence, a disturbance on renal electrolytes excretion, and a decrease in GFR have also been described, implying an
307 increase in water retention and high systolic blood pressure (SBP) [15,102,103]. The main mechanism that leads to all
308 these functional alterations related to oxidation seems to be the lipid peroxidation in kidney cells, the OS generated in
309 mitochondria which affects apoptosis and inflammation, and the high systemic OS generated [15]. Lipid peroxidation of
310 nephron epithelial cells interferes with carrier functions such as Na^+K^+-ATPase activity, affecting sodium and potassium
311 excretion [104]. After a large amount of EtOH exposure, such as that which occurs during BD, these oxidative effects are
312 greater, as well as the anti-natriuretic effect provoked. It has been reported that the high systemic OS caused by BD
313 exposure stimulates the Sympathetic Nervous System (SNS), the Hypothalamus-hypophysis-adrenal axis (HHA), and the

Renin-Angiotensin-Aldosterone System (RAAS), contributing to an increase in Aldo and AGTII concentration and to their anti-natriuretic effects, renal vasoconstriction and high SBP [105,106].

5.2.2. Se Supplementation and antioxidant effects

During BD exposure BACs are high and EtOH arrives in greater amount to kidney, which actively collaborates in EtOH metabolism, leading to high ROS production. The descent of kidney Se levels provoked by BD is correlated with a decrease in the expression of kidney GPx1< GPx4 <GPx3 (Figure 2a). This fact, together with the antioxidant enzyme imbalance that takes place (high SOD, CAT and GR activities), leads to cytosolic lipids and protein oxidation (Figure 2a) [15]. Furthermore, the amount of acetaldehyde generated by ADH and CYP2E1 enters the mitochondria, where it is oxidized to acetate by ALDH. This acetate together with the acetate taken up from blood, highly increases the KC and Ox-Phos pathways leading to mitochondrial OS. This is related to higher caspase-3 activation and a lower NFkB activation, thus increasing apoptosis (Figure 2a). The EtOH-OS-apoptosis relationship occurs mainly in tubular epithelial cells [107]. Recently Li et al. found that in pigs Se deficiency disrupts oxidative balance and activates inflammation in kidneys, leading to inflammatory lesions and renal tubular atrophy by downregulating, among others, selenoproteins GPx1 and GPx3 [108]. However, little is known about BD renal Se deposits and NFkB related to inflammation and/or fibrosis.

GPx3 is the main selenoprotein expressed in kidney [109]. It acts both on the proximal tubes of nephrons, reducing H_2O_2 to water, and acts also on plasma being the largest source of plasma GPx [86]. Kidney probably acts as a GPx3 reservoir that can be mobilized when needed to combat oxidative challenges in plasma or in other parts of the body, such as the challenges which occur after BD exposure. Therefore, this decrease in GPx3 expression contributes to inducing OS in plasma and kidney cells after BD exposure. Moreover, kidney is also an important Se reservoir [108], since the excess of Se is mostly excreted into urine or retained in kidney. After BD exposition, Se renal clearance is decreased [15], however serum Se values and kidney deposits are decreased. This confirms the fact that repeated BD exposure consumed Se drastically.

Sodium selenite supplementation in drinking water administered to adolescent BD rats increased GPx1 expression and activity by increasing renal Se deposits and reduced GR activity. Despite the fact that SOD and CAT activity remained high, cytosolic lipid oxidation was prevented completely (Figure 2b) [15]. Sodium selenite supplementation also increased GPx4 expression. This probably decreased mitochondrial oxidation which, in turn, decreased caspase-3 and increased NFkB activation avoiding apoptosis. GPx3 expression is also increased, thus intensifying the activity against ROS in kidney and in plasma [86,110].

5.2.3. Physiological implications

These improvements in oxidative balance and GPxs, NFkB p65 and cleaved caspase-3 expression following Se supplementation are related to better kidney functional parameters in adolescent rats exposed to a repeated BD exposure model. In this model, BD leads to a lower GFR, causing hypernatremia, hypokalemia, hyperaldosteronism, and a low relative Aldo clearance value [15]. Therefore, BD consumption during adolescence, when the RAAS system is especially active, leads to a large hydric and electrolyte disturbance that, together with a systemic oxidative process, cause an increase in SBP [111]. Supplementation with the antioxidant Se principally improves electrolyte balance-related functions. This is due to the fact that lipid peroxidation interferes with carrier functions such as Na^+K^+-ATPase activity, increasing Na^+ reabsorption and K^+ excretion [104], especially in the renal papillary collecting duct cells [112]. Moreover, Se supplementation also reduces serum Aldo levels and SBP by decreasing systemic OS and RAAS stimulation and, since Se improves hepatic function, by increasing its renal excretion probably by improving hepatic Aldo clearance [30,113]. However, the functions related to filtration processes are not improved by Se supplementation. This could be due to the fact that the GFR reduction is mainly related to the inflammatory process generated in podocytes, these latter being highly OS resistant [114].

5.3. Effects in heart

5.3.1. BD damage in heart function

Different studies report a J-shaped curve relationship between the amount of alcohol consumption and CVD, the dose and pattern of alcohol consumption being the greatest modulators of these effects [115]. In this context, repeated BD consumption during adolescence is clinically associated with a higher risk of HT, vascular dysfunction and cardiac arrhythmias [3,4,16]. Acute EtOH induces general oxidation which activates the SNS and RAAS, leading to HT [11,105]. The mechanisms implicated in cardiovascular damage are complex; BD in young adults produce vascular OS, inflammation, activation of the SNS and RAAS, impairment of the baroreceptors, changes in endothelial and smooth cell function and vascular reactivity which affects coronary arteries and heart function. Moreover, BD also directly affects heart function since it provokes OS and apoptosis and increases the vulnerability of the myocardium to the development of arrhythmias by altering myocardial electrophysiological properties [116,117]. Recently Lizhuo et al. [118] have found that BD exposition in adolescent rats impedes the normal rapid physiological growth of heart and reorients it towards pathological hypertrophy. These cardiac structural alterations persist through adolescence even after cessation of EtOH exposure. They also concluded that the adolescent heart is substantially more sensitive to EtOH damage than adult ones.

5.3.2. Se Supplementation and antioxidant effects

372 The excess of EtOH in blood after BD exposure could be oxidized in heart (Figure 3a). Due to the lack of ADH in the
373 heart, cardiomyocytes metabolize EtOH mainly through the enzyme CAT, which also acts upon myocardial morphology
374 and hemodynamics [119]. However, depending on EtOH concentration, CYP2E1 could be up-regulated in heart
375 contributing to ROS generation [120]. These ROS generated, together with the antioxidant enzyme imbalance (high CAT
376 and GR and low GPx1 activities) [55], leads to cytosolic oxidation of lipids and proteins.
377 Like in kidney, the acetate generated by EtOH metabolism together with the acetate taken up from blood in an
378 uncontrolled manner [44], increases mitochondrial ROS overproduction (Figure 3a). This fact together with the extremely
379 lower GPx4 expression found in BD heart, leads to mitochondrial oxidation [55], caspase-3 activation and to a higher
380 NFkB p65 activation. In heart, prolonged and excessive ROS production can activate NFkB, leading to the activation of
381 proinflammatory and proapoptotic pathways, increasing harmful cytokines production [121].
382 Since expression of GPx3 is not affected after BD exposure, despite it being halfway down the Se-specific hierarchy, it
383 probably has another action in heart [55]. Apart from its ability to serve as an ROS scavenger in extracellular matrix
384 spaces [122], it has been defended that an increase in GPx-3 may play a significant role in protecting cardiomyocytes from
385 OS caused by hyperglycemia. In this context, adolescent BD rats also present hyperglycemia [30]. GPx3 could, therefore,
386 play an important role in the heart of BD animals, preventing OS generated by hyperglycemia in myocytes and for this
387 reason it is either conserved or derived from blood.
388 By increasing heart Se deposits, sodium selenite supplementation in adolescent BD rats increases GPx1 expression and
389 activity; thus, it decreases intracellular myocyte lipid and protein oxidation [55]. It also greatly increases GPx4 expression
390 and protects mitochondria from oxidation [123], decreasing the release of cyt. c owing to its inner membrane location in
391 mitochondria and its ability to repair cardiolipin peroxidation [124]. For these reasons, Se supplementation decreases
392 caspase-3 activation in myocytes, decreasing apoptosis [55]. Moreover, GPx4 also protects from ferroptotic cell death (a
393 lipid ROS-induced cell death programmed) in cardiomyocytes during metabolic stress [125]. The higher GPx4 expression
394 could specifically interfere with NFkB activation by interleukin-1, decreasing the synthesis of leukotrienes and
395 prostanoids, modulating inflammatory process [84] (Figure 3b).
396 *5.3.3. Physiological implications*
397 It can be concluded that BD is related to cardiac oxidation, apoptosis and inflammation in adolescent rats and that Se
398 supplementation decreases these alterations. Previous studies find a relationship among EtOH consumption and these
399 biomolecular alterations and an increase in stroke volume and SBP [120,126,127]. However, it is also related to

myocardial contractile dysfunction which affects heart rate (HR), since OS alters myocardial electrophysiological properties [116,117], increasing the vulnerability of the myocardium to developing arrhythmias. Moreover, it is also recognized that, following BD consumption, mitochondria are the main organelles in heart damaged by OS [128]. This affects their function – intimately linked to cardiovascular biology – since cardiomyocyte mitochondrial damage alters calcium dynamics and leads to cardiac fibrosis [11]. In this context, it is important to point out that Se deficiency is profoundly associated with cardiac pathology [105,121,129,130]. In fact, adolescent BD rats present higher SBP, DBP, MBP and HR [55].

Se supplementation to BD rats protects mitochondria mainly by increasing GPx4 which is especially important for a correct cardiac energy function. These actions have a great effect on heart function by sharply decreasing cardiac HR and preventing tachycardia. Despite these important protective roles in heart, and the fact that Se supplementation improves electrolyte renal imbalance, and decreases serum Aldo values, this therapy only partially decreases SBP. This was the reason for undertaking vascular studies.

It has been demonstrated that BD exposition to adolescent rats leads to systemic OS by leading to lipid and protein plasma oxidation and to a dangerous oxidation in lymphocytes DNA [34] together to an unbalanced antioxidant system in which serum GPx (GPx3) is decreased [15]. Systemic OS is intimately related to vascular function and blood pressure (Figure 4) [131]. According to that, it has been found that BD exposition increased serum vascular endothelial markers such as Vascular Endothelial Growth Factor (VEGF), Connective Tissue Growth Factor (CTGF), Caveolin 1 (Cav-1) and Plasminogen Activator Inhibitor-1 (tPAI-1) [55]. These results indicate that BD exposition affects vascular endothelial function contributing to blood pressure dysfunctions. The beneficial actions of Se on vasculature physiology have been previously described. It has anti-atherosclerotic properties possibly by regulating cholesterol (Chol) metabolism and reducing OS through GPx and SelP activities [132]. Sodium selenite supplementation to BD adolescent rats by increasing serum Se levels increased GPx3 activity avoiding serum lipid oxidation and lymphocyte DNA oxidation contributing to lower systemic OS [15,55]. This supplementation also decreased the levels of proangiogenic growth factors VEGF and CTGF, which have deleterious effects in vascular function; however, Se supplementation increased even more serum Cav-1 and tPAI-1 levels in BD rats (Figure 4) [55]. Se is a mineral intimately related to lipid homeostasis [133], in this context, t-PAI-1 secretion is modulated by triacylglycerol in liver [134], maybe Se and tPAI-1 synthesis could be related via lipid homeostasis. In the same line, among other functions, Cav-1 plays an important role in Chol trafficking [135], being crucial for controlling mitochondrial Chol levels avoiding this organelle dysfunction [136]. However, these

relationships among Se and t-PAI-1 and Cav-1 should be deeply studied, in order to know if these effects are beneficial or not to vascular endothelial function.

6. Conclusions

In summary, BD is a potent pro-oxidant pattern of alcohol consumption, since during its oxidative metabolism in different tissues great amount of ROS in cytoplasm and organelles -especially mitochondria- are generated. This OS affects organs functions, and increased risk for developing HT and steatosis, which could lead to chronic conditions such as CVD or insulin resistance in later life. Furthermore, in all the tissues studied there is a depletion of Se deposits. However, antioxidant selenoproteins expressions are affected in different ways, in part by their Se-hierarchy, in part by the kind of EtOH-oxidative enzymes presented in each tissue. For instance, in liver where there are high ADH and CYP2E1 activities, OS mainly takes place in cytosol and there is a deep decrease in cytosolic GPx1 expression. In kidney, where there is a moderate activity of ADH and CYP2E1 together with an increase in acetate import from blood, GPx3 expression is mainly affected. In heart, where there is a moderate activity of CAT and CYP2E1 along with an increase in acetate import from blood, OS takes place mainly in mitochondria, being GPx4 expression severely impaired. The OS generated is also related to inflammation, apoptosis and an unbalanced energy process in tissues. However, sodium selenite supplementation to BD adolescent rats increases Se deposits in all the tissues studied and the expression of all the selenoproteins affected. Therefore, further animal and human studies should be considered to support the theory that Se supplementation to BD adolescents could be a cheap and efficient therapy for mitigating the adverse effects of alcohol in heart, kidney, and liver functions, while decreasing the possibility of developing CVD during adolescence or later in life.

Limitations of the revision:

In order to extrapolate to humans, the results exposed above, there are two main limitations, both related to the fact that most of the studies analyzed are obtained by an experimental rat model of BD. The first one is that certain authors defend that some characteristics found in human adolescents are clearly unique, although there are other key characteristics of this developmental stage that are common across species. However, it seems that those related to alcohol intake are mainly common among human and rats [8,137]. The BD i.p. model mainly analyzed in this review assesses the validity of animal models in human psychopathology based on Face validity, Predictive validity, and Construct validity.

The second limitation of the data analyzed in this revision is related to the fact that peak BACs are not similar among humans and rats. Although in both cases BACs are higher than to 0.08 % according to BD definition, these values remain longer in humans. However, they present similar BACs levels in the first hour after exposition [138].

It is also important to point that the history of the BD behavior in humans is difficult to investigate. However, forced rodent models of BD, such as the i.p. model analyzed in this review, allow greater control over environmental parameters,

such as Se intake. In summary, data obtained from this revision could lead to future clinical BD-exposed teenagers' studies, which could analyze hepatic profile and cardiovascular risk factors, related for instance to Se, GPx1 and SelP serum levels.

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Declarations

Conflicts of Interest: The authors declare no conflict of interest.

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FIGURE CAPTIONS.

Fig. 1 EtOH metabolism in liver: oxidative implications. **Effects of sodium selenite supplementation** (**A**) EtOH is oxidized in hepatocytes, mostly through the alcohol dehydrogenase (ADH) enzyme, which in turn produces an increase in cytoplasmic NADH/NAD^+ ratio. In BD exposure, ADH is saturated (KM < 5 mM) and CYP2E1 increases its activity, generating a large amount of ROS, that together with an imbalance of the antioxidant enzymes Superoxide Dismutase (SOD), Catalase (CAT), Glutathione Peroxidase 1 (GPx1) and Glutathione Reductase (GR), leads to cytosolic lipid and protein oxidation (OS). This large amount of ADH- and CYP2E1-generated acetaldehyde enters the mitochondria and is oxidized into acetate by acetaldehyde dehydrogenase (ALDH), increasing intramitochondrial NADH/NAD^+ ratio. The acetate formed is converted into Acetyl CoA which enters the Krebs cycle (KC) and via oxidative phosphorylation (Ox-Phos) produces ATP and ROS. At blood alcohol levels greater than 0.01 g/dL, hepatic KC is markedly suppressed, and the remaining acetate is exported into the blood. The increase in ATP and ROS production in mitochondria decreases AMP-dependent protein kinase (AMPK) activity. This decrease leads to higher Acetyl CoA carboxylase (ACC) activity and higher Malonyl CoA levels which increase lipogenesis and prevents lipolysis. High mitochondrial ROS production, together with lower GPx4 expression, leads to mitochondrial OS. This, in turn, is related to higher caspase-3 activation and apoptosis, as well as to a lower NFkB activation. Despite the lower Se deposits in liver caused by BD, expression of the main hepatic selenoprotein SelP is not affected by BD exposure, and, therefore, its action delivering Se to serum and other tissues seems to be unaffected; (**B**) Sodium selenite supplementation in adolescent BD rats by increasing hepatic Se deposits, increases GPx1 expression and activity, preventing cytosolic lipid and protein oxidation. It also increases GPx4 expression and decreases mitochondrial OS. This latter reduces apoptosis, increases NFkB activation and increases AMPK activity, while also improving hepatic lipid profile. Solid lines and hatched lines indicate stimulatory and inhibitory actions, respectively.

Fig. 2 EtOH metabolism in kidney: oxidative implications. **Effects of sodium selenite supplementation** (**A**) EtOH is mostly oxidized in hepatocytes, but when EtOH arrives in large amounts to blood, as occurs in BD exposure, other tissues collaborate with liver. This is the case of kidney; kidney cells contain the enzyme alcohol dehydrogenase (ADH), which in turn produces an increase in cytoplasmic NADH/NAD^+ ratio. If this is not sufficient, it could increase CYP2E1 activity generating large amount of ROS, which together with antioxidant enzyme imbalance leads to cytosolic lipids and protein oxidation. The amount of acetaldehyde generated by ADH and CYP2E1 enters the mitochondria and is oxidized to acetate by acetaldehyde dehydrogenase (ALDH), this acetate production, together with the acetate taken up from blood increases intramitochondrial NADH/NAD^+ ratio. Acetate is converted to Acetyl CoA which enters the Krebs cycle (KC) and via oxidative phosphorylation (Ox-Phos) produces ATP and ROS. Mitochondrial ROS production, together with a lower GPx4 expression, leads to mitochondrial OS. This, in turn, is related to higher caspase-3 activation and apoptosis, and to a lower NFkB activation. The lower Se deposits in kidney caused by BD also affects expression of the main kidney selenoprotein, GPx3, which decreases. Therefore, its action delivering Se to serum decreases; **(B)** Sodium selenite supplementation in adolescent BD rats by increasing renal Se deposits increases GPx1 expression and activity, preventing cytosolic lipid oxidation. Supplementation also increases GPx4 expression and decreases mitochondrial OS, decreasing apoptosis and increasing NFkB activation. It also increases GPx3 expression which probably will shunt Se to serum. Solid lines and hatched lines indicate stimulatory and inhibitory actions, respectively.

Fig. 3 EtOH metabolism in heart: oxidative implications. **Effects of sodium selenite supplementation** (**A**) Heart, due to the lack of ADH, may oxidize some ethanol mainly through CAT and/or CYP2E1, but these rates are low, however, it could generate ROS that joint to an imbalanced antioxidant system leads to cytosolic oxidation of lipids and proteins. The acetaldehyde generated by CAT and CYP2E1 enters the mitochondria and is oxidized to acetate by acetaldehyde dehydrogenase (ALDH). This acetate, together with the acetate taken up from blood in an uncontrolled manner, increases the intramitochondrial NADH/NAD^+ ratio. Acetate is converted to Acetyl CoA which then enters the Krebs cycle (KC) and via oxidative phosphorylation (Ox-Phos) produces ATP and ROS. Mitochondrial ROS production, together with the extremely low GPx4 expression, leads to mitochondrial OS. This, in turn, is related to higher caspase-3 activation and apoptosis, and to a higher NFkB activation (fibrosis). The lower heart Se deposits caused by BD do not affect the extracellular expression of GPx3 in heart, a protein is related to serum glucose alteration; **(B)** Sodium selenite supplementation in adolescent BD rats increases Se heart deposits; increases GPx1 expression and activity preventing cytosolic lipid and protein oxidation. It also increases GPx4 expression and decreases mitochondrial OS, thus decreasing apoptosis and NFkB activation. Solid lines and hatched lines indicate stimulatory and inhibitory actions, respectively.

Fig. 4 EtOH metabolism in plasma. Effects of sodium selenite supplementation High EtOH consumption leads to large amount of acetate and ROS in plasma, but it also provokes an unbalanced antioxidant system in which serum GPx (GPx3) decreases, generating lipid and protein oxidation in serum. BD exposure also generates profound oxidation in lymphocytes DNA; therefore, systemic OS appears. This OS could be related to the increase in serum endothelial markers such as Vascular Endothelial Growth Factor (VEGF), Connective Tissue Growth Factor (CTGF), Caveolin 1 (Cav-1) and Plasminogen Activator Inhibitor-1 (tPAI-1). By increasing serum Se levels, sodium selenite supplementation in adolescent BD rats increases GPx3 activity preventing serum lipid oxidation and lymphocyte DNA oxidation, leading to

lower systemic OS. This supplementation also decreases the levels of proangiogenic growth factors VEGF and CTGF, something that is considered beneficial; however, the increase in serum Cav-1 and tPAI-1 was even greater.