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Effect of Weekend Alcohol Consumption on Hepatic Antioxidant Enzyme Activity: Role of Concentration and Gender

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Abstract: Background/Objectives: It is known that chronic alcohol consumption causes alterations to various organs of the body, mainly the liver, but there are no reports of the damage that weekend alcohol consumption can cause to the liver. The liver is the main organ responsible for metabolizing ethanol and therefore experiences the most significant adverse effects of this xenobiotic's toxicity. In this study, we evaluated the effect of weekend alcohol consumption on the activity of hepatic antioxidant enzymes. **Methods:** Wistar rats weighing 170–200 g were divided into the following groups: (1) control group and (2) weekend alcohol consumption group, 2 days per week for 12 weeks at two different concentrations: (1) group of males and females consuming a 40% alcohol solution and (2) group of males and females consuming a 5% alcohol solution. At the end of the experiment, liver samples were obtained. The activity of the enzymes catalase, superoxide dismutase, glutathione reductase, and glutathione peroxidase, as well as the levels of total antioxidant capacity and thiobarbituric acid reactive substances, were determined. **Results**: surprisingly, the results showed an increase in the activity of antioxidant enzymes, as well as a decrease in thiobarbituric acid reactive substances. **Conclusions:** weekend alcohol consumption for a period of 3 months led to an elevation in antioxidant enzyme activity, but it was not sufficient to prevent the damage caused to the liver by weekend alcohol consumption.

Keywords: alcohol; weekend consumption; damaged liver; antioxidant enzymes

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1. Introduction

Alcohol consumption causes progressive damage to various organs and tissues of the human body [1–4]. Worldwide there is excessive and varied consumption of alcohol, specifically in Mexico, where the main alcoholic beverages consumed are beer and spirits (brandy, tequila, rum, whiskey, cognac, vodka, etc.) [3], which contain approximately 5% and 36–40% alcohol, respectively [1]. Regarding alcohol consumption patterns, daily, excessive, and weekend consumption have been reported and have been associated with gender, age, socioeconomic level, consumption habits, and types of alcoholic beverages (wine and mixed drinks) [5,6]. According to the ENCODAT 2016 report, 2.9% of young Mexicans engage in daily alcohol consumption and 8.5% have habitual weekend consumption. It

was also found that the main consumers of weekend alcohol are men; on the other hand, there are more and more women who consume weekend alcohol and are prone to liver damage due to alcohol [3,7].

There are few studies on ethanol consumption during the weekend. Morales-González et al. [8] reported the harmful effects caused by alcohol consumption over the weekend, with a higher impact observed in the female group. They found that weekend alcohol consumption leads to liver damage, characterized by biochemical and histological alterations that initially present acutely. Prolonged consumption can result in more severe and irreversible damage [8]. González-López et al. [9] studied the effects of weekend alcohol consumption on the oral cavity, discovering that this pattern of alcohol intake leads to tissue alterations in the oral cavity, likely associated with an increase in oxidative stress (OS) [9]. This is probably due to elevated oral peroxidase activity in individuals who regularly consume alcohol, producing oxidative stress and damage to the oral cavity [10].

Liu et al. [11] reported an increase in total cholesterol and HDL-C levels with daily versus weekend alcohol consumption and found a decrease in LDL-C levels with daily and moderate alcohol consumption, while LDL-C levels were significantly elevated with weekend alcohol consumption. Finally, the authors reported a greater increase in blood alcohol levels and weight gain with weekend alcohol consumption, concluding that weekend alcohol consumption had a greater impact on the body and favored the development of atherosclerotic plaque (increase plaque, decreased lumen diameter, etc.), while the opposite occurred with moderate daily alcohol consumption [11]. Reports found in the literature demonstrate the damage to the liver caused by alcohol consumption [12–15], but the damage or alterations caused by weekend alcohol consumption to the liver have not been described to date; in particular, there are no reports on changes in the activity of antioxidant enzymes with this type of alcohol consumption in liver tissue.

The levels of antioxidant enzymes are influenced by the timing of ethanol administration [16,17]. Parra et al. [18] administered a single ethanol dose of 1.5 g/kg bw and observed an increase in thiobarbituric acid reactive substances (TBARSs) content and a decrease in superoxide dismutase (SOD) enzyme activity. Morales-González et al. [19] administered a daily ethanol dose of 1.5 g/Kg bw and found an increase in TBARSs, along with a surprising increase in antioxidant defenses [total antioxidant capacity, catalase, SOD, glutathione reductase (GR), and gluthathione peroxidase (GP)]. Ramirez et al. reported the increase in TBARS content in both serum and liver due to ethanol consumption [20].

2. Materials and Methods

2.1. Experimental Design

Wistar rats (Rattus norvegicus) weighing 200 g were used. Rodents were housed at room temperature with access to water and food ad libitum (LabDiet Formulab diet A-8003-037). All procedures were approved by the research committees and by CICUAL, with registration numbers ESM.CI-01/13-06-2017 and ESM.CICUAL-12/23-06-2017, respectively. The procedures were carried out in accordance with the Mexican Official Standard for the Use and Care of Laboratory Animals (NOM-062-ZOO-1999).

The rats were divided into experimental groups based on alcohol consumption:

(a) control group: female or male rats that received only water and food ad libitum without ethanol.

(b) the 40% group: female or male rats that consumed 40% alcohol with ad libitum access in the drinking bowl, 2 days a week for 3 months.

(c) the 5% group: female or male rats that consumed 5% alcohol with ad libitum access in the drinking bowl, 2 days a week for 3 months.

After 3 months of treatment, the experimental rats were euthanized by decapitation after prior anesthesia with sodium pentobarbital (40 mg/kg of bw).

2.2. Liver Samples

The liver was briefly treated as usual: it was isolated, weighed, and placed in a PBS buffer, then homogenized using a sucrose buffer (0.25 M sucrose, 10 mM TRIS, and 0.3 mM EGTA at pH 7.4). The total protein concentration of the homogenate was determined using the Lowry method [21], with a BSA solution as standard.

2.3. Determination of Antioxidant Enzymes

Catalase enzyme activity was measured using the Catalase Assay Kit (707002); superoxide dismutase enzyme activity was measured using the superoxide dismutase Assay Kit (706002); glutathione reductase enzyme activity was measured using the Glutathione Reductase Assay Kit (703202); and glutathione peroxidase enzyme activity was measured using the Glutathione Peroxidase Assay Kit (703102), following the manufacturer's instructions (Cayman Chemical, Ann Arbor, MI, USA). The results are expressed in nmol/mg (catalase and glutathione reductase) and as U/mg (superoxide dismutase and glutathione peroxidase).

2.4. Total Antioxidant Capacity in Liver and Determination of Thiobarbituric Acid Reactive Substances

Total antioxidant capacity (TAC) was determined using an Antioxidant Assay Kit (709001), and thiobarbituric acid reactive substances (TBARSs) were determined using the TBARS Assay Kit (10009055), following the manufacturer's instructions (Cayman Chemical, Ann Arbor, MI, USA) and reporting results in nmol/mg (Trolox) (TAC) and in nmol/mg of protein (TBARSs).

2.5. Statistical Analysis

The results were analyzed using the statistical program SigmaPlot ver. 12.3. Results are expressed as mean ± SEM, as appropriate. Statistical analysis was performed using Student's *t*-test and/or analysis of variance (ANOVA). We considered differences between groups to be statistically significant when $p < 0.05$.

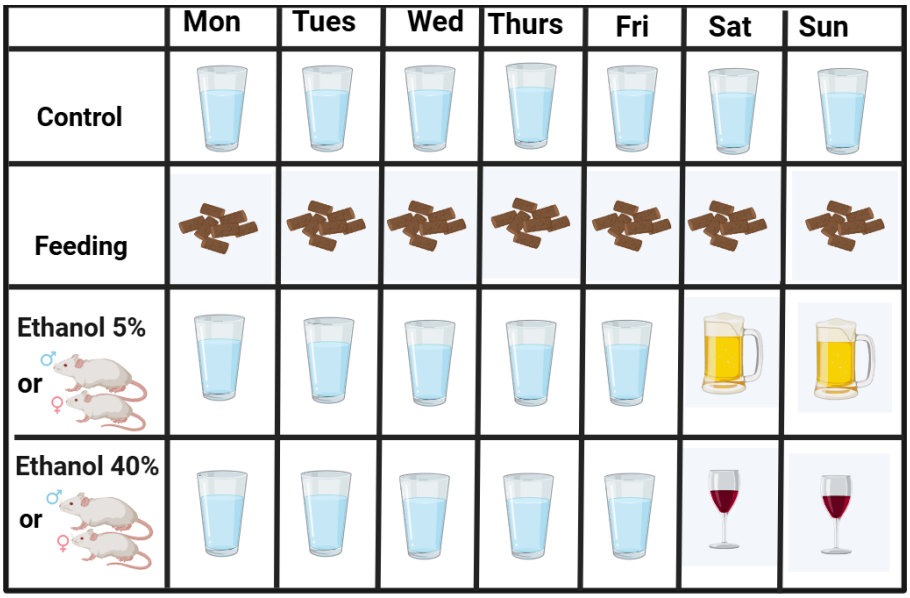
3. Results

3.1. Effect of Weekend Alcohol Consumption on Weight Gain and Alcohol Consumption

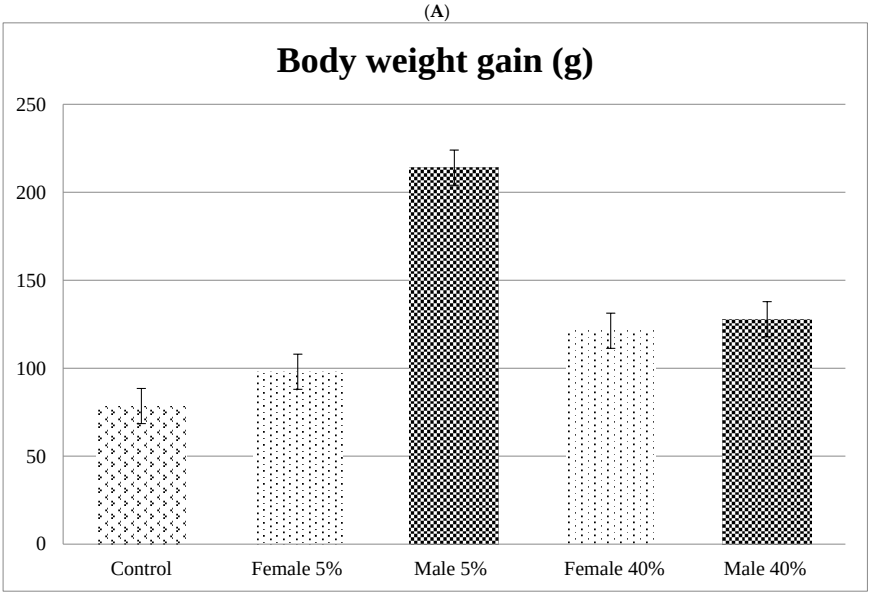
The mean alcohol consumption per group was as follows: in the females, alcohol consumption at 5% was 0.83 g/kg per day; in the male group at 5%, it was 1.63 g/kg per day, and in the female and male groups at 40%, it was 5.52 and 2.26 g/kg per day, respectively. Regarding body weight gain, the most significant increase occurred in the male group at 5% alcohol consumption (108%), followed by the male group at 40% alcohol consumption (73%) (Figure 1).

3.2. Effect of Weekend Alcohol Consumption on Catalase Activity

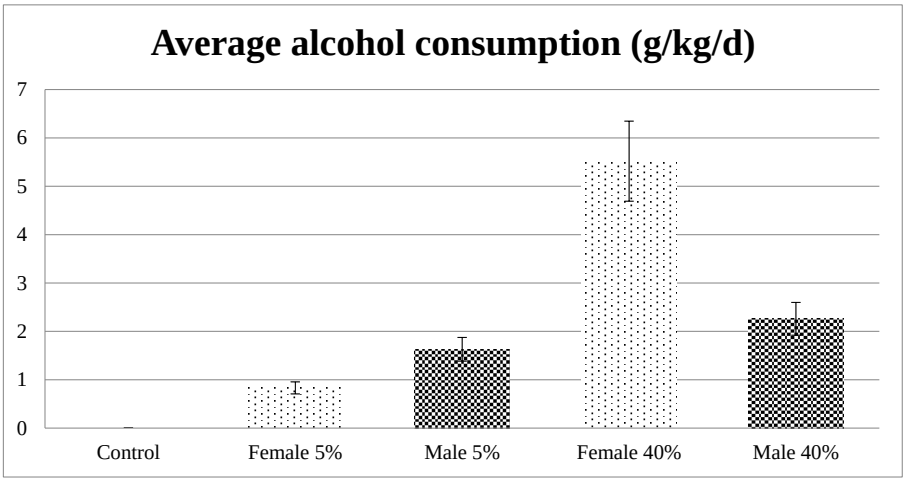
Table 1 shows the levels of catalase enzyme activity. When comparing the group of males with 5% alcohol consumption (1628.97 ± 451.22 nmol/mg) versus the group with 40% alcohol consumption (4117.9 ± 158.67 nmol/mg), a statistically significant difference was observed ($p < 0.05$). In the group of females with 5% alcohol consumption, catalase levels were 1267.86 ± 277.46 nmol/mg versus the group of females with 40% alcohol consumption, showing a statistically significant difference ($p < 0.05$). A significant difference ($p < 0.05$) was also observed between the male and female groups at 40% concentration compared to the control group.



(**A**)



(**B**)



(**C**)

Figure 1. Schematic diagram of the study design. Alcohol feeding regimen (**A**), effect of weekend alcohol consumption on weight gain (**B**), and alcohol consumption (**C**). Created with BioRender.com (**A**).

Table 1. Levels of catalase enzyme activity in the groups studied.

Group	nmol/mg
Control	650.43 ± 208.20
Females 5%	1267.87 ± 277.46 [a]
Males 5%	1628.97 ± 451.22 [a,b]
Females 40%	8141.51 ± 107.45 [a]
Males 40%	4117.9 ± 158.67 [a,c]

Values are expressed as mean ± SE in each experimental group (n = 5). [a] $p < 0.05$ vs. control group, [b] $p < 0.05$ vs. 5% group, [c] $p < 0.05$ vs. 40% group.

3.3. Effect of Weekend Alcohol Consumption on Superoxide Dismutase (SOD) Enzyme Activity

The control group had SOD levels of 388.95 ± 63.51 U/mg. The male group with 5% alcohol consumption showed levels of 449.72 ± 140.15 U/mg versus 253.38 + 52.96 U/mg in the male group with 40% consumption; however, this difference was not statistically significant between groups (5% versus 40%), nor when comparing these groups to the control. In the female group with 5% alcohol consumption, SOD levels were 214.46 ± 23.58 U/mg, whereas in the group with 40% alcohol consumption, the levels were 471.81 ± 138.37 U/mg, showing no statistically significant difference. A statistically significant difference ($p < 0.05$) was observed when comparing the female group with 40% alcohol consumption to the control group (Table 2).

Table 2. Levels of SOD enzyme activity in the various groups.

Group	U/mg
Control	388.95 ± 63.51
Females 5%	214.46 ± 23. 58 [a]
Males 5%	449.72 ± 140.15 [a,b]
Females 40%	471.81 ± 138.37 [a]
Males 40%	253.38 ± 52. 96 [a,c]

Values are expressed as mean ± SE in each experimental group (n = 5). [a] $p < 0.05$ vs. control group, [b] $p < 0.05$ vs. 5% group, [c] $p < 0.05$ vs. 40% group.

3.4. Effect of Alcohol Consumption During the Weekend on Glutathione Reductase (GR) Enzyme Activity

The male group with 5% alcohol consumption presented a GR activity of 759.08 ± 79.20 nmol/mg, whereas the male group with 40% alcohol consumption showed 595.33 ± 77.05 nmol/mg with no statistical significance observed. In the female group with 5% alcohol consumption, the GR level was 723.53 ± 149.45 nmol/mg versus 896.08 ± 131.44 nmol/mg in the female group with 40% alcohol concentration, which did not show statistical significance. However, when comparing the female group with 40% alcohol concentration versus the control group (586.82 ± 49.72 nmol/mg), a statistically significant difference was observed ($p < 0.05$) (Table 3).

Table 3. Levels of glutathione reductase enzyme activity in the various groups.

Groups	nmol/mg
Control	586.82 ± 49.72
Females 5%	723.53 ± 149.45 [a]
Males 5%	759.07 ± 79.20 [a,b]
Females 40%	896.08 ± 131.44 [a]
Males 40%	595.33 ± 77.05 [a,c]

Values are expressed as mean ± SE in each experimental group (n = 5). [a] $p < 0.05$ vs. control group, [b] $p < 0.05$ vs. 5% group, [c] $p < 0.05$ vs. 40% group.

3.5. Effect of Weekend Alcohol Consumption on Glutathione Peroxidase (GPx) Enzyme Activity

In Table 4, the GPx levels are observed. In the control group, the GPx level was 1465.58 ± 54.53 U/mg. When comparing this group with the male group at both 5% (7085 ± 198.51 U/mg) and 40% (4092.79 ± 707.84 U/mg) alcohol concentrations, statistically significant differences were observed ($p < 0.05$). Similarly, when comparing the control group with the female group at 5% (2842.33 ± 821.67 U/mg) and 40% (4787.91 ± 106.63 U/mg) alcohol concentrations, a statistically significant difference was observed ($p < 0.05$). A comparison was made between the male group at both alcohol concentrations (5% and 40%) showing statistical significance, as well as between the female groups at alcohol concentrations of 5% and 40% ($p < 0.05$).

Table 4. Levels of glutathione peroxidase enzyme activity in the various groups.

Group	U/mg
Control	1465.58 ± 54.53
Females 5%	2841.33 ± 821.67 [a]
Male 5%	7085 ± 198.51 [a,b]
Females 40%	4787.91 ± 106.63 [a]
Male 40%	4092.79 ± 707.84 [a,c]

Values are expressed as mean ± SE in each experimental group (n = 5). [a] $p < 0.05$ vs. control group, [b] $p < 0.05$ vs. 5% group, [c] $p < 0.05$ vs. 40% group.

3.6. Effect of Weekend Alcohol Consumption on Total Antioxidant Capacity (TAC)

The amount of TAC in the control group was 1307.5 ± 71.78 nmol/mg. When compared with the male and female groups at 40% alcohol consumption, which showed levels of 1729.21 and 2043.44, respectively, a statistically significant difference was observed ($p < 0.05$). However, no significant difference was observed between the control group and the groups of both males and females at 5% alcohol consumption. The TAC levels in the male group with 5% alcohol consumption were 1628 ± 274.65 nmol/mg, and in the female group with the same alcohol concentration, it was 1962.7 ± 335.94 nmol/mg (Table 5).

Table 5. Levels of total antioxidant capacity in the various groups.

Group	nmol/mg
Control	1307.5 ± 71.78
Females 5%	1962.7 ± 335.94 [a]
Males 5%	1628.57 ± 274.65 [a,b]
Females 40%	2043.44 ± 281.27 [a]
Males 40%	1729.24 ± 101.31 [a,c]

Values expressed as mean ± SE in each experimental group (n = 5). [a] $p < 0.05$ vs. control group, [b] $p < 0.05$ vs. 5% group, [c] $p < 0.05$ vs. 40% group.

3.7. Effect of Weekend Alcohol Consumption on Thiobarbituric Acid Reactive Substances (TBARSs) Levels

Table 6 shows the TBARS levels. The control group had TBARS levels of 3.03 ± 0.80 nmol/mg. The male group with 5% alcohol consumption had levels of 2.36 ± 0.59 nmol/mg, while the female group with the same alcohol concentration had levels of 2.69 ± 0.50 nmol/mg. In the male and female groups at 40%, the levels were 1.38 ± 0.26 and 2.49 ± 0.79, respectively. However, when comparing the groups, no statistically significant differences were observed.

Table 6. Levels of thiobarbituric acid reactive substances (TBARSs) in the various groups.

Group	nmol/mg
Control	3.03 ± 0.80
Females 5%	2.69 ± 0.50 [a]
Males 5%	2.36 ± 0. 59 [a,b]
Female 40%	2.49 ± 0. 79 [a]
Males 40%	1.38 ± 0. 26 [a,c]

Values are expressed as mean ± SE in each experimental group (n = 5). [a] $p < 0.05$ vs. control group, [b] $p < 0.05$ vs. 5% group, [c] $p < 0.05$ vs. 40% group.

4. Discussion

Alcohol consumption is currently increasing dramatically among the young population, and the resulting damage and consequences significantly impact various aspects of an individual's health and well-being. While there is vast evidence on the effects of alcohol consumption on different organs and tissues of the human body, many studies focus on models that consider chronic daily alcohol consumption, overlooking the more common weekend consumption pattern among the young population. In this study, we evaluated the effect of weekend alcohol consumption on the levels of antioxidant enzymes over a 12-week period using a female and male rodent model.

The profile of reactive oxygen species or the activity of antioxidant enzymes in the liver depends on the timing and dosage of ethanol administration. Morales-González et al. [19] reported that after the administering ethanol intragastrically at a dose of 1.5 g/kg of body weight (using a 40% EtOH solution in isotonic saline solution) daily for 7 days, resulting in blood alcohol levels between 75 and 150 mg/dL, there was an increase in TBARSs as well as in endogenous antioxidant defenses (catalase, SOD, GPx, and GR). These findings suggest that the continuous ROS production induced by daily ethanol administration promotes the enhancement of antioxidant and detoxifying defenses within 7 days. Conversely, Namachivayam and Valsala Gopalakrishnan [22] orally administered ethanol to rats for 56 days at a daily dose of 5 mL/kg b/w. They observed increased levels of reactive oxygen species and lipid peroxidation (MDA) in liver samples, along with decreased antioxidant activity (glutathione peroxidase, superoxide dismutase, and glutathione reductase). With prolonged ethanol administration, the antioxidant defenses do not recover, leading to cellular exhaustion.

Surprisingly, there is an elevation of all antioxidant enzymes by the consumption of weekend alcohol for 3 months, probably due to the fact that this consumption is two days a week, causing a certain recovery of the liver. But this elevation of the antioxidant systems is not enough to prevent the damage caused by weekend alcohol to various organs, such as the liver and the oral cavity, which has been previously reported by Morales-González [8] and González-López [9]. Excessive alcohol consumption causes liver damage (an elevation of transaminases), stimulates extensive damage to hepatocytes (morphological alterations), and mainly causes liver dysfunction (bilirubin and albumin) [8,12,13,19,22].

Importantly, it is observed that the group that consumed 40% ethanol showed the highest ethanol consumption (Figure 2) and also showed the highest elevation of antioxidant defenses (Tables 1–3 and 5). On the other hand, in the reports of Morales-González [8] and González-López [9], this group of females that consumed 40% alcohol is the group with the greatest damage to the liver and the oral cavity with weekend alcohol consumption. This is probably due to the fact that females have a lower metabolism of ethanol [23–25], and therefore a delay in ethanol metabolism, a greater production of ROS (Table 6), and greater liver damage, and therefore the cells try to defend themselves through the formation of antioxidant enzymes.

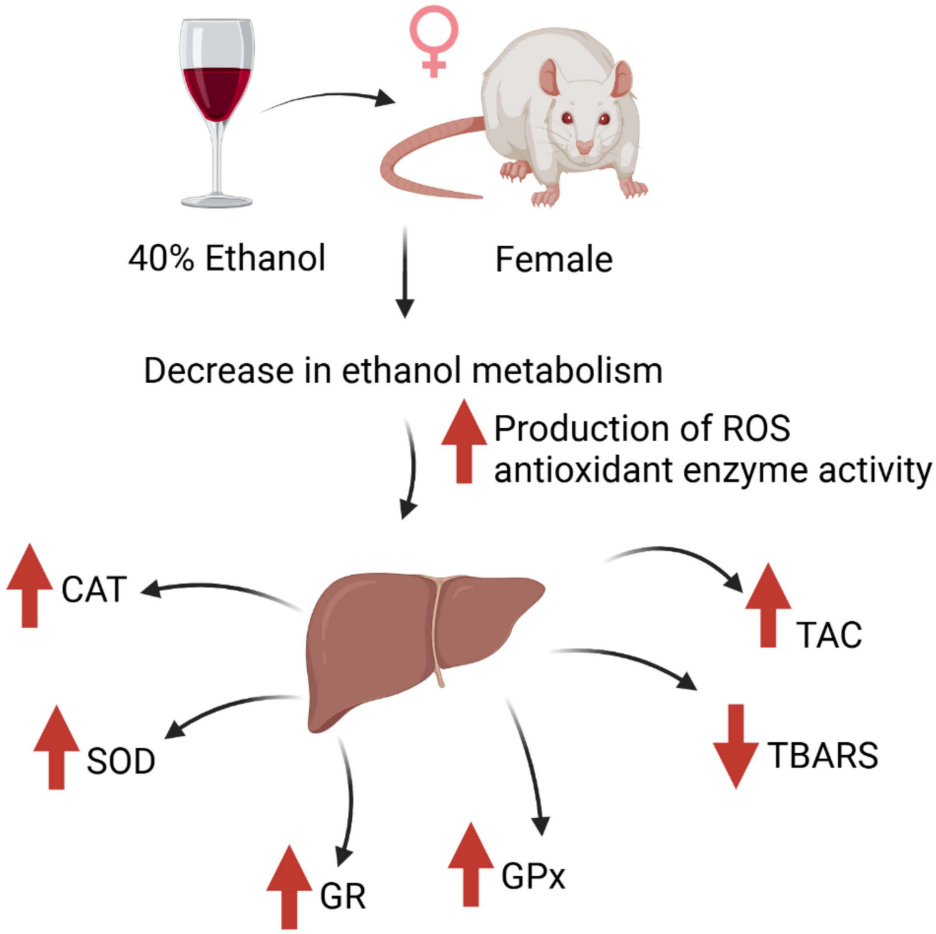


Figure 2. Females have a lower metabolism of ethanol; consequently, they present a higher production of ROS (Table 6) and greater liver damage, and then their cells try to defend themselves through the formation of antioxidant enzymes, which could explain why this group presented greater alteration in these enzymes. Created with BioRender.com.

The product of alcohol metabolism in the liver is acetaldehyde, which promotes the formation of reactive oxygen species, which are highly toxic. The continuous consumption of alcohol and therefore its metabolism in the hepatocyte causes alterations in the redox state, as well as an imbalance between the formation of reactive oxygen species/endogenous antioxidant levels, which favors damage to this organ [26,27]. On the other hand, it is known that the transcriptional factor Nrf2 has cytoprotective functions; for example, it controls the expression of numerous genes that encode antioxidant proteins (CAT, SOD, GR, and GPx) and detoxifying enzymes (Nqo1) [28,29]. And, it is likely that the elevation of reactive oxygen species causes the activation of Nrf2 caused by alcohol consumption [19].

Finally, with the data reported in this research, we can hypothesize the participation of NRF2, which can be activated by the formation of free radicals from ethanol metabolism, and its NRF2 response will depend on the damage caused to the liver by the type of alcohol consumption (daily or weekend consumption), as proposed in Figure 3.

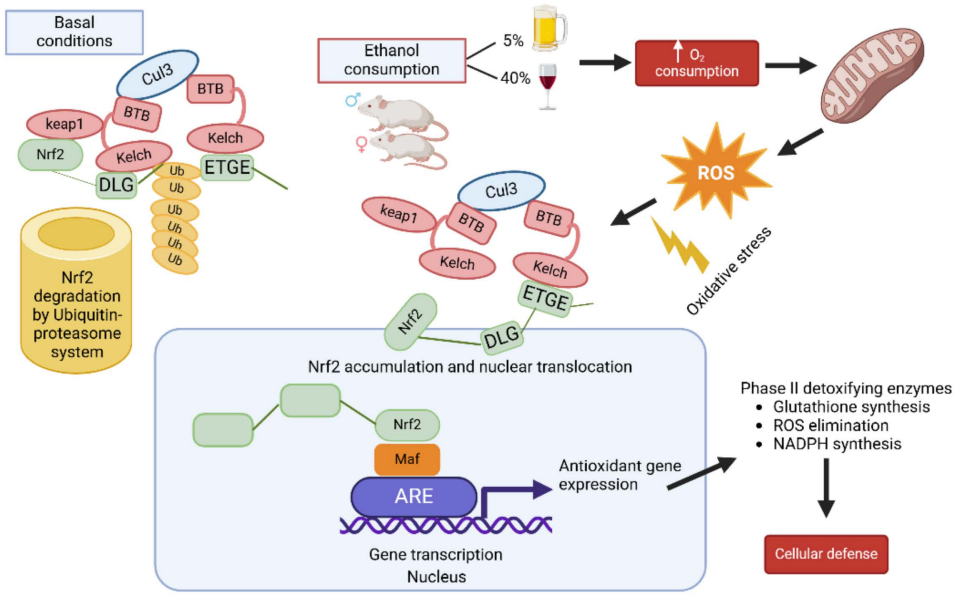


Figure 3. Model proposing how alcohol consumption (daily or weekend) activates the nuclear factor erythroid 2-related factor 2 (Nrf2)–Keap1 pathway. Under normal conditions, Nfr2 is bound to Keap1 through the DLG and EGTE motifs in the Neh2 domain of Nrf2 by the ubiquitin ligase complex Cullin (Cul)3-RING-box protein (Rbx)1 (Cul3). This complex ubiquitinates Nrf2 for rapid proteasomal degradation. When alcohol is consumed, this xenobiotic is metabolized mainly in the liver. In this process, metabolic pathways that produce reactive oxygen species (ROS) are stimulated, increasing oxidative stress (OS). The latter induces the oxidation of cysteine residues present in Keap1, favoring the conformational change in Keap1; consequently, ubiquitination is prevented and Nrf2 dissociates from the inhibitory complex. Nrf2 accumulates and translocates to the nucleus and heterodimerizes with MAF proteins, binding at a specific DNA sequence called antioxidant response element (ARE) and inducing the expression of antioxidant genes: (a) phase II antioxidant enzymes; (b) glutathione synthesis; (c) ROS scavenging; and (d) NADPH synthesis, among others. Along with these, an increase in cytoprotective cellular defenses occurs. Created with BioRender.com.

5. Conclusions

Alcohol consumption during the weekend conditions a continuous production of ROS, which favors the elevation of antioxidants that ultimately leads to cellular depletion. This elevation of antioxidant systems is not sufficient to prevent the damage caused by alcohol during the weekend, and this damage is probably also favored by the increased fat deposition in the liver associated with the increase in body weight due to ethanol consumption.

Author Contributions: Conceptualization, E.V.R.-N. and J.A.M.-G.; Methodology, Á.M.-G.; Validation, E.O.M.-S.; Formal analysis, E.O.M.-S.; Writing—original draft, J.G.-M. and J.A.M.-G.; Writing—review & editing, E.V.R.-N., J.G.-M. and J.A.M.-G. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: All procedures were approved by the research committees and CICUAL, with registration numbers ESM.CI-01/13-06-2017 and ESM.CICUAL-12/23-06-2017, respectively. All procedures were performed according to the Official Mexican Guidelines for Laboratory Animal Use and Care (NOM-062-ZOO-1999).

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

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

Abbreviations

TBARSs	Thiobarbituric acid reactive substances
OS	Oxidative stress
GP	Gluthathione peroxidase
GR	Glutathione reductase
Nrf2	Nuclear factor erythroid-like 2

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