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Research Article

Effects of Remdesivir on Liver Enzymes, Oxidative Stress and Liver Histopathology in Rats

Mehran Mesgari Abbasi[1], Roya Darbani[1,*], Oldouz Rabet[1], Amir Ghorbanihaghjo[2], Nadereh Rashtchizadeh[3], Sina Raeisi[4], Monireh Khordadmehr[5]

[1]Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Department of Clinical Biochemistry and Laboratory Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Biotechnology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[4]Pediatric Health Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[5]Department of Pathobiology, Faculty of Veterinary Medicine, University of Tabriz, Tabriz, Iran

Abstract

Background & Aims: Remdesivir (REM) has been widely used to treat subjects affected by COVID-19 due to its broad-spectrum activity. The aim was to assess the REM effect on liver histopathology, enzymes, and alterations in oxidative stress markers. *Methods:* Forty-eight Wistar rats were separated into eight groups as follows: Group A (Control) received normal saline intraperitoneally (IP) for 10 days; Group B (Low-dose REM) received REM (2.8 mg/kg for the first day and 1.4 mg/kg for days 2 to 10, IP); Group C (High-dose REM) received REM (8.5 mg/kg IP for the first 17 days and days 2 to 10); Group D (High-dose REM+DEX (Dexamethasone)+ HEP (Heparin) received DEX (7 mg/kg intramuscularly for 10 days) and HEP (333 IU/kg subcutaneously on the first day and 250 IU/kg subcutaneously every 12 hours from day 2 to day 10); Group E (High-dose REM+ DEX); Group F (High-dose REM+ HEP); Group G (DEX); Group H (HEP). For statistical analysis, non-parametric tests (Kruskal-Wallis H and Mann-Whitney U) were used for pathological lesions (semi-quantitative data) between the different groups, and a $p < 0.05$ was considered significant. *Results:* There were mild to severe pathological changes in the treated groups, including cell swelling, vascular congestion. Also, the D and G groups showed similar pathological lesions, which were more severe than in other treated groups with a significant difference ($p < 0.05$). Conclusions: This study identified Remdesivir-induced liver toxicity and oxidative stress alterations in rats, underscoring the need for careful liver function monitoring, especially in patients with hepatic dysfunction. The findings recommend caution in using Remdesivir as a first-line treatment in such cases, and further studies are required to validate these effects and explore broader clinical implications.

Keywords

Remdesivir, COVID-19, Liver Enzymes, Oxidative Stress

[*]Corresponding author: roya.darbani129@gmail.com (Roya Darbani)

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1. Introduction

A novel coronavirus, COVID-19, that caused by (SARS-CoV-2), was first reported in December 2019, leading to respiratory distress and finally, COVID-19 disease [1]. Coronaviruses, which belong to the Coronaviridae family, are enveloped RNA viruses [2, 3]. The main targets of COVID-19 are the lungs, however, it led to damage to the liver, kidneys, gastrointestinal tract, nervous system, and heart [4]. COVID-19 causes numerous clinical presentations and may be mild, moderate, or severe. The most common symptoms of this disease are fever, anorexia, dry cough, myalgia, cough, fatigue, anosmia, loss of taste, abdominal pain, diarrhea, nausea, and vomiting. Asymptomatic cases have also been reported [5]. Antiviral drugs (favipiravir, ritonavir, remdesivir, and lopinavir) were used for COVID-19 [6].

COVID-19 leads to different abnormal laboratory items, including abnormal liver and kidney function tests [7]. Remdesivir (Veklury) is a nucleotide analog that inhibits RNA polymerase and is the first antiviral medicine for COVID-19 approved by the FDA with a broad-spectrum effect against zoonotic and human coronaviruses. It has been approved for treating COVID-19 in patients over 12 years and adults who are hospitalized and is administered intravenously [8]. However, the efficacy of remdesivir for treating COVID-19 patients remains controversial. Initial studies revealed that treatment with remdesivir resulted to faster recovery [9]. The trial carried out by the World Health Organization (WHO) indicated that using remdesivir did not improved the mortality rate significantly, however it had some advantages in low-risk patients, so the WHO had not recommended using remdesivir for treating COVID-19 patients [10]. However, an evaluation of viral loads that carried out in hospitalized subjects showed a significantly faster viral clearance (by a median of 0.7 days) after treatment with remdesivir [11]. Remdesivir was utilized with dexamethasone and heparin according to a protocol implemented during the outbreak of the Corona disease, because dexamethasone was a corticosteroid and heparin was an anticoagulant to prevent thromboembolism [12].

It was discovered during clinical trials that Remdesivir was hepatotoxic. An evaluation of the side effects of remdesivir in the VigiBase database showed that rising liver enzymes had occurred in 32.1% of the cases [13]. The results of a study carried out by Zampino et al revealed a significant elevation in AST, ALT, and bilirubin levels in patients affected by COVID-19 who receiving remdesivir [14].

Recent studies revealed the important role of Oxidative stress in viral infections (including SARS-CoV and also SARS-CoV-2 infections) [15, 16]. Elevated oxidative stress in viral infections, including severe COVID-19, leads to dysfunction of endothelial cell, inflammation, and thrombosis that can cause multiorgan damage [17, 18]. Administrating Remdesivir led to damage of the renal tubular epithelial cells, mitochondrial toxicity and also injury of hepatocytes that cause to the aggregation of free radicals and also oxidative damage, which leads to necrosis and deterioration of liver and kidney tissues [19].

Most mechanisms of tissue injury caused by SARS-CoV-2 infection are directly regard to oxidative stress [20]. Nevertheless, according to our knowledge, there are limited studies conducted to assess oxidative stress markers in patients with SARS-CoV-2 infection. Taking into account that more recent studies revealed important role of oxidative stress in COVID-19 severity, free radical removing by specific natural and/or synthetic antioxidants may be advantageous to preventing the advancing of COVID-19 [20].

At the present, there are limited studies which conducted to evaluate using Remdesivir in subjects with cardiac, hepatic, or renal impairment, and there is insufficient data in regard to the potential side effects of this drug. We aimed to assess the effects of Remdesivir on hepatic histopathology and enzymes, with particular focus on alterations in oxidative stress in rats.

2. Materials and Methods

2.1. Animals

In this cross-sectional study, 48 Wistar rats were examined. These rats were acquired from the Pasteur Institute (Tehran, Iran). The animal protocol that utilized was according to the Guideline of Care and Use of Laboratory Animals (US Department of Health, Education, and Welfare (DHEW), Publication Number 78–23, National Institutes of Health (NIH), revised 1978), and local guidelines for compassionate utilize of animals in studies. The animals were kept in similar laboratory conditions (18 to 23 ℃ room temperature and controlled humidity) with alternating 12-h light and dark cycles. The study protocol was registered and approved by the Research Ethics Committees of Laboratory Animals – Tabriz University of Medical Sciences (Approval ID: IR. TBZMED. AEC.1401.006).

2.2. Group Design (Drug Treatment)

In this study, 48 male Wistar rats were assigned to eight groups (six rats per group) as follows:

1. Control group: Normal saline administered intraperitoneally (IP) for 10 days.
2. Low-dose Remdesivir group: 2.8 mg/kg for the first day and 1.4 mg/kg for days (2 to 10) IP.
3. High-dose Remdesivir group: 8.5 mg/kg IP for the first 17 days and days 2 to 10.
4. High-dose Remdesivir+ Dexamethasone (7 mg/kg intramuscularly for 10 days) + Heparin (333 IU/kg subcutaneously on the first day and 250 IU/kg subcutaneously every 12 hours from day 2 to day 10).
5. High-dose Remdesivir+ Dexamethasone group.
6. High-dose Remdesivir+ Heparin group.

7. Dexamethasone group.
8. Heparin group.

On the morning of day 11, after anesthesia (ketamine 60 mg/kg BW IP and xylazine 10 mg/kg BW IP), blood was collected via cardiac puncture. Serum was disintegrated by centrifugation and stored at -80 ℃ until further analysis. Euthanasia was performed with an overdose of ketamine (200 mg/kg BW IP), and liver tissue was collected, fixed in 10% formalin for histological studies, and a portion transferred to -80 ℃ for oxidative stress analysis. Liver enzymes were assessed from serum, liver histopathology from formalin-fixed samples, and other tests from frozen liver samples. Results were analyzed and reported.

2.3. Histological Assessment

For histopathological examination, the tissue samples (liver) were taken, routinely fixed in 10% buffered formalin, embedded in paraffin, segmented at about 5 µm, and stained with common hematoxylin and eosin (H&E). The tissue sections were evaluated microscopically by using a light microscope (Olympus-CH30, Japan). Microscopic analyses were conducted as previously described [21] with some modifications. The evaluated criteria included vascular congestion, cell swelling, inflammation, hemorrhage, hepatocyte degeneration, and necrosis. Four microscopic scores consisting of normal (0), mild (+1), moderate (+2), and severe (+3) were considered for the mentioned parameters. Of the taken hepatic samples, 100 mg was homogenized in 1 ml ice cold phosphate buffer solution (PBS) (pH, 7.4) using a glass tissue homogenizer 6E. Then, the homogenized samples were centrifuged for 10 min at 10000g. and then the supernatants were removed. The oxidative stress markers (liverTAC, SOD, GPx, Catalase, and MDA) tests was conducted on supernatants.

2.4. Statistical Analysis

The one-sample Kolmogorov–Smirnov test was used for checking the normality of variables. All variables had normal distributions and were presented as mean ± standard deviation. Statistical comparisons of the groups were performed by one-way analysis of variance (ANOVA) and Bonferroni's post-hoc analysis. Pearson's correlation coefficient was also calculated. Statistical significance was set at a p-value of less than 0.05. Statistical analyses were carried out by SPSS software (version 18). For pathological lesions (semi-quantitative data) between the various groups, non-parametric tests (Kruskal-Wallis H and Mann-Whitney U) were used, and a $p < 0.05$ was considered significant.

3. Results

In this cross-sectional study, 48 Wistar rats were enrolled and divided into 8 groups of 6 rats. The data of AST (aspartate aminotransferase), ALT (Alanine transaminase), ALP (Alkaline phosphatases), LDH (Lactate dehydrogenase), CK (Creatine Kinase), Albumin, and Protein parameters are presented in Table 1 and Figure 1.

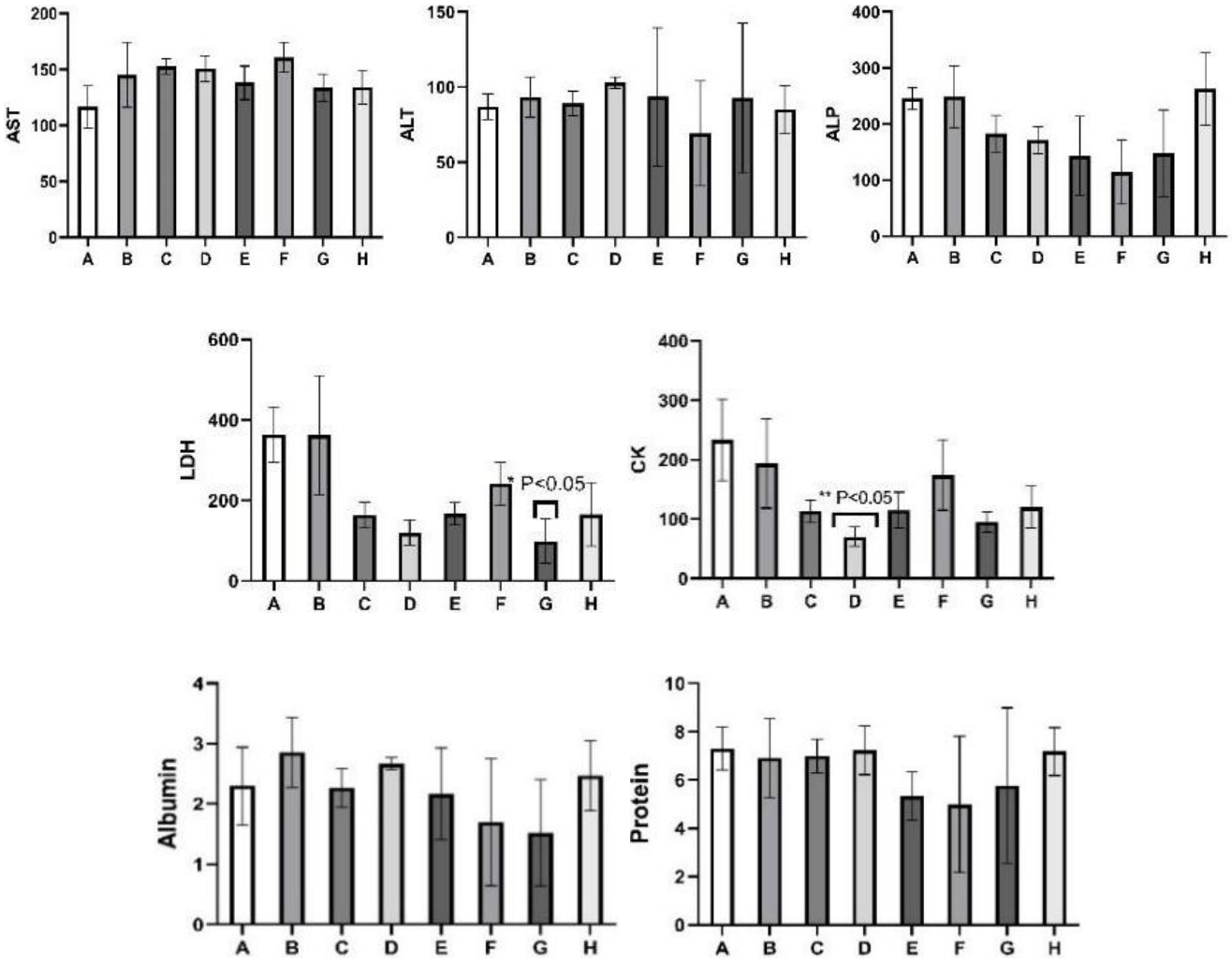
The mean level of LDH in the DEX group (118.25±34.55, IU/L) was significantly higher than that in the control (363.83±98.47, IU/L; p = 0.007) and Low-dose REM (386±284.5, IU/L; P<0.05) groups. The mean level of CK in the High-dose REM + DEX + HEP (70.25±20.78b, U/L) was significantly higher than that in the control (235.17±89.27, U/L; P<0.05) group.

Table 1. *AST, ALT, ALP, LDH, CK, Albumin, and Protein levels of the study groups.*

Parameters	Group A	Group B	Group C	Group D	Group E	Group F	Group G	Group H
AST (U/L)	119.83±34.55	143.5±34.87	152.67±12.82	150.75±27.32	138±16.82	158.8±23.34	133.75±13.75	134.17±14.84
ALT (U/L)	87±18.89	89±21.62	87.33±12.72	103±8.17	112.33±7.51	83±17.18	124.5±59.12	86.83±21.36
ALP (U/L)	245.33±70.36	248.67±75.21	190.67±86.73	171.5±44.28	171.67±17.9	137.2±11.95	175.5±75.19	266.17±95.29
LDH (IU/L)	363.83±98.47	386±284.5	163.5±59.25	120.25±40.33	167.25±36.32	241.33 ±103.79	118.25 ±34.55[a]	165.33±99.84
CK (U/L)	235.17±89.27	193.67±143.2	113±24.32	70.25±20.78[b]	115.5±65.22	175.5±61.12	94.75±22.41	114.83±59.15
Albumin (g/dL)	2.22±1.08	2.93±1.06	2.27±0.31	2.67±0.12	2±1.14	1.94±0.92	1.82±0.62	2.47±0.58
Protein (g/dl)	7.3±1.43	6.92±2.07	6.99±0.71	7.23±1.12	5±1.55	5.26±3.61	6.92±4.1	7.18±2.78

AST: aspartate aminotransferase, ALT: Alanine transaminase, ALP: Alkaline phosphatases, LDH: Lactate dehydrogenase, CK: Creatine Kinase

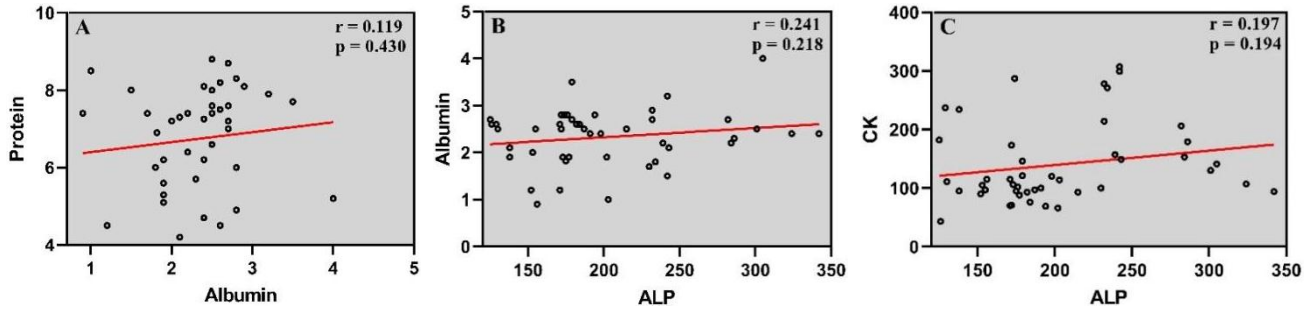
a P<0.05 compared to Group B, b P<0.05 compared to Group A.

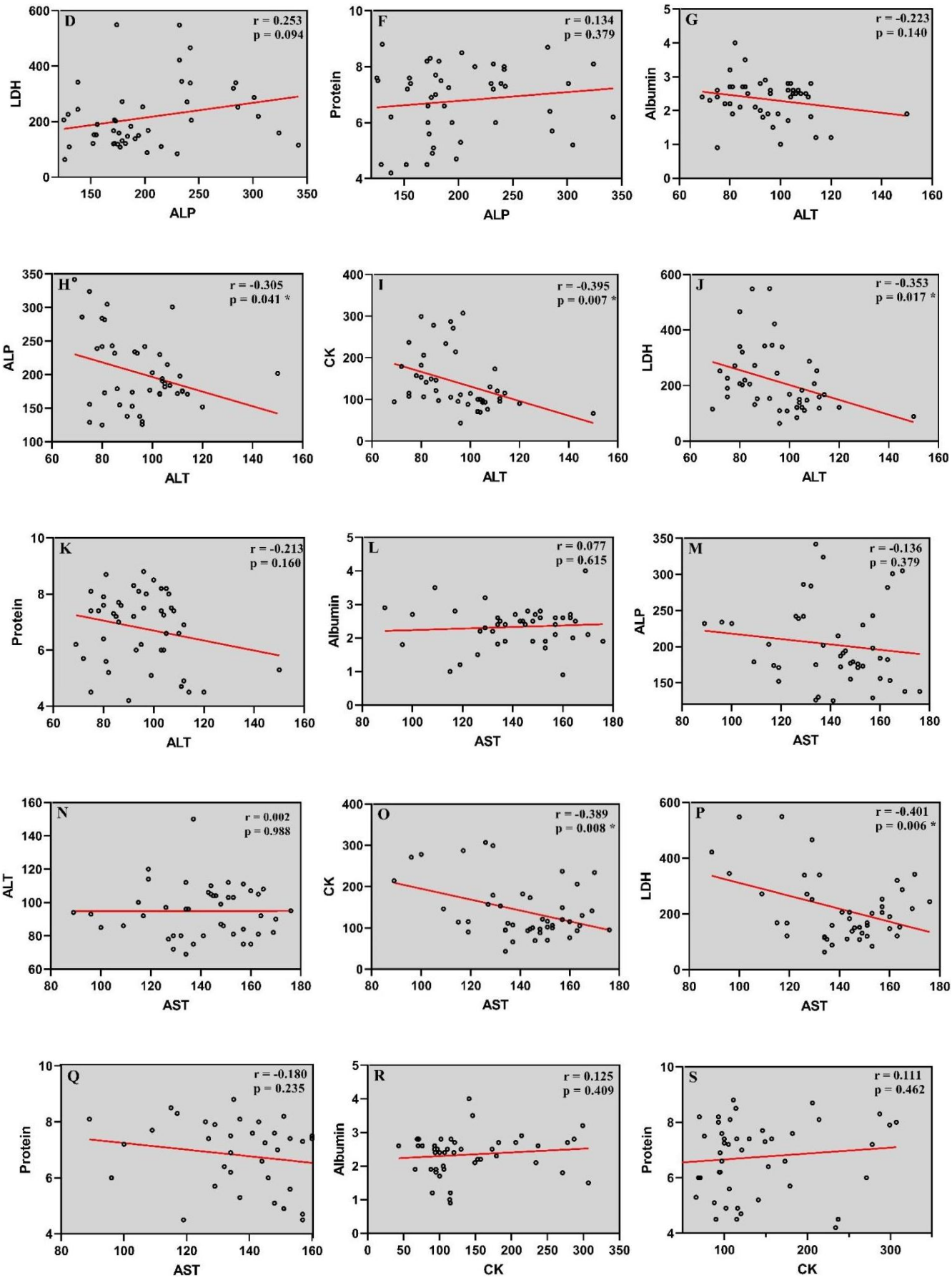


* P<0.05 compared to Group B, ** P<0.05 compared to Group A

Figure 1. *The data of AST, ALT, ALP, LDH, CK, Albumin, and Protein levels of the study groups.*

Figure 2 shows the correlations between the biochemistry parameters. As shown in Figure 2 H, I, and J, Liver ALT level was negatively correlated with liver ALP level ($r = -0.305$, $p = 0.041$), CK level ($r = -0.395$, $p = 0.007$), and LDH level ($r = = -0.353$, $p = 0.017$). Also, liver AST level was negatively correlated with CK level ($r = -0.389$, $p = 0.008$) (Figure 2 O). Also, liver AST level was negatively correlated with LDH level ($r = -0.401$, $p = 0.006$) (Figure 2 P). Also, liver CK level was positively correlated with LDH level ($r = -0.871$, $P<0.001$) (Figure 2 U).

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LDH
ALP
F
r = 0.134
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Protein
ALP
G
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p = 0.140
Albumin
ALT
H
r = -0.305
p = 0.041 *
ALP
ALT
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r = -0.395
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CK
ALT
J
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K
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ALT
AST
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CK
AST
P
r = -0.401
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AST
Q
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CK
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Protein
CK

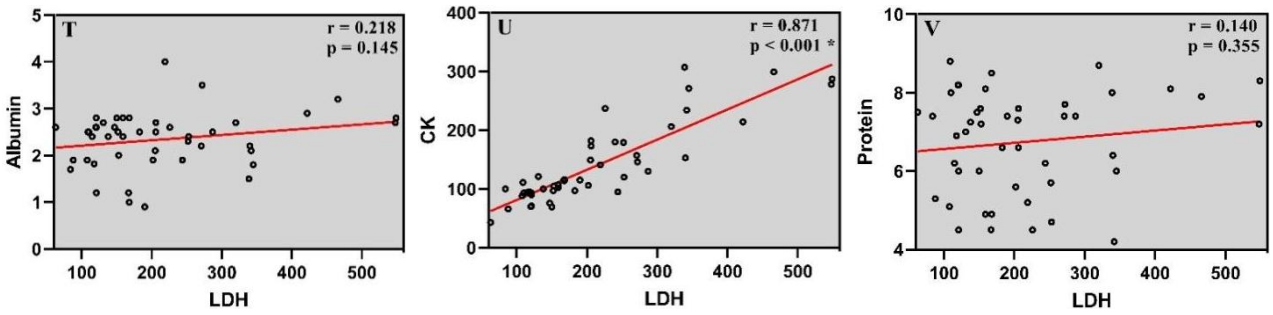


Figure 2. *Shows the correlations between the biochemistry parameters. As shown in Figure 2 H, I, and J, liver ALT level was negatively correlated with liver ALP level (r = − 0.305, p = 0.041), CK level (r = − 0.395, p = 0.007) and LDH level (r = = − 0.353, p = 0.017). Also, liver AST level was negatively correlated with CK level (r = − 0.389, p = 0.008) (Figure 2 O). Also, liver AST level was negatively correlated with LDH level (r = − 0.401, p = 0.006) (Figure 2 P). Also, liver CK level was positively correlated with LDH level (r = − 0.871, P<0.001) (Figure 2 U).*

The data of liverTAC (total antioxidant capacity), liverSOD (superoxide dismutase), liverGPx (glutathione peroxidase), liver catalase, and liverMDA (malondialdehyde) parameters are presented in Table 2 and Figure 3. The mean level of liverTAC in the High-dose REM (458.73±67.84 ng/mL), High-dose REM + Heparin (498.82±37.99 ng/mL), DEX (467.06±37.49 ng/mL), and Heparin (472.71±84.06 ng/mL) groups was significantly higher than the control group (353.86±27.7 ng/mL; P<0.05).

The mean level of liverGPx in the High-dose REM + DEX + HEP (30.26±6.36 pg/mL), High-dose REM + DEX (22.56±4.96[a] pg/mL), High-dose REM + HEP (23.8±5.58 pg/mL), DEX (472.71±84.06 pg/mL), and HEP (26±3.17 pg/mL) groups was significantly higher than that in the control group (10.89±1.86 pg/mL; P<0.05).

The mean level of liver catalase in the Low-dose REM (24.24±3.05 U/gm), and High-dose REM + DEX (22.95±4.41 U/gm) groups was significantly higher than that in the control group (25.72±3.23 U/gm; P<0.05).

The mean level of liver catalase in the Low-dose REM (24.24±3.05), and High-dose REM + DEX (22.95±4.41) groups was significantly higher than that in the control group (25.72±3.23; P<0.05).

The mean level of liverMDA in the Low-dose REM (3.82±0.8 µmol/l), High-dose REM (2.39±0.84 µmol/l), High-dose REM+ DEX + HEP (3.12±0.52 µmol/l), DEX (3.11±1.07 µmol/l), and HEP (3.64±0.35 µmol/l) groups was significantly higher than that in the control group (7.3±1.13 µmol/l; P<0.05).

Table 2. *The data of liverTAC, SOD, GPx, Catalase, and MDA levels of the study groups.*

Parameters	Group A	Group B	Group C	Group D	Group E	Group F	Group G	Group H
LiverTAC (ng/mL)	353.86 ±27.7	377.39 ±54.37	458.73 ±67.84[a]	346.63 ±34.39[c]	364.58 ±26.4	498.82 ±37.99[abde]	467.06 ±37.49[ad]	472.71 ±84.06[abde]
LiverSOD (U/mL)	3.82±1.12	5.12±4.71	3.94±0.8	1.23±0.33	2.92±0.82	3.26±0.76	2.69±1.06	2.39±0.93
LiverGPx (pg/mL)	10.89±1.86	15.53±2.25	14.46±2.86	30.26±6.36[abc]	22.56±4.96[a]	23.8±5.58[ac]	21.73±7.06[a]	26±3.17[abc]
Livercatalase (U/gm)	25.72±3.23	24.24±3.05	25.56±2.21	25.7±2.81	22.95±4.41	28.28±4.7	29.12±4.42	31.7±3.24[be]
LiverMDA (µmol/l)	7.3±1.13	3.82±0.8[a]	2.39±0.84[a]	3.12±0.52[a]	5.69±0.67[cd]	6.96±1.47[bcd]	3.11±1.07[aef]	3.64±0.35[aef]

TAC: total antioxidant capacity, SOD: *superoxide dismutase*, GPx: glutathione peroxidase, MDA: malondialdehyde
a P<0.05 compared to Group A, b P<0.05 compared to Group B, c P<0.05 compared to Group C, d P<0.05 compared to Group D, e P<0.05 compared to Group E, f P<0.05 compared to Group F

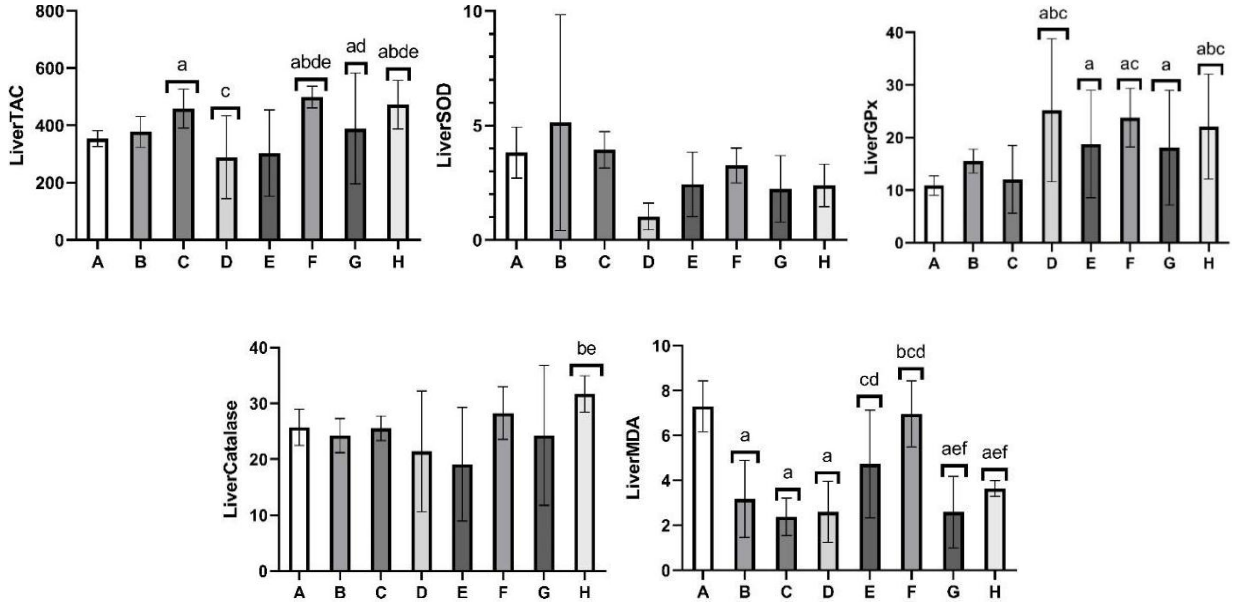
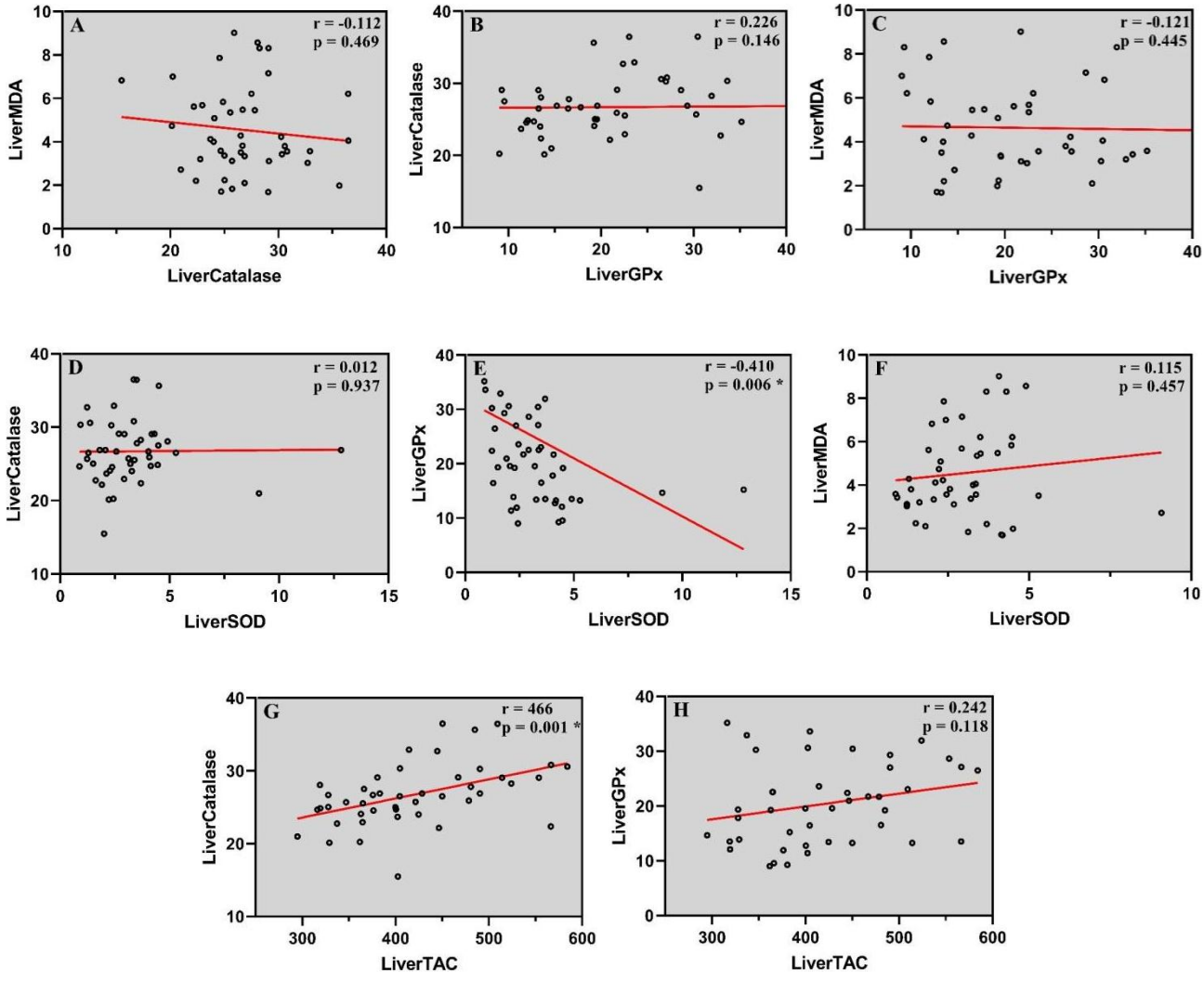


Figure 3. *The data of liverTAC, SOD, GPx, Catalase, and MDA levels of the study groups.*

a P<0.05 compared to Group A, b P<0.05 compared to Group B, c P<0.05 compared to Group C, d P<0.05 compared to Group D, e P<0.05 compared to Group E, f P<0.05 compared to Group F



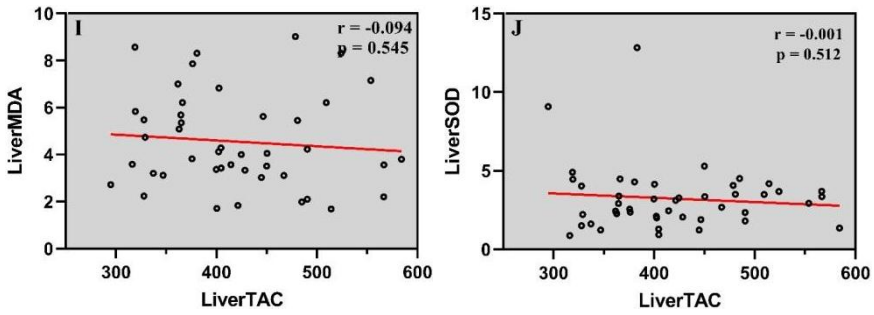


Figure 4. *Shows the correlations between the Oxidative stress parameters. As shown in Figure 4 E, liver GPx level was negatively correlated with liver SOD level (r = − 0.410, p = 0.006). Also, liver catalase level was positively correlated with liver TAC level (r = 0.466, p = 0.001) (Figure 4 G).*

Histopathological findings are presented in Table 3 and figure 5. Healthy control rats presented a normal liver with the uniform pattern of polyhedral hepatocytes radiating from the central vein towards the periphery. By contrast, there were mild to severe pathological changes in the treated groups, including cell swelling, vascular congestion, hepatocyte atrophy, degeneration, and focal necrosis. There were no hemorrhage and inflammation in all treated groups. Of note, focal mild hepatocyte necrosis was observed in the C group (High-dose Rem.). Similar pathological changes with mild score were found in the B, F, and H groups, which were not significantly different ($P > 0.05$). On the other hand, the D and G showed similar pathological lesions which were more severe than other treated groups with a significant difference ($p < 0.05$) compared to others.

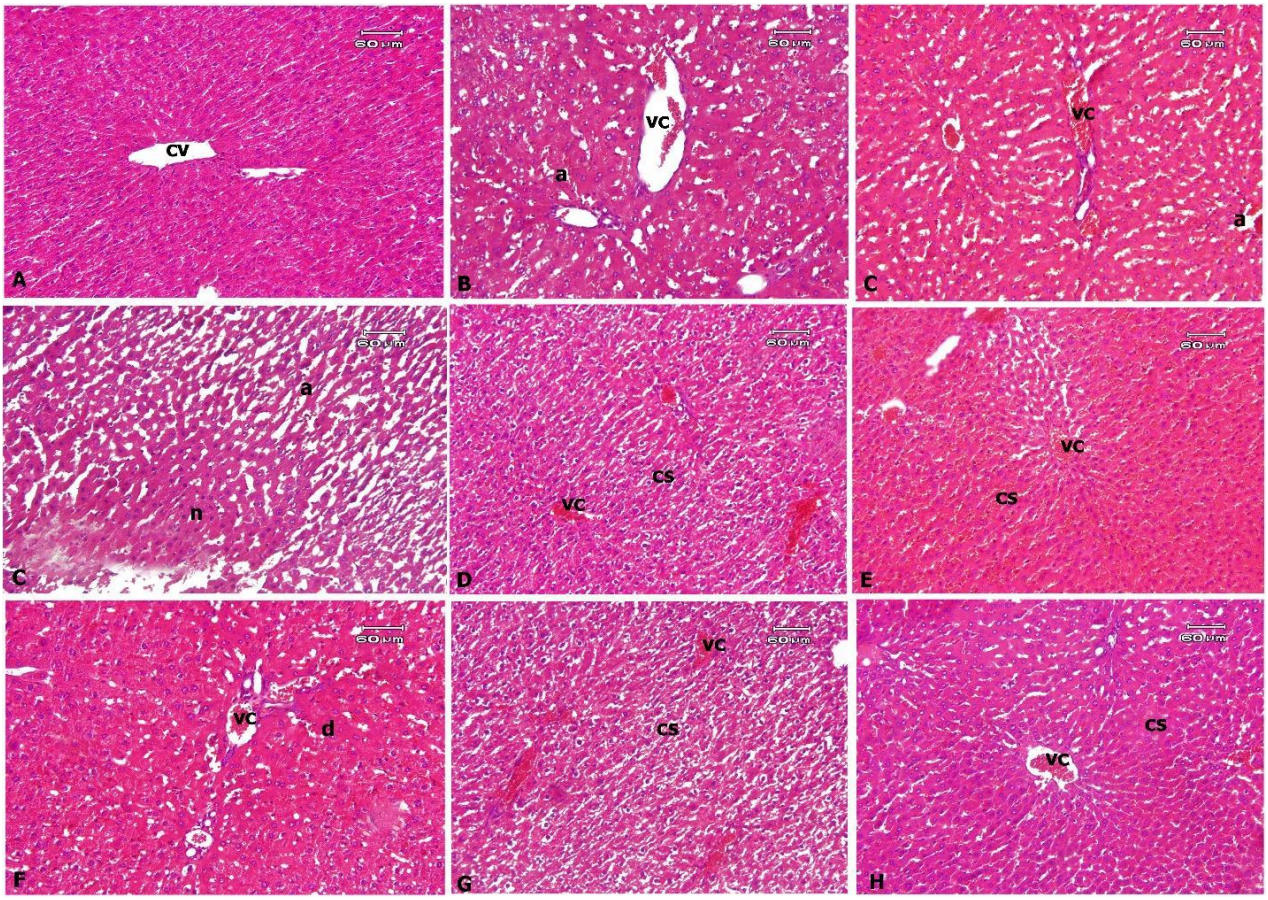


Figure 5. *Liver, rat. A: normal control group with a normal construction of central vein (cv) and hepatocytes. B: Low-dose Rem; C: High-dose Rem; D: Rem + Dex + Hep; E: Rem + Dex; F: Rem + Hep; G: Dex; H: Hep. There were vascular congestion (vc) in all treated groups with severe grade in the E group, moderate grade in the C, D, and G groups, and mild grade in the B, F, and H groups. Of note, the C group presented mild focal necrosis (n) associated with mild hepatocyte atrophy (a). However, hepatocyte atrophy (a), degeneration (d), and cell swelling (cs) were observed in most groups. H&E.*

Table 3. Pathological findings of the liver sections (n = 5).

Groups	Cell swelling	Vascular congestion	Hepatocyte atrophy	Hepatocyte degeneration	Necrosis
A*	0**	0	0	0	0
B	0	+1	+1	0	0
C	0	+2	+1	+1	+1
D	+2	+2	0	0	0
E	+1	+3	0	+1	0
F	0	+1	+1	+1	0
G	+1	+2	0	0	0
H	+1	+1	+1	0	0

A: healthy control; B: Rem Low-dose; C: Rem High-dose; D: Rem + Dex + Hep; E: Rem + Dex; F: Rem + Hep; G: Dex; H: Hep.
**normal (0), mild (+1), moderate (+2), and severe (+3).

4. Discussion

This study was conducted to assess the effects of Remdesivir on liver histopathology and enzymes, with particular attention to alterations in oxidative stress in rats. Remdesivir inhibits RNA polymerase and is the first antiviral medicine that utilized for COVID-19 patients and approved by the FDA with a broad-spectrum effect against zoonotic and human coronaviruses [8]. However, the effectiveness of Remdesivir in patients affected by COVID-19, remains litigious [9].

The result of clinical trials showed that Remdesivir was hepatotoxic. An examination of the side effects of remdesivir upon to VigiBase database showed that increased liver enzymes occurred in 32.1% of subjects [13]. In a retrospective study, after administrating remdesivir, elevations of ALT and AST has been showed in 43% and 45% of subjects, respectively. Suggesting that hepatocytes directly affected [22, 23].

A study conducted by Wang et al on subjects that treated with Remdesivir showed that 12 of them had increased liver enzymes [24]. Consistent with our findings, Hariri B et al, showed that administrating Remdesivir cause to increasing level of ALT, AST, and slight non-significant elevating level of ALP [25].

In this study, there were mild to severe pathological changes in the treated groups, including cell swelling, vascular congestion, hepatocyte atrophy, degeneration, and focal necrosis. In one case study, abrupt hepatic failure developed in an obese patient after taking Remdesivir therapy [26].

Therefore, it is critical to control liver function and assess hepatic safety while administering Remdesivir in COVID-19 patients [14]. Taking Remdesivir led to acute hepatotoxicity because of the direct cytokines produced inflammatory effect following COVID-19. Administering this drug causes rising liver enzymes, damage to the liver consistent with other studies [27]. Remdesivir led to mitochondrial toxicity and damage to hepatocytes, leading to oxidative damage, which advances to necrosis and hepatic degeneration [19]. Increased liver enzymes are common in patients affected by COVID-19 (with and without chronic liver diseases) [28-31].

In our study, we used dexamethasone and heparin according to the protocol implemented during the outbreak of the Corona disease, because dexamethasone was a corticosteroid and heparin was an anticoagulant to prevent thromboembolism [12].

There were vascular congestion (vc) in all treated groups with severe grade in the (High-dose REM + DEX) group, moderate grade in the (High-dose Rem), (Rem + Dex + Hep), and (Dex) groups, and mild grade in the (Low-dose Rem) group, (Rem + Hep), and (Hep) groups. Of note, the (High-dose Rem) group presented mild focal necrosis (n) associated with mild hepatocyte atrophy. These findings suggested that high dose remdesivir might led to vascular congestion and its effect could modified by administrating HEP.

In this study, the mean level of LDH in the DEX group was considerably higher than control and Low-dose REM groups. The mean level of CK in the (High-dose REM + DEX + HEP) group was considerably higher than control group. It can be concluded that, releasing LDH and CK might be increased by administrating DEX. Also, liver AST level was negatively correlated with CK, and LDH level, as well as liver CK level, was positively correlated with LDH level. On the other hand, the High-dose REM+ DEX+ HEP and DEX groups showed similar pathological lesions, which were more severe than other treated groups with a significant difference compared to others. It can be concluded that, Remdesivir effect on liver biochemistry was notable and administrating DEX led to increasing ALT level. Using HEP led to increasing ALP level.

On the other hand, low dose remdesivir elevate LDH level. It can be concluded that administrating DEX might prevent releasing LDH and CK in serum and also lower hepatic injury reduce serum level of AST and might led to reducing CK and LDH plasma level.

The Serum concentrations of Oxidative stress markers including MDA, SOD, and GPX were considerably higher in COVID-19 patients [32, 33]. In a study conducted by Lage et al, the obtained results revealed higher serum activity of SOD and CAT in COVID-19 patients. In contrast, in a study conducted by Yaghoubi et al, the obtained results showed no significant difference in plasma activity of CAT and SOD in patients affected by COVID-19 [34, 35].

The mean level of liverTAC in the High-dose REM, High-dose REM + Heparin, DEX, and Heparin groups was considerably higher than the control group. The mean level of liverGPx in the High-dose REM + DEX + HEP, High-dose REM + DEX, High-dose REM + HEP, DEX, and HEP groups was considerably higher than the control group. The mean level of liver catalase in the Low-dose REM, and High-dose REM + DEX groups was considerably higher than the control group. The mean level of liverMDA in the Low-dose REM, High-dose REM, High-dose REM+ DEX + HEP, DEX, and HEP groups was considerably higher than the control group. liver GPx level was negatively correlated with liver SOD level. Also, liver catalase level was positively correlated with liver TAC level. Similar pathological changes with a mild score were found in the Low-dose Remdesivir, High-dose REM+ HEP, and HEP groups, which showed no significant difference. It can be concluded that, using Remdesivir significantly elevate the level of oxidative stress markers and administrating HEP had a synergistic effect. The level of liver TAC, liver GPx, liver catalase, and liver MDA might elevated by administrating DEX.

In conclusion, the present study has revealed that Remdesivir exerts hepatotoxic effects and influences oxidative stress markers in rat models. These findings underscore the necessity of vigilant monitoring of liver function in patients undergoing Remdesivir therapy, particularly those with pre-existing liver dysfunction. The results contribute to a deeper understanding of the hepatic biochemical alterations that may occur during the course of COVID-19 treatment. Our data suggest that Remdesivir should be used with caution, especially in cases of hepatic impairment, and may not be the optimal first-line therapeutic option in such instances. Future research is essential to explore these effects in greater detail, particularly through studies that incorporate varying dosages, drug combinations, and treatment durations in animal models. Moreover, additional clinical and paraclinical studies are required to thoroughly investigate the adverse hepatic effects of antiviral therapies. Given the limited scope of the present study, we advise caution in drawing definitive conclusions about the extent of liver injury and oxidative stress dysregulation in patients with COVID-19."

Abbreviation

REM	Remdesivir
DEX	Dexamethasone
HEP	Heparin
IP	Intraperitoneally
WHO	World Health Organization
FDA	Food and Drug Administration
COVID-19	Coronavirus Disease 2019
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
DHEW	Department of Health, Education, and Welfare
NIH	National Institutes of Health
H&E	Hematoxylin and Eosin
PBS	Phosphate Buffer Solution
ANOVA	Analysis of Variance
SPSS	Statistical Package for the Social Sciences
AST	Aspartate Aminotransferase
ALT	Alanine Transaminase
ALP	Alkaline Phosphatases
LDH	Lactate Dehydrogenase
CK	Creatine Kinase
TAC	Total Antioxidant Capacity
SOD	Superoxide Dismutase
GPx	Glutathione Peroxidase
MDA	Malondialdehyde

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Author Contributions

Mehran Mesgari-Abbasi: Conceptualization, Resources, Experiment design, Histopathology testing, Animal experiments and interventions

Roya Darbani: Conceptualization, Data curation, Sample preparation, Biochemical tests, Data analysis, Drafting of manuscript

Oldouz Rabet: Sample preparation, Animal experiments and interventions, Biochemical tests, Data analysis, Drafting of manuscript

Amir Ghorbanihaghjo: Histopathology testing

Nadereh Rashtchizadeh: Histopathology testing

Sina Raeisi: Animal experiments and interventions

All authors read and approved the final manuscript

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Conflicts of Interest

The authors declare no conflicts of interest.

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