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RESEARCH ARTICLE

Mitigating Effect of Vitamin C on Favipiravir-Induced Adverse Effects: Pathological, Biochemical, and Molecular Insights in Rat Tissues.

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ABSTRACT

In this study, the mitigating effect of vitamin C with an anti-covid-19 drug (Favipiravir) had been assessed through the pathological, biochemical and gene expression changes in rat tissues. Thirty-six rats were split randomly into 6 groups, Group 1: water control, Group 2: were given 150 mg/kg vitamin C, Group 3: administered 200 mg/kg favipiravir, Group 4: received 400 mg/kg favipiravir, Group 5 were given 200 mg/kg favipiravir + 150 mg/kg vitamin C and Group 6: received 400 mg/kg favipiravir + 150 mg/kg vitamin C. Histopathological examination showed that favipiravir caused various lesions in the examined organs, including thickening of the interalveolar septa, inflammatory edema and necrosis in the lungs, microsteatosis and multifocal necrosis in the liver and variable degrees of degeneration in the renal tissues. However, when vitamin C was given along with favipiravir, the severity of these lesions was greatly reduced.In addition, coadministration of vitamin C with favipiravir reduced hepatic function markers (alanine transaminase ALT, aspartate aminotransferase AST, and C-reactive protein CRP), and renal function markers (urea and creatinine), while simultaneously elevating antioxidant levels (total antioxidant capacity) and decreased oxidative stress markers such as malondialdehyde in liver and kidney tissues compared to groups that were exposed to favipiravir only. Splenic tissues' gene expression revealed a decrease in NF-kb, TNF, and IL6 when animals were given vitamin C and favipiravir in comparison to favipiravir only. In conclusion, administration of vit C with favipiravir can alleviate the negative consequences induced by treatment with favipiravir only.

Keywords: COVID-19, Favipiravir, Vitamin C, Histopathology, Antioxidant.

Introduction

At the end of December 2019, a peculiar respiratory disorder was spreading in China. It was later identified as a viral infection caused by a Coronavirus and given the acronym SARS-CoV-2 which stands for "Severe Acute Respiratory Syndrome Coronavirus 2. World Health Organization named this pandemic pneumonia (COVID-19) [1, 2]. SARS-CoV-2 is a small virus averaging from 60 to 140 nm in diameter that belongs to the Nidovirales order and Coronaviridae family. Coronaviruses appear as a crown under an electron microscope because it contains spikes protruding from its surface, which are responsible for connecting the virus to the host cell [3, 4].

Favipiravir (Fav) and Vitamin C (Vit C) have been utilized in combination for treatment of COVID-19 patients [5]. Favipiravir, an antiviral drug branded as (Avigan) has been used in the treatment of diseases caused by influenza and emerging RNA viruses. It is a purine nucleoside analog administered as a prodrug and metabolized inside the host cell into its active Ribofuranosyl triphosphate (RTP) form. During RNA viruses' replication favipiravir-RTP is incorporated into the viral RNA resulting

in viral genome mutations and eventually inhibiting viral replication [6].

Favipiravir is known to have a short half-life in the plasma (2.5 to 5) hours where it reaches its maximum concentration after about 2 hours from oral administration. It has a very good bioavailability that reaches 94% and plasma protein binding of 54%-60% [7]. Favipiravir metabolisms occur mainly in the liver via aldehyde oxidase (AO) and partially by xanthine oxidase (XO), while cytochrome P450 plays no role in its metabolism, the drug inhibits one of its components which warrants caution when administered with a drug metabolized by the CYP450 system. The inactive favipiravir metabolite (M1) is then excreted through the kidneys and it has been reported that as little as (1%) of the given favipiravir only is eliminated unmodified; while the vast majority of it is metabolized [7–9].

While considered a relatively safe drug, administration of FPV orally for a duration extended to 10 days in people infected with COVID-19 lead to increasing levels of uric acid in the blood, where the metabolite M1 interfered with kidneys' elimination of uric acid and enhanced its uptake [9,10]. Moreover, it was shown to induce inflammatory liver damage in rats at high doses [11]. Ascorbic acid (AA), also recognized as Vitamin C (Vit C), is a cheap antiviral, antioxidant, and anti-inflammatory compound with low molecular weight. It is a water-soluble vitamin easily destroyed by high temperature, alkaline pH, and light [12]. Some investigations were performed to explore the effects of coadministration of Fav and Vit C. Vitamin C was shown to ameliorate the favipiravir induced erosive and ulcerative effects on the oral and nasal mucosa [13] and the histopathological damage to the periodontium in rats [14]. In addition, Vit C was shown to reduce the pro-inflammatory, oxidative and histopathologic effects of Fav on liver and kidney tissues in one study on a rat model [15].

In this research project, we sought to investigate the adverse effects of favipiravir, a commonly used antiviral medication during the COVID-19 pandemic, when administered alone or in combination with vitamin C. To achieve this, we conducted a study on albino rats, examining their tissue histopathology and analyzing serum biochemical parameters, specifically liver and kidney function, to identify any biochemical and histopathological changes resulting from the treatment and changes in gene expression of some proinflammatory and immune markers (IL6, NF-kB, and TNF-α) in the splenic tissue. Given that the typical treatment regimen of COVID19 patients starts with a higher loading dose followed by a lower maintenance dose [16], two different doses of favipiravir were included in our study.

Materials and Methods

Drugs

Favipiravir: a pharmaceutical product manufactured by EVA Pharma for Pharmaceuticals & Medical Appliances. One film-coated tab has 200 mg and is designed for use in the health care industry and was dissolved in distilled water.

Vitamin C: Effervescent tablets, each tablet contains 1 gm ascorbic acid purchased from Chemical Industries Development Co. (CID) and was dissolved in distilled water.

Experimental animals

Thirty-six albino rats, each weighing 195 ± 5 grams at the starting of the experiment, had been obtained from the animals' house, Faculty of Veterinary Medicine, Zagazig University, Egypt. Every 6 rats were kept at (25 ±0.5) ℃

under a 12:12 light/dark cycle in a separate cage with free water and feed access. Rats were acclimatized for 10 days before the beginning of the experiment and rats of all groups were kept under the same environmental conditions. ZU-IACUC/2/F/284/2023 is the ethical approval number for this investigation.

Experimental design

Experimental groups

Thirty-six rats, specifically albino ones, were randomly divided into six groups, each consisting of six rats. Group 1 was designated as the control group, where the rats had free access to food and water (negative control), while Group 2 was given 150 mg/kg of vitamin C. [13–15], Group 3 administered 200 mg/kg of favipiravir [11, 13], Group 4 administered 400 mg /kg of favipiravir [11,17], Group 5 received 200 mg/kg of favipiravir and 150 mg/kg of vitamin C, Group 6 was given 400 mg /kg of favipiravir and 150 mg/kg of vitamin C. On the 14th day [14] after 13 days of administration of drugs, all experimental groups were sacrificed (Table 1).

Table1. Animal groups and numbers, drug doses and sacrifice time.

Group	Drug	Dose
Group 1	Water	1 mL
Group 2	Vitamin C	150 mg/kg vit C
Group 3	Favipiravir	200 mg/kg
Group 4	Favipiravir	400 mg/kg
Group 5	Favipiravir +Vitamin C	200 mg/kg fav+ 150 mg/kg vit C
Group 6	Favipiravir+ Vitamin C	400 mg/kg+ 150 mg/kg vit C

All interventions for all groups were administered orally, daily for 13 days, and then on the 14th day all experimental groups were sacrificed.

Collection of Samples and tissue

Under the influence of anesthetic, blood was collected from the tail vein and medial canthus of the eye and placed in sterile blood collection tube, that were then left in a horizontal position for 1 hour until the blood was clotted. It was then placed in the fridge for 5hrs until retraction of the clot and centrifuged to collect serum which was ultimately preserved in sterile tubes at -20 °C to be utilized in the analysis of several biochemical variables. Phosphate-buffered saline (PBS), or ice-cold phosphate-buffered saline was used to rinse specimens of liver and kidney tissues and used for assessment of total anti-oxidant capacity (TAC) and malondialdehyde (MDA) antioxidant parameters. Parts of the spleen were preserved at −80°C for gene expression determination. For histopathological examination, tissues from the liver, kidneys, and lungs were gathered and preserved in (10%) neutral buffered formalin.

Biochemical studies

The Liver functions were detected by using kits from Labtest Diagnóstica S.A, Lagoa Santa, Brazil according to manufacturer's instructions. Also, the kidney functions were detected by using commercial kits provided by Stress Marq Biosciences Inc., Canada, for estimation of the level of urea. moreover, commercial kits provided by Biomerieux, France were used for estimating the level of Creatinine according to the manufacturer's instructions. However, detection of the total antioxidant capacity test (TAC) was carried out by using phosphate buffer saline (pH 7.0, containing 0.25 M sucrose) and Ferric Reducing Antioxidant Power (FRAP). Finally, detecting the (MDA) was accomplished by using thiobarbituric acid (TBA) according to manufacturer's instructions.

Gene expression analysis

A forementioned methodology was followed for carrying out the real-time Polymerase Chain Reaction [17]. In a nutshell, 20 mg of splenic tissue were treated with Trizol (Invitrogen; Thermo Fisher Scientific, Inc.) to extract total RNA. The Livak approach [18] was followed in the analysis, and the primer sequences employed are displayed in Table (2).

Table 2. The primers utilized in PCR.

	Forward primer (5′–3′)	Reverse primer (5′–3′)	Size	Accession no.	Reference
NF kB	CAGGACCAGGAACAGTTCGAA	CCAGGTTCTGGAAGCTATGGAT	150NM	199267.2	[19]
IL6	ATATGTTCTCAGGGAGATCTTGGAA	GTGCATCATCGCTGTTCATACA	80 NM	012589.2	[19]
TNF-α	AGGGTCTGGGCCATAGAAC	CCACCACGCTCTTCTGTCTAC	103 NM	012675.3	[19]

Histopathological specimens

The formalin-fixed specimens of kidneys, lungs and liver were immersed in increasing concentrations of alcohol (70–100%), clarified in xylene, and embedded in paraffin wax. The tissues were then sliced into 4-5 µm thick paraffin sections and finally stained with H&E (Hematoxylin and Eosin). The tissue sections were examined and photomicrographed microscopically using a light microscope (AmScope, Irvine, CA, USA) attached to a digital camera (AmScope MU1803-HS) [18].

Statistical analysis

The Anderson-Darling test was used to find out if all numerical data were normal once they were gathered. With the help of SPSS software (version 16.0; Chicago, USA), statistical analysis was done. The standard error of mean (SEM) is used to express the data. The study employed One-Way ANOVA with post hoc analysis "Duncan's test" to identify significant changes in aspartate aminotransferase, alanine aminotransferase, Urea, Creatinine, and C-reactive protein across all groups. Additionally, gene expression (TNF-α, NF-kB, and IL6) was estimated. However, the significant differences

between TAC (ng/min/g tissue) and MDA (nmol/g tissue) in renal and hepatic tissues in each of the fore-mentioned groups were found using the student t-test (independent t-test).

Results

Clinical changes

All treated groups were apparently healthy and showed normal behavior and no mortalities were recorded during the experimental period.

Parameters of serum biochemistry

There was a noticeable rise in the AST and ALT levels in groups 3 and 4 which received (200mg/kg) and (400mg/kg) Fav, respectively when compared to the groups where only water or vit C was administered. An increase in the levels of AST and ALT was also observed in group 4 compared to group 3. However, there was a significant decrease in aspartate aminotransferase and alanine aminotransferase values when Vit C was co-administered with Fav in groups 5 and 6 compared to their counterparts where the same dose of Fav was administered alone. The level of urea significantly increased in groups 3 (200mg/kg Fav) and 4 (200mg/kg Fav) as well with a higher level recorded in group 4 than group 3 but significantly decreased in groups 5 (200mg/kg Fav + vit C) and 6 (200mg/kg Fav + vit C) compared to groups 3 and 4 respectively. A similar behavior was recorded in levels of both creatinine and CRP (Figure 1).

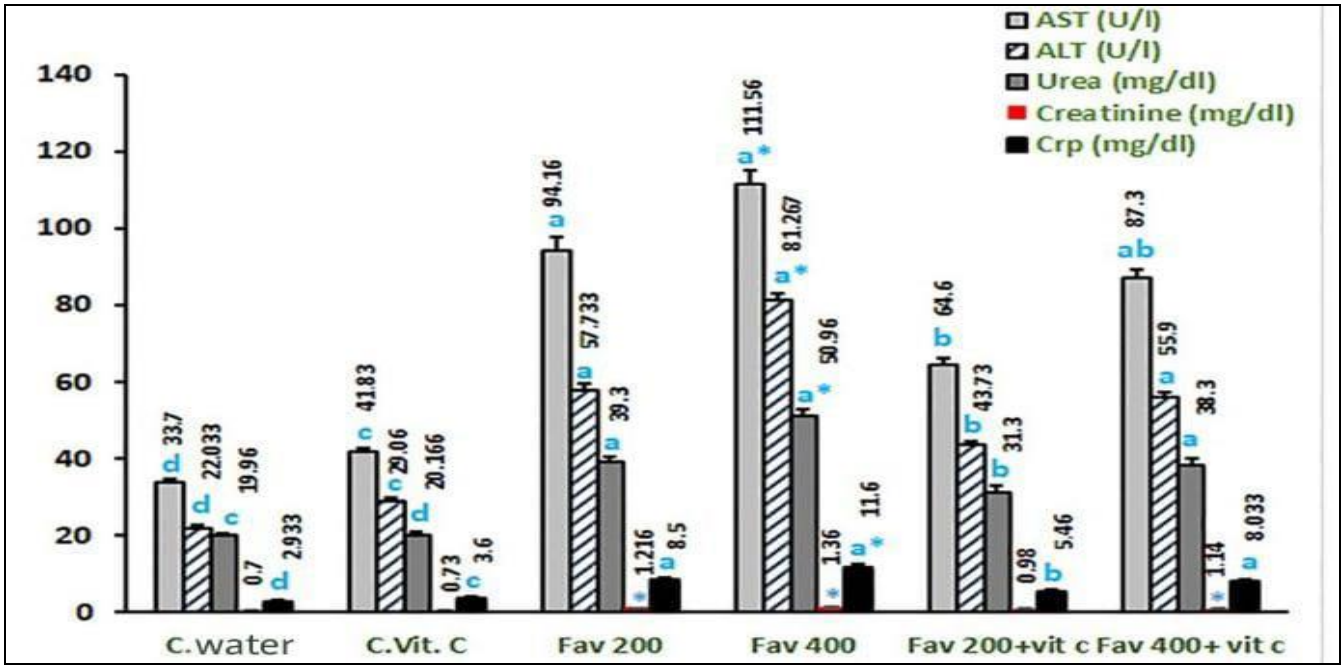

Figure 1. shows the level of AST, ALT, Urea, Creatinine, and CRP in all experimental groups. The columns with the same color and holding different letters (a*, a, ab, b, c, and d) are significantly different. The data are expressed as the Mean ±SEM; differences are regarded significant at p≤ 0.05 (one-way ANOVA test followed by the post-doc Duncan test).

TAC levels were markedly lower in the tissues of the kidneys and liver in group 4 which received 400 mg/kg Fav and significantly increased in groups 2 which received Vit C only and group 6 which received 400 mg/kg Fav and Vit C. However, there was no significant difference between group 3 (200 mg/kg Fav) and group 5 (200 mg/Kg Fav + Vit C). A similar pattern in the opposite direction was observed in the levels of MDA in hepatic and renal tissues where a

significant increase in the MDA levels in both groups 3 and 4 compared to the control group was followed by a significant decrease in its levels in groups 5 and 6 where Vit C was used simultaneously with favipiravir (Figures 2 and 3).

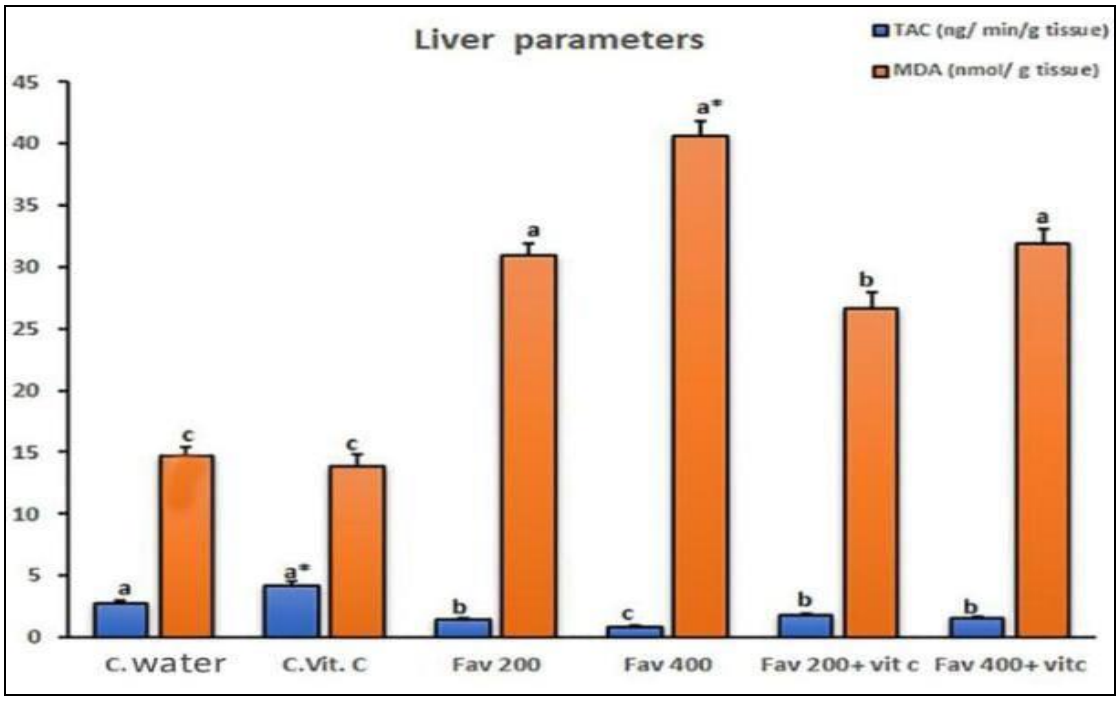

Figure 2. Shows TAC and MDA levels in the tissues of the liver in all experimental groups. Columns have the same color and holding different letters (a*, a, b, and c) are significantly different. The data are expressed as the Mean ±SEM; differences are considered significant at p≤ 0.05 (independent T-test).

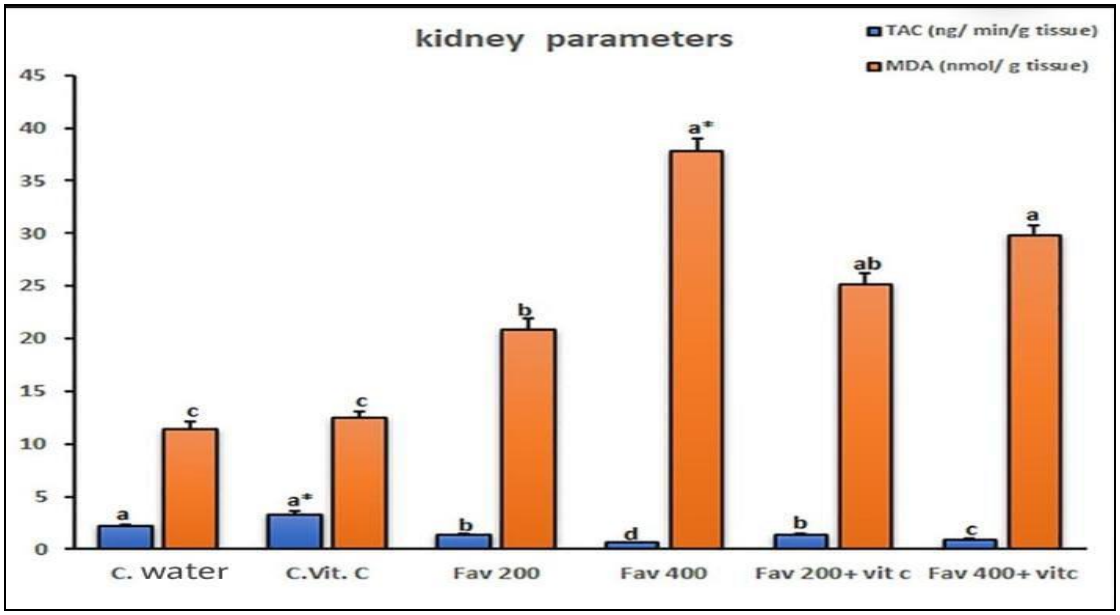

Figure 3. Shows TAC and MDA levels in the kidney tissues of all experimental groups. The columns have the same color and hold different letters (a*, a, ab, b, c, and d) are significantly different. The data are expressed as the Mean ±SEM; differences are considered significant at p≤ 0.05 (independent T-test).

Histopathological changes

Examined lung sections of rats from the water and Vit C control groups (groups 1 and 2) showed normal histological structure of the lungs (Figure 4A and B). Lung sections from the 200 mg/Kg fav exposed group showed moderate thickening in the interalveolar septa, mild catarrhal inflammation and desquamation of the bronchial epithelium with mild hyperplasia of the peri bronchial lymphoid tissues and prominent perivascular lymphoid aggregates (Figure 4C). Lung sections from the 400 mg/kg fav exposed rats showed a myriad of changes ranging from inflammatory edema and filling of the alveolar spaces with homogenous eosinophilic material to areas of necrosis and complete destruction of the lung parenchyma with presence of large number of inflammatory cells among the edematous and necrotic lung parenchyma and inside the bronchial and bronchiolar lumina. Increased thickness of the interalveolar septa was also observed in some examined sections (Figure 4D-F). Lung sections from rat groups that received Vit C with Fav showed only mild thickening of the interalveolar septa in some sections with slight hyperplasia of alveolar macrophages (Figure 4G-I).

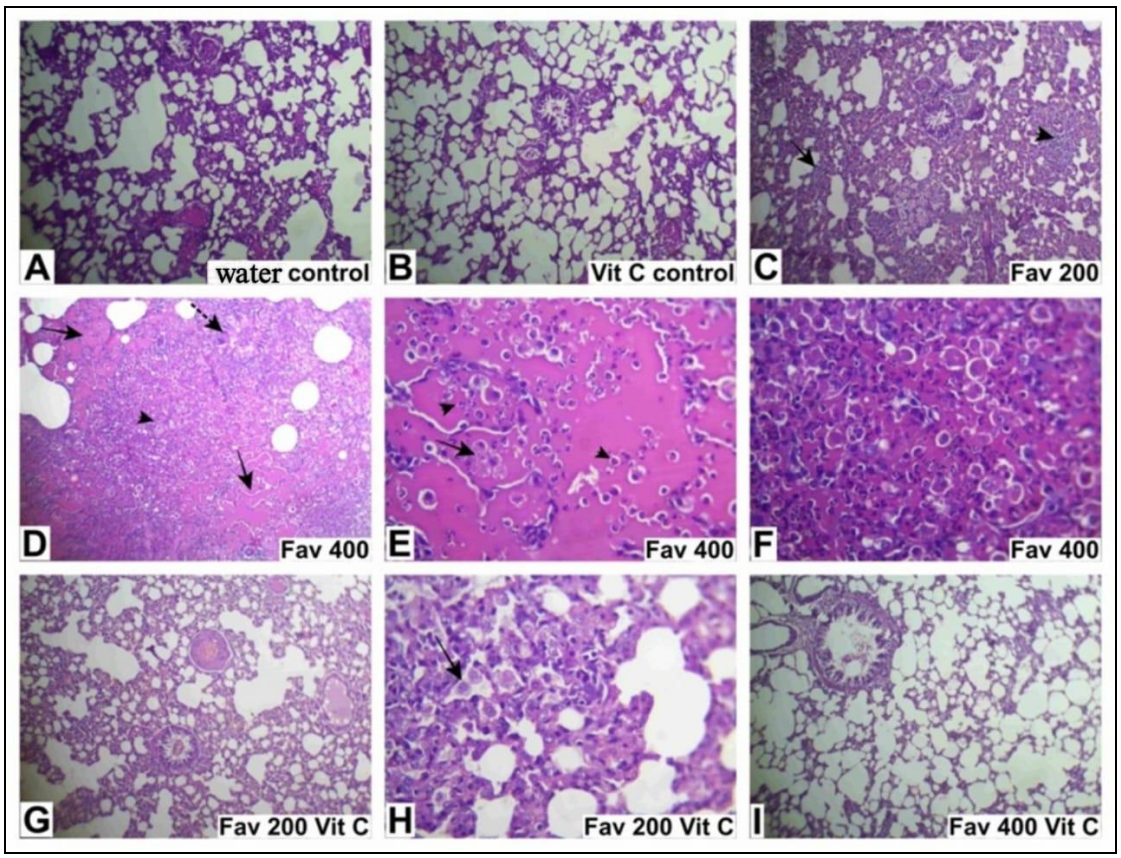

Figure 4. Shows representative photomicrographs of H&E-stained lung sections of rats exposed to favipiravir (Fav) & and/or Vitamin C (Vit C). A and B: Lung sections from Water control and Vit C control groups respectively showing normal lung architecture x100. C: Lung section from rats received 200 mg/kg favipiravir showing marked thickening of inter-alveolar septa (arrow) and perivascular lymphoid aggregations (arrowhead) x100. D: Lung section from rats received 400 mg/kg favipiravir showing inflammatory edema (arrows) and necrosis (arrowhead) with the presence of many inflammatory cells among edematous and necrotic alveoli and inside the bronchiolar lumen (dashed arrow) x100. E and F are higher magnifications of D showing inflammatory edema and necrosis respectively. The arrow in E points to the alveolar macrophages and the arrowheads point to neutrophils x400. G: Lung section from rats received 200

mg/kg favipiravir and 150mg/kg vitamin C showing mild thickening of inter-alveolar septa, and dilation of blood vessels x100. H: is a higher magnification of G showing the thickened interalveolar septa with alveolar macrophages (arrow) x400. I: Lung section from rats received 400 mg/kg favipiravir and 150mg/kg vitamin C showing almost normal histologic lung features x100.

Liver sections from rats in the water and Vit C control groups showed normal liver histological architecture (Figure 5A and B), while sections from the favipiravir only exposed groups (groups 3 and 4) showed multifocal areas of coagulative and lytic necrosis. While non-necrotic hepatocytes showed microsteatosis (Figure 5C-F). Liver sections from group 5 which received vit C and 200 mg/Kg Fav showed few apoptotic hepatocytes (Figure 5G). Liver sections from group 6 which received vit C and 400 mg/Kg Fav showed mild perivascular edema and fibrosis in addition to bile ductular hyperplasia (Figure 5H and I).

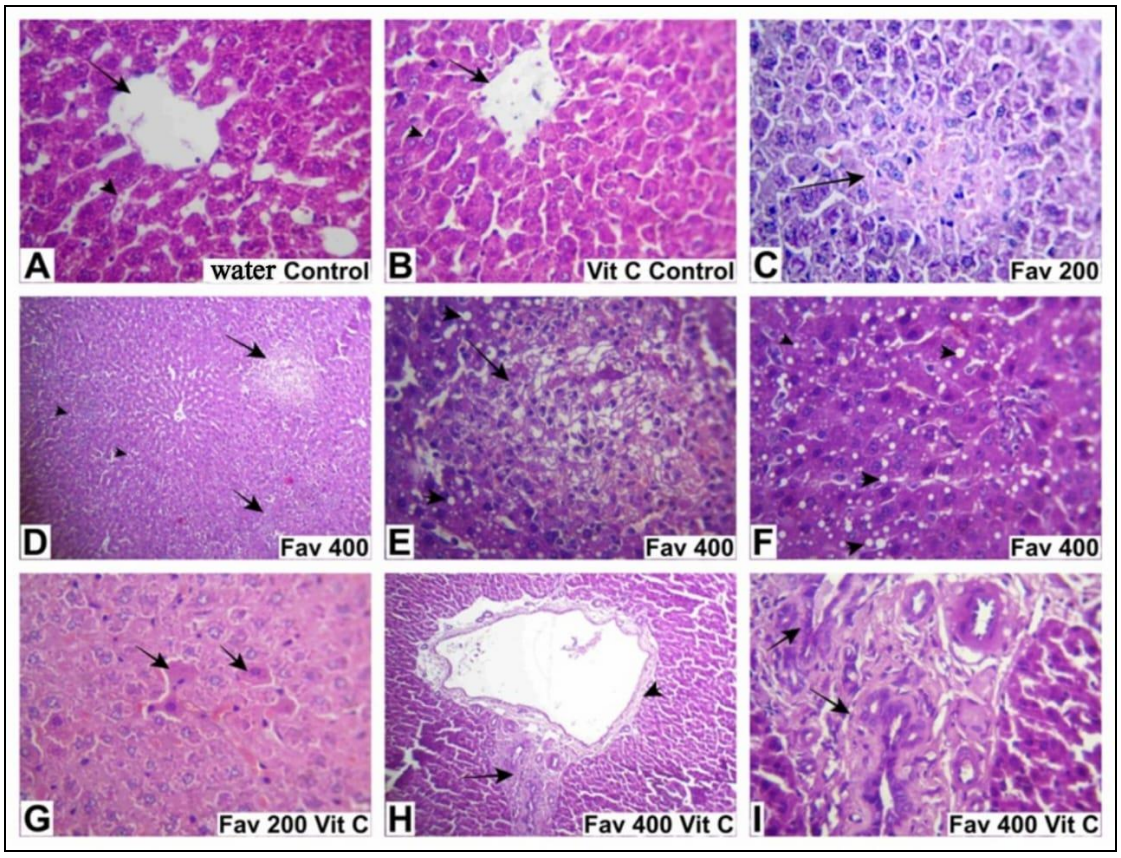

Figure 5. representative photomicrographs of H&E-stained liver sections of rats exposed to favipiravir (Fav) & and/or Vitamin C (Vit C). A and B: Liver sections from the Water control and Vit C control groups respectively show normal liver architecture with normal central veins (arrows) and sinusoids (arrowheads) x400. C: Liver sections from rats received 200 mg/kg favipiravir showing focal necrosis (arrow) x400. D: Liver sections from rats received 400 mg/kg favipiravir showing multifocal necrosis (arrows) and microsteatosis (arrowheads) x100 E and F: are higher magnifications of D showing focal necrosis and microsteatosis respectively. The arrow in E points to fibrin and inflammatory cells replacing the necrotic hepatocytes and the arrowheads point to lipid vacuoles inside the hepatocytes x400. G: Liver section from rats received 200 mg/kg favipiravir and 150mg/kg vitamin C showing scattered single apoptotic hepatocytes (arrows) x400. H: Liver section from rats received 400 mg/kg favipiravir and 150mg/kg vitamin C showing mild perivascular edema and fibrosis (arrowhead) and bile ductular hyperplasia (arrow) x100. I: is a higher magnification of H showing bile ductular hyperplasia x400.

Examined kidney sections from rats in the water and vit C control groups showed normal renal parenchymal histological structures (Figure 6A and B). Kidney sections from rats in group 3 which received 200 mg/kg Fav showed mildly hyperemic glomerular capillaries and mild vacuolation of the renal tubules. Similar lesions were observed in the examined kidney sections from rats received 400 mg/kg Fav where glomerular capillaries were dilated, and renal tubules showed variable degrees of vacuolation in addition to presence of numerous shrunken glomeruli and hyaline droplet degeneration of the renal tubular epithelium. Moreover, mild extravasation of RBCs was observed in some sections (Figure 6C-F). In rats that received both vit C and Fav (groups 5 and 6), the kidneys almost regained their normal histologic structure with only mild vacuolation of renal tubular epithelium and occasional dilation of some intertubular blood vessels (Figure 6G-I).

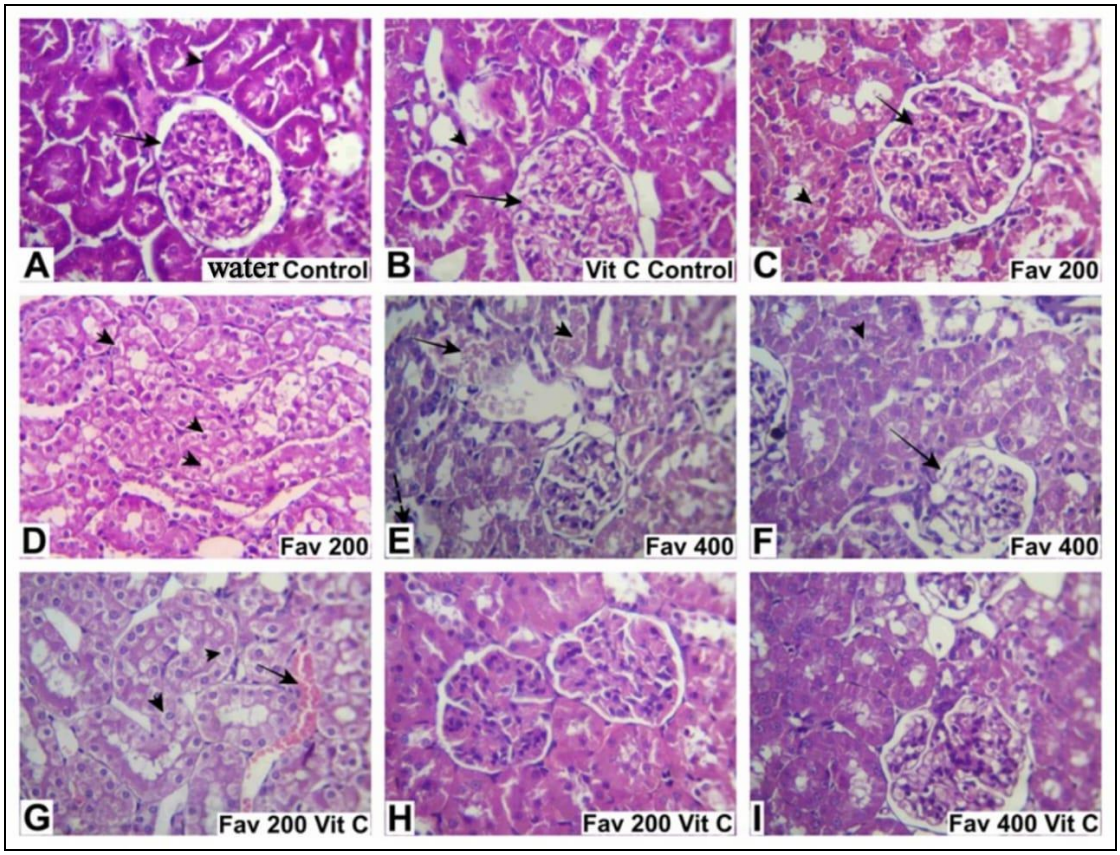

Figure 6. shows representative photomicrographs of H&E-stained Kidney sections of rats exposed to favipiravir (Fav) & and/or Vitamin C (Vit C) x400. A and B: Kidney sections from Water control and Vit C control groups respectively showing normal kidney architecture with normal glomeruli (arrows) and renal tubules (arrowheads) x400. C and D: Kidney sections from rats received 200 mg/kg favipiravir showing mildly hyperemic glomerular capillaries (arrows) and vacuolated renal tubules (arrowheads) x400. E: Kidney section from rats received 400 mg/kg favipiravir showing hemorrhage (arrow) hyaline droplet degeneration of some renal tubules (arrowhead) and a mildly shrunken glomerulus (dashed arrow) x400. F: Kidney section from rats received 400 mg/kg favipiravir showing markedly dilated glomerular capillaries (arrow) and hyaline droplet degeneration of renal tubules (arrowhead) x400. G: Kidney section from rats received 200 mg/kg favipiravir and 150mg/kg vitamin C showing vacuolated renal tubular epithelium (arrowhead) and dilated inter-tubular blood vessel (arrow) x400. H: Kidney section from rats received 200 mg/kg favipiravir and 150mg/kg vitamin C showing almost normal renal histologic features x400. I: Kidney section from rats received 400 mg/kg favipiravir and 150mg/kg vitamin C showing almost normal renal architecture with mildly dilated glomerular capillaries x400.

Gene expression

There was a notable rise in the expression of TNF-α, IL-6, and NF-Kb genes in groups 3 and 4 where rats received 200 and 400 mg/kg Fav respectively compared to the water and vit C control groups. However, these expressions were significantly decreased when vit C was administered with Fav simultaneously in groups 5 and 6 compared to the favipiravir only groups (Figure 7).

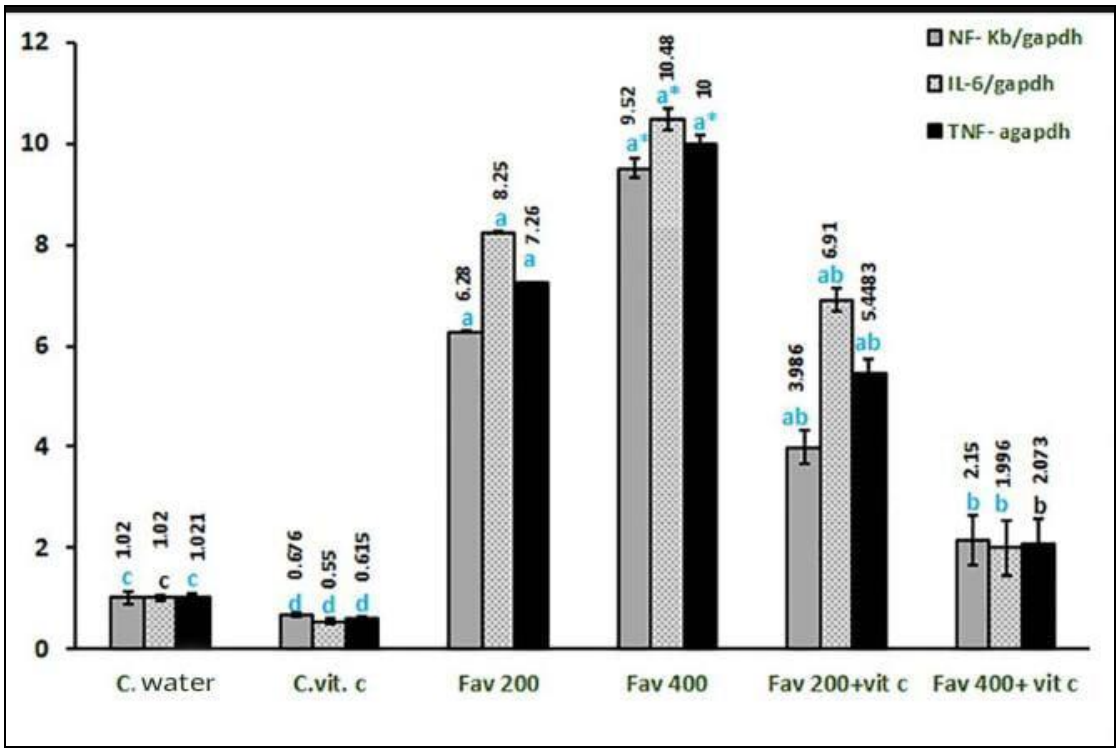

Figure 7. shows Gene expression of NF-Kb/gapdh, IL-6/gapdh, and TNF/gapdh in all experimental groups. The columns with the same color and holding different letters (a*, a, ab, b, c, and d) are significantly different. The data are expressed as the Mean ±SEM; differences are considered significant at p≤ 0.05 (one-way ANOVA test followed by the post-doc Duncan test).

Discussion

In this experiment, we explored the histopathological, biochemical, and molecular effects of administering the antiviral drug Fav to rats, as well as the modulatory effects of Vit C when co-administered with Fav.

Our results showed that favipiravir has adverse effects on the liver and kidney functions where it increased the levels of aspartate aminotransferase, alanine aminotransferase, creatinine and urea in the exposed rats. A retrospective single-center cohort study performed on COVID19 patients in Saudi Arabia reported a significant increase in the liver enzymes in patients treated with Fav [20]. A finding that corroborated another study done earlier in 2020 based on a WHO database and suspected that favipiravir was the cause of increased hepatic enzymes in about quarter of the patients that showed adverse drug effects [21] and a case report from a COVID patient where favipiravir induced cholestatic liver damage [22]. Experimentally, these results are in accordance with those described by Kara *et al*. [23], who reported an increase in AST, ALT, urea and creatinine in rats treated with favipiravir in a dose and time dependent

manner. However, in another experimental study favipiravir was not shown to affect liver or kidney functions when administered in rats but that was most probably attributed to the mode of administration of the drug via inhalation where the drug reached high pulmonary concentrations without much systemic absorption. More interestingly, this mode of administration of favipiravir was not associated with oxidative lung damage [24].

Increased blood uric acid is a common adverse effect of favipiravir and has been recorded by several studies [10]. Although the precise mechanism behind this effect is not elucidated yet, a recent study suggests that hyperuricemia induced by favipiravir administration is most probably due to the inhibition of the Organic Anion Transporters (OAT1 and OAT3) which play a role in uric acid secretion in the kidneys [9].

Our results here suggest that favipiravir induce oxidative damage in treated rats, a finding that supports other studies reporting elevation of oxidative damage markers in various tissues of favipiravir treated rats including ovaries [17], liver and kidneys [11,15]. Although our findings showed an increase in CRP levels in sera from rats treated with favipiravir, this was not in agreement with a clinical study in humans reporting a decrease in CRP levels in favipiravir treated patients [25]. IL6, Nf-Kb and TNF-α are all indicators of the inflammatory status in tissues. In the current study these cytokines were shown to be elevated in tissues from favipiravir treated rats corroborating results from previous experimental studies [15, 23].

Vit C is recognized for its antioxidant and anti-inflammatory effects through modulating the production of proinflammatory mediators such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), and interleukin-1 beta (IL-1beta) [26]. In addition, it was also shown that vit C inhibits the activation of Nf-kB; a major regulator of the inflammasome and subsequently attenuates expression of inflammatory genes and mitigates the inflammatory process [27]. It's also a scavenger of reactive oxygen species and enhances the activity of antioxidative enzymes thus further dampening the inflammatory response [28]. In our study vit C coadministration with favipiravir was shown to significantly reduce sera AST, ALT, urea and creatinine in treated rats compared to those treated with favipiravir only. In addition, it reduced the acute phase inflammatory protein CRP and the oxidative marker MDA while increasing the total antioxidant capacity. Finally, combining vit C with favipiravir decreased the expression of the proinflammatory genes IL6, TNF-α and Nf-kB in rat tissues, an effect that supports previous studies showing a desirable effect of combining favipiravir with vit C either in clinical trials or rat experimental models [13–15]. However, Hailat *et al.* [29] reported through an experimental investigation in rats a possible effect for vit C on Fav metabolism through inhibiting fav metabolizing enzymes aldehyde oxidase and xanthine oxidase, thus increasing its plasma concentration with subsequent increase in fav undesirable effects [29].

Our biochemical and gene expression data were well translated into histopathological findings in the examined rat tissues and these findings where in partial agreement with Kara *et al.* [23] who reported hepatic necrosis with collagen deposition and dilated vessels and sinusoids, and renal tubular dilation with loss of brush border and moderate collagen deposition in kidneys of rats after receiving Fav for 10 days. Elma *et al.* [16] also described Fav pulmonary induced histopathologic lesions almost consistent with our findings here represented mainly by thickened interalveolar septa and

pronounced lymphoid hyperplasia, while in agreement with our findings, combining vit C with Fav could mitigate the pathologic effect of Fav on different rat tissues including liver, kidneys, alveolar bone and oral and nasal mucosa [13–15].

Conclusion

In conclusion, our findings underscore the potential mitigating effect of vitamin C when administered alongside favipiravir, an antiviral drug used in the treatment of COVID-19 patients. Further research is warranted to elucidate the underlying mechanisms and optimize the therapeutic course for clinical application.

Conflict of Interest

The authors declare no conflict of interest.

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الملخص بالعربي

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في هذه الدراسة، تم تقييم التأثير التخفيفي لفيتامين C مع دواء مضاد لكوفيد-19 (فافيبيرافير) من خلال التغيرات المرضية والكيميائية وتعبير الجينات في أنسجة الجرذان البيضاء. تم تقسيم 36 جرذًا عشوائيًا إلى 6 مجموعات، المجموعة 1: المجموعة الحاكمة السلبية وتلقت ماء فقط، المجموعة 2: تلقت 150 ملغ/كغ من فيتامين C، المجموعة 3: تلقت 200 ملغ/كغ من فافيبيرافير، المجموعة 4: تلقت 400 ملغ/كغ من فافيبيرافير، المجموعة 5: تلقت 200 ملغ/كغ من فافيبيرافير + 150 ملغ/كغ من فيتامين C، والمجموعة 6: تلقت 400 ملغ/كغ من فافيبيرافير + 150 ملغ/كغ من فيتامين C. أظهرت النتائج النسجية أن فافيبيرافير تسبب في كثير من التغيرات المرضية فى الأعضاء التي تم فحصها والتي تتراوح بين زيادة سمك الحاجز بين الحويصلات، والوذمة الالتهابية والنخر في الرئتين، والتنكس الدهني المجهري والنخر متعدد البؤر في الكبد ودرجات متفاوتة من التنكس في أنسجة الكلى، فإن معظم هذه الآفات تم تقليلها بشكل ملحوظ عند تناول فيتامين C مع فافيبيرافير. بالإضافة إلى ذلك، يقلل من مؤشرات وظائف الكبد (ألانين أمينو ترانسفيريز، أسبارتات أمينو ترانسفيريز، وبروتين التفاعل الكاشف) ومؤشرات وظائف الكلى (اليوريا والكرياتينين). كما زادت مستويات المضادات الأكسدة (السعة الكلية للأكسدة) وانخفضت علامات التوتر الأكسدي مثل المالونديالدهيد في أنسجة الكبد والكلى مقارنة بالمجموعات التي تعرضت فقط لفافيبيرافير. أظهر تعبير الجينات في أنسجة الطحال انخفاضًا في عوامل NF-kb و TNF و 6IL عند تعرض الحيوانات لفيتامين C وفافيبيرافير مقارنة بالفافيبيرافير فقط. بختام الدراسة، يمكن أن نسخلص أن إعطاء فيتامين C مع فافيبيرافير يخفف من الآثار الضارة التي تسببها علاج الفافيبيرافير.