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Effect of low and high dose of favipiravir on ovarian and reproductive function in female rats: Biochemical and histopathological evaluation

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Abstract. Favipiravir is a drug which shows antiviral activity by inhibiting RNA-dependent RNA polymerase. Favipiravir causes severe adverse effects at high doses. The aim of this study was to investigate the effects of low and high dose favipiravir on ovarian and reproductive function in female rats. The rats were divided into three groups: HG group (healthy rats), FAV-100 group (rats administered 100 mg/kg favipiravir), and FAV-400 group (rats administered 400 mg/kg favipiravir) with 12 rats in each group. Favipiravir was administered orally twice daily for 1 week. Six rats from each group were euthanized and their ovaries were removed. Oxidative and antioxidant parameters were measured in ovarian tissues and examined histopathologically. The remaining animals were kept to breed. Animals receiving favipiravir had increased oxidant content, decreased antioxidant activity, decreased histopathological damage, infertility, and gestational delay. Favipiravir treatment should be used with caution, especially in women of reproductive age.

Key words: Favipiravir — Ovarian tissue — Reproductive function

Introduction

Favipiravir is an antiviral drug approved against influenza in Japan. Later, it was learned that it is effective against many RNA viruses such as Ebola, Norovirus, Enterovirus (McCreary and Pogue 2020). Based on its mechanism of action, favipiravir was thought to be effective against acute respiratory syndrome coronavirus-2 (SARS-CoV-2), and it was decided to be used in the treatment (Łagocka et al. 2021). Favipiravir is converted to its active form, which is favipiravil-ribofuranosyl-50-triphosphate metabolite, by ribosylation and phosphorylation in the body (Furuta et al. 2013). Favipiravir exerts its antiviral effect by inhibiting RNA-dependent RNA polymerase (RdRp), which prevents genome RNA transcription and replication (Furuta et al. 2005). As the antiviral effect of favipiravir against Ebola and SARS-CoV is seen at high doses, it has been recommended to be used in high doses in COVID-19 infection as well (Beigel et al. 2020). However, favipiravir causes more severe side effects at high doses (Pilkington et al. 2020). It is reported that the most common adverse effects during the use of favipiravir are diarrhea, nephrotoxicity, increase in serum uric acid and transaminase levels, and decrease in white blood cell and neutrophil levels; less frequently, nausea, vomiting, abdominal pain, skin rash, itching, delirium, hallucinations and convulsions are shown (Chen et al. 2020; Doğan et al. 2021). Severe and fatal adverse effects have been reported to occur more frequently in men and those over 64 years of age (Kaur et al. 2020). Also, it has been documented that

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favipiravir is teratogenic in more than one species and its use in pregnancy is contraindicated (Hayden and Shindo 2019). Studies investigating the effects of favipiravir on ovarian tissue and reproductive function in animals were not found in the literature.

Information reported in previous test studies shows that reactive oxygen species (ROS) have a role in the pathogenesis of organ and tissue damage (Mittal et al. 2014). Also, whether tissue damage occurs is evaluated with the oxidant/antioxidant balance (Aguilar et al. 2007). In various damage models generated in living tissues, the oxidant/antioxidant balance changes in favour of oxidants, and an increase in oxidant levels and a decrease in antioxidant levels are found (Iraz et al. 2006). This information remarks that the toxic effect of favipiravir on organs and tissues may be due to oxidative stress. The aim of our study was to investigate the effects of low and high-dose favipiravir on ovarian tissue and reproductive function in female rats using biochemical and histopathological methods.

Materials and Methods

Animals

Albino Wistar female rats used in our study were obtained from Erzincan Binali Yildirim UniversityExperimental Animals Application and Research Center. A total of 36 rats, weighing between 245–256 g, were housed and fed at normal room temperature (22°C) for 12 h in light and 12 h in darkness before the test. In order for the animals to adapt to the environment, they had been kept in the laboratory environment where the test would be performed for one week. The protocols and procedures were approved by the local Animal Experimentation Ethics Committee (11.11.2021, meeting/decision No: 04/18).

Chemicals

Thiopental sodium used in the experiment was obtained from IE Ulagay (Turkey), favipiravir from Training and Research Hospital (Turkey) affiliated to the Ministry of Health.

Experimental groups

Rats were divided into HG group (healthy rats), FAV-100 group (rats administered 100 mg/kg favipiravir), and FAV-400 group (rats administered 400 mg/kg favipiravir).

Experimental procedure

For application of the test, FAV-100 (n = 12) and FAV-400 (n = 12) animal groups were administered orally to their stomach by gavage at 100 and 400 mg/kg doses of favipiravir, respectively. Distilled water was administered orally (0.5 ml) to the HG (n = 12) group. This procedure was repeated twice a day for a week. At the end of this period, 6 rats from each group were euthanized with high-dose (50 mg/kg) thiopental anesthesia and their ovaries were removed. Malondialdehyde (MDA), total glutathione (tGSH), superoxide dismutase (SOD), total oxidant status (TOS) and total antioxidant status (TAS) levels were measured in the ovarian tissues excised. Tissues were also examined histopathologically. For reproduction of the remaining animals (6 female rats from each group) were kept in the laboratory environment with mature male rats for two months. During this period, the rats that became pregnant were taken to separate cages and kept alone in a suitable environment. Rats that did not become pregnant or gave birth within two months were considered infertile. In addition, the time remaining from the day the female rats were placed in the same cage with the male rats to the day the pups were born was determined. The normal gestation period of 21 days was subtracted from this period and the day on which the rats became pregnant was calculated.

Biochemical analyzes

SOD activities, GSH and MDA and protein (catalogue No: 704002) levels from the supernatants obtained from tissue homogenates were measured with ELISA kits obtained from Cayman company.

Determination of malondialdehyde (MDA) levels

The Cayman TBARS Measurement Kit (10009055) is a simple, repeatable, and standardized measurement tool for assessing lipid peroxidation in tissue homogenates. MDA-TBA, which is formed by the reaction of MDA and thiobarbutyric acid (TBA) under acidic conditions and high temperature (90–100°C), was measured colorimetrically at 530–540 nm.

Determination of glutathione (GSH) levels

The Cayman GSH Measurement Kit (Item No: 703002) uses an optimized enzymatic recycling method *via* glutathione reductase to quantify GSH. The sulfhydryl group of GSH reacts with 5,5'-dithio-bis-2 nitrobenzoic acid (DTNB) to form yellow 5-thio-2-nitrobenzoic acid (TNB). GSTNB, a disulfide mixture between simultaneously produced GSH and TNB, is reduced by GR to recycle GSH and produce more TNB. The production rate of TNB is directly dependent on the concentration of GSH in the sample and the TNB absorbance value at 405–414 nm provides an accurate assessment of the GSH in the sample.

Determination of superoxide dismutase (SOD) activity

The Cayman SOD Measurement Kit (Item No: 706002) is based on the principle of using a tetrazolium salt for the detection of hypoxanthine and superoxide radicals produced by xanthine oxidase. One unit of SOD is defined as the amount of enzyme required for 50% dismutation of the superoxide radical to occur. In SOD measurement, all three types of SOD (Cu/Zn-SOD, Mn-SOD, and Fe-SOD) were measured. This method provides a simple, repeatable, and rapid measurement of SOD activity in tissue homogenates.

Determination of TOS and TAS levels

TOS and TAS levels of tissue homogenates were determined using a novel automated measurement method and commercially available kits (Rel Assay Diagnostics, Turkey), both developed by Erel (Erel 2004, 2005).

Histopathological procedures

For histopathological evaluation, ovary was fixed determined in 10% formalin solution. After going through routine histological tissue follow-up stages, it was embedded in paraffin. Sections of 5 μm thickness were taken on by the microtome. Sections taken were stained with Hematoxylin-Eosin (H&E) and examined under a light microscope (Olympus BX53, Japan). For histopathological evaluation, an average of 12–15 areas was evaluated by random sampling for each animal in the groups. The histopathological damage severity in each ovary tissue section was scored between grades 0–3 (0 – normal, 1 – mild damage, 2 – moderate damage, and 3 – severe damage) according to criteria reported in previous studies (Karacor et al. 2020). Ovarian tissue of all animals in the groups was examined blindly by the same histologist.

Statistical analysis

The results obtained from the experiments were expressed as mean value ± SEM. The significance of the difference between groups was determined using the one-way ANOVA test. Then Fisher's *post-hoc* LSD (least significant differences) test was made. All statistical operations were performed in the "SPSS for Windows, 22.0" statistical software and $p < 0.05$ was considered significant. GraphPad Prism-8 Program was used for graphics.

Results

Tissue MDA, tGSH, and SOD analysis results

At least one group was statistically different when MDA data from study groups were evaluated ($F(2,15) = 1314.711$, $p < 0.001$). As can be seen from Figure 1, the amounts of MDA in the ovarian tissues of the FAV-100 (2.71 ± 0.15) and FAV-400 8.42 ± 0.05) groups were found to be significantly higher than in the HG group (1.42 ± 0.19) ($p < 0.001$). Also, the amount of MDA in the FAV-400 group showed a more significant increase compared to the FAV-100 group ($p < 0.001$).

When animal groups were compared for tGSH ($F(2,15) = 419.510$, $p < 0.001$) and SOD ($F(2,15) = 452.396$, $p < 0.001$) data, at least one group was statistically different from the others. Favipiravir caused a decrease in antioxidants such as tGSH and SOD in the ovarian tissues of animals. tGSH and SOD levels in the ovarian tissues of the FAV-100 (6.42 ± 0.13; 18.50 ± 0.76, respectively) and FAV-400 (1.93 ± 0.16; 5.62 ± 0.10, respectively) groups were significantly lower than those of the HG (8.69 ± 0.20; 34.33 ± 0.88, respectively) group ($p < 0.001$) (Fig. 1). Moreover, tGSH and SOD levels were significantly decreased in the FAV-400 group compared to that of FAV-100 group ($p < 0.001$).

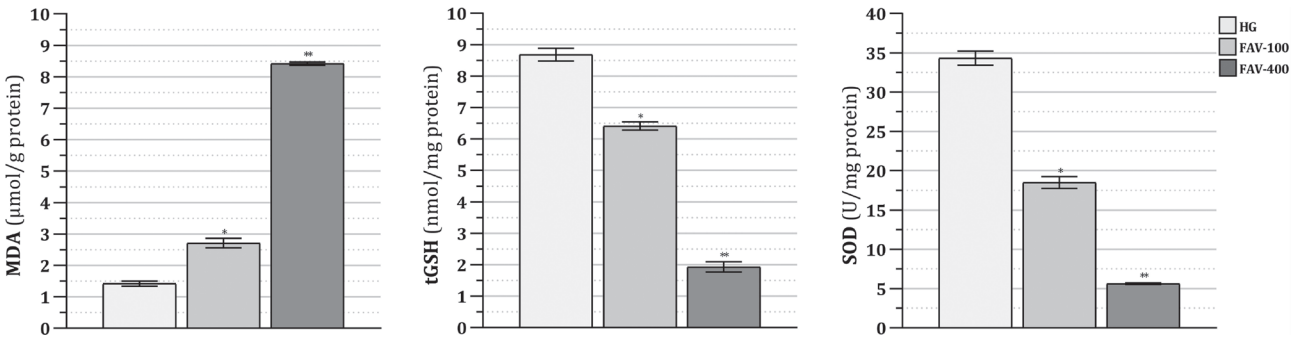

Figure 1. The effect of favipiravir on the amounts of MDA, tGSH and SOD in the ovarian tissues of experimental animals. Data are mean ± SEM, $n = 6$. * $p < 0.001$ *vs*. HG group, ** $p < 0.001$ *vs*. HG and FAV-100 groups. MDA, malondialdehyde; tGSH, total glutathione; SOD, superoxide dismutase; HG, control group (healthy rats); FAV-100, rats treated with favipiravir 100 mg/kg; FAV-400, rats treated with favipiravir 400 mg/kg.

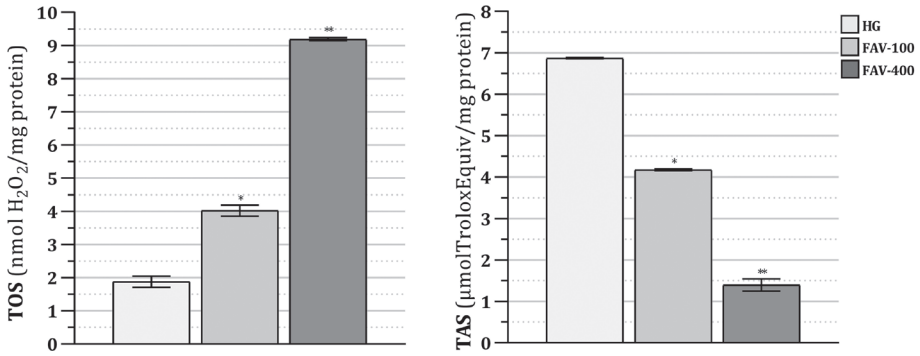

Figure 2. The effect of favipiravir on the amounts of TOS and TAS in the ovarian tissues of experimental animals. Data are mean ± SEM, $n = 6$. * $p < 0.001$ *vs.* HG group, ** $p < 0.001$ *vs.* HG and FAV-100 groups. TOS, total oxidant status; TAS, total antioxidant status. For more abbreviations, see Fig. 1.

Tissue TOS and TAS analysis results

At least one group differed from the others in comparing TOS ($F(2,15) = 739.033$, $p < 0.001$) and TAS ($F(2,15) = 959.170$, $p < 0.001$) data. Favipiravir caused an increase in TOS level and a decrease in TAS level in rat ovarian tissues. When the FAV-100 (4.02 ± 0.17; 4.18 ± 0.02, respectively) and FAV-400 (9.19 ± 0.05; 1.40 ± 0.15, respectively) groups were compared with the HG (1.88 ± 0.18; 6.87 ± 0.02, respectively) group for TOS and TAS values, statistical differences were found ($p < 0.001$). While the TOS level in the FAV-400 group was higher than that of the FAV-100 group, the TAS level was calculated to be low ($p < 0.001$) (Fig. 2).

Reproduction test results

As seen in Table 1, all rats in the HG group gave birth. In the FAV-100 group, 4 of the 6 rats included in breeding gave birth and 2 remained infertile. In the FAV-400 group, no rat gave birth within 2 months. 6 female rats in the control group gave birth on the 21st and 26th days. In the FAV-100 group, 4 rats gave birth on days 33 to 36. Maternity time of female rats in the HG group was calculated as 2 days. In the FAV-100 group, this period was 14 days.

Histopathological findings

No pathological findings were found in the ovarian tissue of the control (HG) group (Fig. 3A). However, grade-2 disruption of follicular cell integrity and cortical fibrosis were observed in ovarian tissue of animals treated with 100 mg/kg favipiravir (Fig. 3B). In the histopathological examination of the FAV-400 group, deterioration of follicle cell integrity and cortical fibrosis were evaluated as grade 3, and follicle cell degeneration and necrosis as grade 2 (Fig. 3C, Table 2).

Discussion

As the antiviral effect of favipiravir against Ebola and SARS-CoV is seen at high doses, it is recommended to be used in high doses in COVID-19 infection as well (Beigel et al. 2020). Therefore, in our study, the effect of favipiravir on the ovarian tissue of female rats was investigated at low and high doses. Moreover, reproductive functions of animals administered favipiravir were evaluated. Our biochemical test results revealed that favipiravir increased oxidant levels and decreased antioxidant levels compared to the control group. High dose of favipiravir increased MDA and TOS levels more significantly than low dose, and decreased antioxidant levels such as tGSH, SOD, and TAS. As known, MDA is the major product of lipid peroxidation (LPO) (Duryee et al. 2021). It is the ROS that cause the increase of MDA in the damaged tissue (Ozcicek and Halis 2020). Therefore, MDA is considered to be the most reliable parameter of LPO and oxidative damage. Therefore, an increase in MDA level in a tissue indicates an increase in ROS (Angelova et al. 2021).

Table 1. Reproductive process of rats in experimental groups

Group	Animals taken to breeding	Animals giving birth	Infertile animals	Day of birth	Delay in maternity period (days)	*n*
HG	6	6	0	21–26	2	6
FAV-100	6	4	2	33–36	14	6
FAV-400	6	0	6	–	–	6

HG, control group (healthy rats); FAV-100, rats treated with favipiravir 100 mg/kg; FAV-400, rats treated with favipiravir 400 mg/kg; *n*, number of rats in each group.

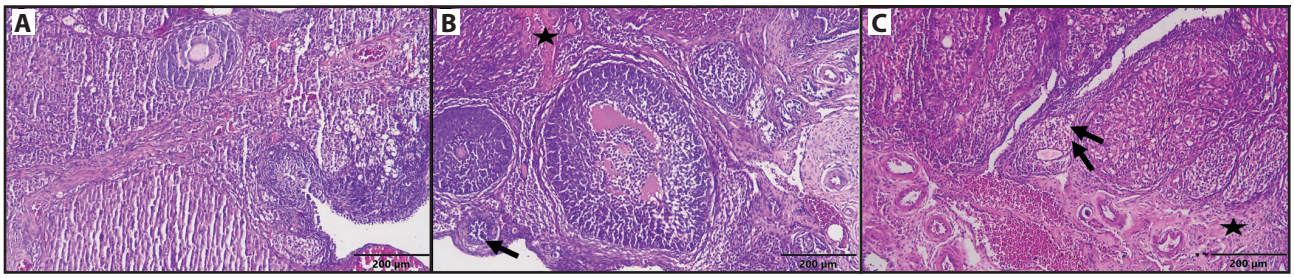

Figure 3. Histopathological evaluation of ovarian tissues in experimental groups. **A.** HG group. Normal histological appearance of ovarian tissue. H&E, 200×. **B.** FAV-100 group. A low degree of deterioration in follicular cell integrity (arrow) and fibrosis in the cortex (star) were observed. H&E, 200×. **C.** FAV-400 group. Severe disruption in follicular cell integrity (arrow), increase in connective tissue in the cortex (fibrosis) (star), moderate degeneration (dashed arrow) and low degree necrosis (arrowhead) in follicular cells were observed. H&E, 200×. For abbreviations, see Fig. 1.

MDA, which occurs as a result of LPO, is also toxic and can cause further destruction (Ayala et al. 2014). Our test results show that high dose of favipiravir can cause severe oxidative damage. In a study supporting our biochemical findings, it was reported that the adverse effects of favipiravir are mild at low doses and severe at high doses (Pilkington et al. 2020). TOS levels were measured to determine whether favipiravir increased other oxidant parameters other than MDA in ovarian tissue. TOS is a parameter that reflects the total state of all oxidants in tissues (Erel 2005).

The effect of favipiravir on antioxidant parameter levels in ovarian tissue was also evaluated by tGSH and TAS measurements. As it is known, in case that antioxidants are insufficient to neutralize oxidants, their levels decrease in parallel with the increase in oxidants (Clarkson and Thompson 2000). As seen in our study results, tGSH and TAS levels decreased in ovarian tissue with high MDA and TOS levels. GSH is a tripeptide endogenous antioxidant molecule. GSH detoxifies by reacting with ROS and protects cells from the toxic effects of ROS (Owen and Butterfield 2010). The decrease in tGSH and TAS levels in ovarian tissue with favipiravir indicates that the oxidant-antioxidant balance in the ovary tissue has changed in favour of oxidants. This condition is known as oxidative stress in the literature (Kisaoglu et al. 2013). In a previous study, whether damage occurred in the ovaries was evaluated by oxidant and antioxidant levels (Salman et al. 2011). Recent studies have shown that histopathological damage in the ovarian tissue is associated with oxidant-antioxidant levels (Ince et al. 2021). No information was found that favipiravir caused oxidative damage in tissues. However, when the other antiviral agents are examined in terms of tissue damage, it was shown that long-term use, especially in HIV-positive patients, resulted in an increase in plasma MDA levels and a decrease in GSH levels (Watanabe et al. 2016).

Our biochemical results obtained from the ovarian tissues of animals in this study are consistent with the histopathological findings. Histopathological examination of the ovarian tissue showed that favipiravir caused damage. Grade-3 disruption, cortex fibrosis, degeneration of follicular cells and grade-2 necrosis were observed in ovarian doses of the high-dose favipiravir group, which had high oxidant levels and low antioxidant levels. However, milder and less frequent histopathological findings were observed in the low-dose favipiravir group. There are studies showing that degeneration develops in follicles in ovarian tissue, whose oxidant levels are measured more dominantly (Kulhan et al. 2019). In another study supporting our biochemical and histopathological findings, cell necrosis in ovarian tissue was associated with oxidative stress (Demiryilmaz et al. 2013). These biochemical and histopathological findings obtained from the ovarian tissues of animals treated with favipiravir are also consistent with the reproductive test results. While the number of animals giving birth decreased in the low dose favipiravir group, it disappeared completely at the high dose. At the same time, a delay was observed in the maternity period of the animals having given birth. Unlubilgin et al. (2017) reported that serious histopathological damage such as secondary follicle degeneration and necrosis in animal

Table 2. Evaluation of histopathological damage severity of ovarian tissue

Group	FCDP	FCDG	FCN	CF	*n*
HG	0.00 ± 0.0	0.00 ± 0.0	0.00 ± 0.0	0.00 ± 0.0	6
FAV-100	1.83 ± 0.2	0.00 ± 0.0	0.00 ± 0.0	2.00 ± 0.3	6
FAV-400	3.00 ± 0.0	2.00 ± 0.0	1.83 ± 0.2	3.00 ± 0.0	6

One way ANOVA was used for statistical analysis. Then Fisher's *post-hoc* LSD test was made. The results were expressed as mean ± SEM. FCDP, follicular cell integrity disruption; FCDG, degeneration of follicular cells; FCN, follicular cell necrosis; CF, fibrosis in the cortex; *n*, number of rats in each group. For more abbreviations, see Table 1.

studies led to infertility. In the test studies of Aynaoglu Yildiz et al. (2021) it was stated that infertility was caused by oxidative ovarian damage. Ince et al. (2021) reported that oxidative stress causes infertility and delayed maternity period.

As a result, favipiravir caused more severe oxidative damage to the ovarian tissue of animals at high doses. Infertility was developed in a proportion of animals administered low-dose favipiravir. In other animals that did not develop infertility, the maternity period was delayed. Infertility was observed in all animals treated with high-dose favipiravir. Our study was the first to reveal the negative effect of favipiravir on ovarian tissue and reproductive function. However, it cannot be said that animal studies will have the same effect on humans. More detailed and comprehensive studies are needed on this subject. Clinical studies for favipiravir should be completed and the appropriate dose for humans to keep minimum side effects to should be determined. The possible side-effect profile of this drug should be clearly revealed and should be shared with patients before treatment. Favipiravir should be used with caution, especially in women of reproductive age, and the benefit/harm calculation should be made.

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

References

Aguilar A, Alvarez-Vijande R, Capdevila S, Alcoberro J, Alcaraz A (2007): Antioxidant patterns (superoxide dismutase, glutathione reductase, and glutathione peroxidase) in kidneys from non-heart-beating-donors: experimental study. Transplant. Proc. **39,** 249-252 https://doi.org/10.1016/j.transproceed.2006.10.212

Angelova PR, Esteras N, Abramov AY (2021): Mitochondria and lipid peroxidation in the mechanism of neurodegeneration: Finding ways for prevention. Med. Res. Rev. **41,** 770-784 https://doi.org/10.1002/med.21712

Ayala A, Muñoz MF, Argüelles S (2014): Lipid peroxidation: production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal. Oxid. Med. Cell Longev. **2014,** 360438 https://doi.org/10.1155/2014/360438

Aynaoglu Yildiz G, Yildiz D, Yapca OE, Suleyman B, Arslan YK, Kurt N, Suleyman H (2021): Effect of diazepam, sertraline and melatonin on the stress-induced reproductive disorders and intrauterine growth restriction in female rats. J. Matern. Fetal Neonatal. Med. **34,** 4103-4109 https://doi.org/10.1080/14767058.2019.1706469

Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, et al. (2020): Remdesivir for the treatment of Covid-19 - final report. N. Engl. J. Med. **383,** 1813-1826 https://doi.org/10.1056/NEJMoa2007764

Chen C, Zhang Y, Huang J, Yin P, Cheng Z, Wu J, Chen S, Zhang Y, Chen B, Lu M (2020): Favipiravir versus arbidol for COVID-19: a randomized clinical trial. MedRxiv. https://doi.org/10.1101/2020.03.17.20037432

Clarkson PM, Thompson HS (2000): Antioxidants: what role do they play in physical activity and health? Am. J. Clin. Nutr. **72,** 637S-646S https://doi.org/10.1093/ajcn/72.2.637S

Demiryilmaz I, Sener E, Cetin N, Altuner D, Akcay F, Suleyman H (2013): A comparative investigation of biochemical and histopathological effects of thiamine and thiamine pyrophosphate on ischemia-reperfusion induced oxidative damage in rat ovarian tissue. Arch. Pharm. Res. **36,** 1133-1139 https://doi.org/10.1007/s12272-013-0173-8

Doğan E, Çeviker S, Vurucu S, Şener A, Yüksel B, Gönlügür U, Şimşek T, Ulusoy M (2021): Investigation of the frequency of adverse effects in patients treated with favipiravir as SARS-CoV-2 treatment. Klimik Dergisi **34,** 95-98 https://doi.org/10.36519/kd.2021.3563

Duryee MJ, Clemens DL, Opperman PJ, Thiele GM, Duryee LM, Garvin RP, Anderson DR (2021): Malondialdehyde-acetaldehyde modified (MAA) proteins differentially effect the inflammatory response in macrophage, endothelial cells and animal models of cardiovascular disease. Int. J. Mol. Sci. **22,** 12948 https://doi.org/10.3390/ijms222312948

Erel O (2004): A novel automated method to measure total antioxidant response against potent free radical reactions. Clin. Biochem. **37,** 112-119 https://doi.org/10.1016/j.clinbiochem.2003.10.014

Erel O (2005): A new automated colorimetric method for measuring total oxidant status. Clin. Biochem. **38,** 1103-1111 https://doi.org/10.1016/j.clinbiochem.2005.08.008

Furuta Y, Gowen BB, Takahashi K, Shiraki K, Smee DF, Barnard DL (2013): Favipiravir (T-705), a novel viral RNA polymerase inhibitor. Antiviral. Res. **100,** 446-454 https://doi.org/10.1016/j.antiviral.2013.09.015

Furuta Y, Takahashi K, Kuno-Maekawa M, Sangawa H, Uehara S, Kozaki K, Nomura N, Egawa H, Shiraki K (2005): Mechanism of action of T-705 against influenza virus. Antimicrob. Agents Chemother. **49,** 981-986 https://doi.org/10.1128/AAC.49.3.981-986.2005

Hayden FG, Shindo N (2019): Influenza virus polymerase inhibitors in clinical development. Curr. Opin. Infect. Dis. **32,** 176-186 https://doi.org/10.1097/QCO.0000000000000532

Ince S, Ozer M, Kadioglu BG, Kuzucu M, Ozkaraca M, Gezer A, Suleyman H, Cetin N (2021): The effect of taxifolin on oxidative ovarian damage and reproductive dysfunctions induced by antipsychotic drugs in female rats. J. Obstet. Gynaecol. Res. **47,** 2140-2148 https://doi.org/10.1111/jog.14769

Iraz M, Ozerol E, Gulec M, Tasdemir S, Idiz N, Fadillioglu E, Naziroglu M, Akyol O (2006): Protective effect of caffeic acid phenethyl ester (CAPE) administration on cisplatin-induced oxidative damage to liver in rat. Cell Biochem. Funct. **24,** 357-361 https://doi.org/10.1002/cbf.1232

Karaçor T, Dogan Z, Elibol E, Bulbul M, Nacar MC (2020): Effects of iloprost on experimental ischemia and reperfusion injury in rat ovary. Biotech. Histochem. **95,** 373-380 https://doi.org/10.1080/10520295.2019.1703219

Kaur RJ, Charan J, Dutta S, Sharma P, Bhardwaj P, Sharma P, Lugova H, Krishnapillai A, Islam S, Haque M, et al. (2020): Favipiravir use in COVID-19: Analysis of suspected adverse drug events reported in the WHO database. Infect. Drug Resist. **13,** 4427-4438 https://doi.org/10.2147/IDR.S287934

Kisaoglu A, Borekci B, Yapca OE, Bilen H, Suleyman H (2013): Tissue damage and oxidant/antioxidant balance. Eurasian J. Med. **45,** 47-49 https://doi.org/10.5152/eajm.2013.08

Kulhan NG, Kulhan M, Turkler C, Ata N, Kiremitli T, Kiremitli S, Keskin Cimen F, Suleyman H, Toprak V (2019): Effect of lycopene on oxidative ovary-damage induced by cisplatin in rats. Gen. Physiol. Biophys. **38,** 253-258 https://doi.org/10.4149/gpb_2019006

Łagocka R, Dziedziejko V, Kłos P, Pawlik A (2021): Favipiravir in therapy of viral infections. J. Clin. Med. **10,** 273 https://doi.org/10.3390/jcm10020273

McCreary EK, Pogue JM (2020): Coronavirus disease 2019 treatment: A review of early and emerging options. Open Forum Infect. Dis. **7,** ofaa105 https://doi.org/10.1093/ofid/ofaa105

Mittal M, Siddiqui MR, Tran K, Reddy SP, Malik AB (2014): Reactive oxygen species in inflammation and tissue injury. Antioxid. Redox Signal. **20,** 1126-1167 https://doi.org/10.1089/ars.2012.5149

Owen JB, Butterfield DA (2010): Measurement of oxidized/reduced glutathione ratio. Methods Mol. Biol. **648,** 269-277 https://doi.org/10.1007/978-1-60761-756-3_18

Ozcicek A, Halis S (2020): Molecular mechanism of ischemia reperfusion injury. Arch. Basic Clin. Res. **2,** 25-27 https://doi.org/10.5152/ABCR.2019.31

Pilkington V, Pepperrell T, Hill A (2020): A review of the safety of favipiravir - a potential treatment in the COVID-19 pandemic? J. Virus Erad. **6,** 45-51 https://doi.org/10.1016/S2055-6640(20)30016-9

Salman S, Kumbasar S, Yilmaz M, Kumtepe Y, Borekci B, Bakan E, Suleyman H (2011): Investigation of the effects of the chronic administration of some antihypertensive drugs on enzymatic and non-enzymatic oxidant/antioxidant parameters in rat ovarian tissue. Gynecol. Endocrinol. **27,** 895-899 https://doi.org/10.3109/09513590.2010.551564

Unlubilgin E, Suleyman B, Balci G, Atakan Al R, Cankaya M, Arslan Nayki U, Suleyman H (2017): Prevention of infertility induced by ovarian ischemia reperfusion injury by benidipine in rats: Biochemical, gene expression, histopathological and immunohistochemical evaluation. J. Gynecol. Obstet. Hum. Reprod. **46,** 267-273 https://doi.org/10.1016/j.jogoh.2016.12.001

Watanabe LM, Barbosa Júnior F, Jordão AA, Navarro AM (2016): Influence of HIV infection and protection. Nutrition **32,** 1238-1242 https://doi.org/10.1016/j.nut.2016.03.024

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