Acta Scientific Gastrointestinal Disorders (ISSN: 2582-1091)

Volume 8 Issue 7 July 2025

Research Article

Investigation of the Effects of Favipiravir Exposure on Kidney and Liver During the Embryonic Period: Genetic Analysis Study

Evrim Suna Arikan Söylemez[1]*, Zafer Söylemez[1], Abdülkadir Bilir[2], Emre Atay[2], İbrahim Halil Kenger[3] and Tolga Ertekin[2]

[1]*Department of Medical Biology, Faculty of Medicine, Afyonkarahisar Health Sciences University, Turkey*

[2]*Department of Anatomy, Faculty of Medicine, Afyonkarahisar Health Sciences University, Afyonkarahisar, Turkey*

[3]*Department of Medical Genetics, Faculty of Medicine, Gaziantep Islam Science and Technology University, Gaziantep, Turkey*

***Corresponding Author:** Evrim Suna Arikan Söylemez, Department of Medical Biology, Faculty of Medicine, Afyonkarahisar Health Sciences University, Turkey.

Received: October 25, 2024

Published: June 05, 2025

Abstract

Favipiravir (T-705) is a small molecule obtained through chemical modification of a pyrazine analogue originally developed in Japan against influenza virus. It is a potent inhibitor of influenza viral RNA polymerase and is effective against all subtypes and strains of influenza viruses. However, there is a risk of teratogenicity and embryotoxicity of favipiravir and therefore its use is approved under limited conditions. Therefore, the aim of this study was to determine the effects of favipiravir on kidney and liver during embryonic development based on genetic analyses. The mRNA levels of TLR4, NFKB1, TRPM2, IL-6, IL-1β and TNFα genes expressed in rat fetal kidney and liver tissues exposed to favipiravir at different doses were determined by Real-Time PCR method using Rotor-Gene Q. There were obvious changes in inflammatory processes and tissue damage in the liver and kidney tissues of the foetuses of pregnant rats treated with favipiravir compared to the control. We suggest that favipiravir may adversely affect the processes in the embryonic period, since there are significant changes in the expression levels of the related genes compared to the control, and different expression levels are observed in the kidney and liver tissues due to the nature of the tissue.

Keywords: Embryonel Development; Favipiravir; Gene Expression

Introduction

The rapid global spread of COVID-19 and the surge in patient numbers created an urgent need for effective antiviral drugs. However, as the disease was novel, no clinically approved antiviral therapies or vaccines were initially available. Consequently, various treatments, including ribavirin, remdesivir, hydroxychloroquine, ivermectin, favipiravir, monoclonal antibodies, antisense RNA, corticosteroids, and convalescent plasma have been tried in the treatment of COVID-19 [1-6]. Also Hanna., *et al.* [7] suggested that that favipiravir is a more effective treatment for COVID-19 infection in patients who have early stage disease, compared to current standard of care.

Favipiravir (T-705), a chemically modified pyrazine analog, was originally developed and approved for influenza treatment in Japan [8,9]. It acts as a selective and potent inhibitor of influenza viral RNA polymerase and is effective against all subtypes and strains of influenza, including those resistant to neuraminidase and M2 inhibitors. Favipiravir has also demonstrated antiviral activity against other RNA viruses, making it a promising drug for treating various RNA virus infections [10].

There is a known risk of teratogenicity and embryotoxicity associated with favipiravir, which led the Japanese Ministry of Health,

Labor, and Welfare to grant its conditional approval under strict regulations [8]. Favipiravir is currently used for COVID-19 treatment in Turkey and is recommended for severe pediatric cases, although there is limited evidence-based data on its use during pregnancy [11]. Available data mainly stem from unplanned pregnancies, highlighting concerns about its embryotoxic and teratogenic potential [7, 8, 12-14]. Due to these contradictions, more research is needed to understand the potential side effects and contraindications of favipiravir in pregnancy [4].

Transient receptor potential melastatin 2 (TRPM2) is a calcium (Ca2+) permeable, non-selective cation channel belonging to the TRP ion channel family. Oxidative stress-induced TRPM2 activation causes abnormal intracellular Ca2+ accumulation and cell death in various cell types [6]. Toll-like receptors (TLRs) belong to the pattern recognition receptor (PRR) family, an important component of the innate immune system. TLRs detect invading pathogens and initiate an immediate immune response against them, followed by a prolonged adaptive immune response. Activation of TLRs leads to the synthesis of pro-inflammatory cytokines and chemokines and the expression of co-stimulatory molecules [17]. Nuclear factor-κB (*NF-κB*), first identified in 1986, acts as an essential transcription factor associated with cell survival, cell growth, cell replication and cell apoptosis [18-20]. The importance of Nfkb1 function can be observed in mouse models where Nfkb1(-/-) mice show increased inflammation and susceptibility to certain types of DNA damage, leading to cancer and exhibiting a rapid ageing phenotype [21,22]. Cytokines play an important role in the development and differentiation of T cells, B cells and haematopoietic cells and in the stimulation or suppression of inflammation. While some cytokines have regional effects, systemic effects of some cytokines are more prominent. TNF is a pleiotropic cytokine with important functions in homeostasis and disease pathogenesis. The TNF receptor signalling model has been extended to include linear ubiquitination and the formation of different signalling complexes linked to different functional outcomes such as inflammation, apoptosis and necroptosis. The identification of different homeostatic or pathogenic TNF-induced signalling pathways has led to the concept of selectively inhibiting the deleterious effects of TNF while preserving its homeostatic bioactivities for therapeutic purposes [23]. The IL-1 family of cytokines includes seven molecules with agonist functions, including IL-1B and IL-1A, three receptor antagonists and one anti-inflammatory cytokine. IL-1 cytokines bind to IL-1R receptors. There are eleven IL-1R receptors. IL-1B and IL-1A are encoded by different genes and bind to both IL-1R1 and IL-1R2, which are present in almost every cell. IL-1B plays its main role as the 'gatekeeper' of inflammation. IL-1B is mainly produced by blood monocytes, tissue macrophages, skin dendritic cells and brain microglia [24].

This study aimed to reveal the effects of favipiravir on the expressions of *TLR4-4, NFKB1, TRPM2, IL-6, IL-1β* and *TNFα* genes in kidney and liver during embryonic development.

Material and Methods

Ethics committee approval and study groups

Within the scope of the study, kidney and liver tissues of the fetuses obtained from the study titled "Investigation of developmental toxicity of favipiravir on fetal bone and embryonic development" [25]. Our study ethically approved in the Afyon Kocatepe University Experimental Animals Application and Research Centre as numbered 2022/155. Related tissues were obtained from the following groups (Table 1). At the end of the experimental protocol, the kidney and liver tissues of the sacrificed pups belonging to the groups were stored in -80°C.

Table 1: Chemical/biological substances and pharmacological agents used in the experiment

Agent	Dose	Way of administration	Volume	Frequency of administration	Exposure time
Group A: Favipiravir	50 mg/kg x 5 days	Oral gavaj	1 ml	2 times	10-14. days
Group B: Favipiravir	50 mg/kg x 1 day + 20 mg/kg x 4 days	Oral gavaj	1 ml	2 times	10-14. days
Group C: Favipiravir	20 mg/kg x 5 gün	Oral gavaj	1 ml	2 times	10-14. days
Control	Serum phsiologic x 5 days	Oral gavaj	1 ml	2 times	10-14. days

RNA extractions and Real time PCR analysis

Total RNA was isolated from liver and kidney tissues using PureZOL RNA isolation kit (Biorad, USA, Cat. No: 732-6890). The obtained RNAs were measured by NanoDrop ND-1000 Spectrophotometer and the microgram values in microlitre were determined. cDNA was obtained from total RNA using iScript Reverse Trancription Supermix cDNA synthesis kit (Biorad, USA, Cat. No: 1708841). The mRNA levels of *TLR4, NFKB1, TRPM2, IL-6, IL-1β* and *TNFα* genes expressed in fetal liver and kidney tissues of A, B, C and control groups were determined by Real-Time PCR using Rotor-Gene-Q (Qiagen, Hilden, Germany). Amplifications were performed in 20 µL total reaction volume using cDNA, site-specific primers (Oligomer, Ankara) (Table 2), Sso Advanced Universal SYBR Green Supermix (Biorad, USA, Cat. No: 1725272) and nuclease free water. For the analyses of each gene, Real-Time PCR reaction mixtures were prepared and distributed into 0.1 ml PCR tubes, the relevant cDNAs were added. Real time PCR reactions were performed using the amplification programmes specified in Tables 3 and 4. As a result of the reactions, treshold Cycle (Ct) values showing the mRNA levels of *TLR4, NFKB1, TRPM2, IL-6, IL-1β* and *TNFα* genes were determined. Primer sequences were designed as mentioned in Iwashita., *et al*. [26] for TNF-α, IL-1β, and IL-6, Le Mandat Schultz., *et al*. [27] for *TLR4*, Kermanian., *et al*. [28] for Nf-κB, Cook., *et al*. [29] for *TRPM2*. Gene expression levels of each tissues were normalised according to *GAPDH* gene expression levels. Each analysis was performed as both intraassay and inter assay with 3 replicates.

Gene	Base sequences 5→3’
Rat-TLR4 F	AATCCCTGCATAGAGGTACTTCCTAAT
Rat -TLR4 R	CTCAGATCTAGGTTCTTGGTTGAATAAG
Rat- NFKB1 F	GCAAACCTGGGAATACTTCATGTGACTAAG
Rat-NFKB1 R	ATAGGCAAGGTCAGAATGCACCAGAAGTCC
Rat-TNF-α F	AAATGGGCTCCCTCTCATCAGTTC
Rat-TNF-α R	TCTGCTTGGTGGTTTGCTACGAC
Rat-IL-1β F	CACCTCTCAAGCAGAGCACAG
Rat-IL-1β R	GGGTTCCATGGTGAAGTCAAC
Rat-IL-6 F	TCCTACCCCAACTTCCAATGCTC
Rat-IL-6 R	TTGGATGGTCTTGGTCCTTAGCC
TRPM2-F	GAAGGAAAGAGGGGGTGTG
TRPM2-R	CATTGGTGATGGCGTTGTAG
Rat-GAPDH F	GAGGACCAGGTTGTCTCCTG
Rat-GAPDH R	GGATGGAATTGTGAGGGAGA

Table 2: Base sequences of target and reference genes.

	Stage	Time	Temperature
	Enzyme Activation/Denaturation	3 m	98°C
40 cycle	Denaturation	15 s	98°C
	Annealing/Extension (Data Collection)	30 s	58°C
	+Melt Curve Analysis	65-95°C, 0.5°C/5 s	

Table 3: *TLR4-4, NFKB1, TRPM2* and *GAPDH* amplification protocol.

Statistical analysis

In order to calculate the relative fold changes between the treatments and the control groups, the amplification efficiency value and average Ct values of each gene were entered into the REST 2009 software programme PfaffI., *et al*. [30].

Results

mRNA analyses of TLR4, NFKB1, TRPM2, IL-6, IL-1β and TNFα genes

Changes in mRNA levels of *TLR4, NFKB1, TRPM2, IL-6, IL-1β* and *TNFα* genes expressed in fetal liver and kidney tissues of A, B, C and control groups were determined compared to the related control groups.

When relative gene expression was evaluated according to each treatment; *TLR*4 gene expression decreased in fetal liver in groups A, B and C compared to control (0.71; 0.47; 0.96, respectively; P > 0.05). *NFKB1* gene expressions were significantly decreased in groups A, B and C compared to the control (0.33; 0.38; 0.35, respectively; P < 0.001). *TRPM2* gene expressions decreased in A, B and C groups compared to control (0.26; 0.002*; 0.31, respectively; *P < 0.001). *IL-6* gene expressions increased in groups A and B (1.44; 1.11, respectively; P > 0.05) and decreased in group C (0.89; P > 0.05). *IL-1β* gene expression was significantly increased in group A (23.43; P < 0.001) and decreased in groups B and C (0.76; 0.67; respectively; P > 0.05). *TNFα* gene expressions decreased in groups A, B and C compared to the control (0.33; 0.01*; 0.19*, respectively; *P < 0.001) (Figure 1).

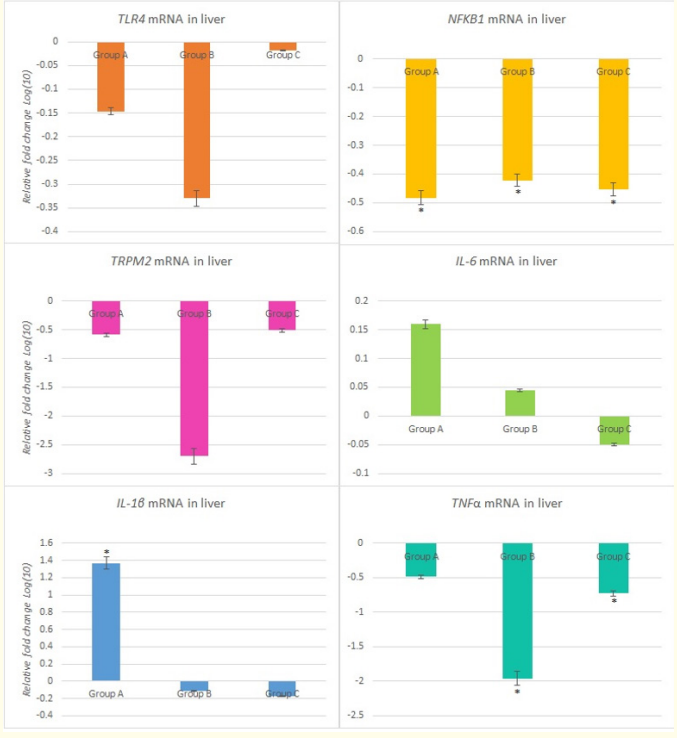

Figure 1: Changes in TLR4, NFKB1, TRPM2, IL-6, IL-1β and TNFα gene expression in fetal liver tissues in treatments compared to control (Group A: 50 mg/kg x 5 days, Group B: 50 mg/kg x 1 day + 20 mg/kg x 4 days, Group C: 20 mg/kg x 5 days, Control: Physiological serum x 5 days). GAPDH was used as the reference gene. * P < 0.001.

In fetal kidney, TLR4 gene expression increased in groups A, B and C compared to control (11.04*; 2.83*; 1.08; respectively, *P < 0.001). The increase in group C was similar to the control. *NFKB1* gene expression increased in groups A and B compared to control (1.295; 1.422, respectively, P > 0.05) and decreased in group C (0.446; P > 0.05). *TRPM2* gene expression increased in groups A and B compared to control (13.88; 2.58, respectively; P > 0.05). The mRNA level was undetectable in group C. *IL-6* gene expressions decreased in groups A, B and C compared to control (0.22; 0.03*; 0.79; respectively, *P < 0.05). *IL-1β* gene expression was undetectable in group A, but decreased in groups B and C (0.006; 0.24; respectively, P > 0.05). *TNFα* gene expression was undetectable in group A, but decreased in groups B and C compared to control (0.002; 0.01; *P < 0.002) (Figure 2).

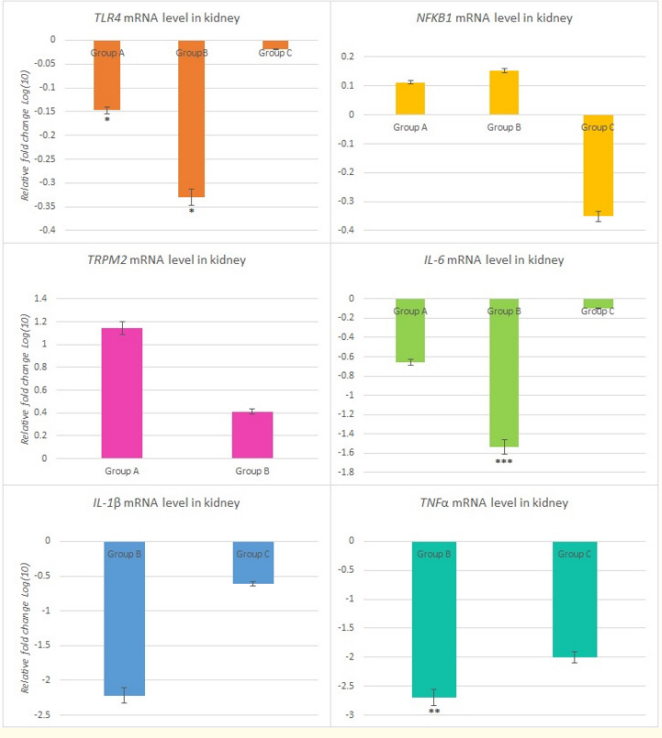

Figure 2: Changes in TLR4, NFKB1, TRPM2, IL-6, IL-1β and TNFα gene expression in fetal kidney tissues in treatments compared to control (Group A: 50 mg/kg x 5 days, Group B: 50 mg/kg x 1 day + 20 mg/kg x 4 days, Group C: 20 mg/kg x 5 days, Control: Physiological serum x 5 days). GAPDH was used as the reference gene. * P < 0.001, ** P < 0.002, *** P < 0.05.

Discussion and Conclusion

Favipiravir is an antiviral drug that, once ribosylated and phosphorylated intracellularly, acts as a purine nucleoside analogue that functions as a competitive substrate inhibitor of viral RNA-dependent RNA polymerase [13,14]. The major route of elimination is the kidney, and inactive metabolites produced by aldehyde oxidase and xanthine oxidase are excreted in the urine. Side effects have been reported to have a safer profile than most antiviral agents [11]. However, its use is contraindicated in patients with severe hepatic and renal failure, hypersensitivity and hyperuricaemia. In addition, it has been stated that it should be classified as contraindicated in pregnant women and women suspected to be pregnant due to the observation of teratogenic potential in animal studies [8,9,13,14,31].

In the study of Tırmıkcıoglu., *et al*. [12] 29 pregnant women with favipiravir exposure were evaluated. It was reported that stillbirth and spontaneous abortion were not observed. However, the presence of patent foramen ovale was detected in one child. As a result of these results, they reported that favipiravir is unlikely to be an important human teratogen, but the experience for a robust risk assessment is still limited [12]. In addition, it was also reported that high doses of favipiravir caused abnormalities in muscle structure and death during long-term administration of favipiravir in young animals [2]. According to the results of other studies available in the literature, pregnant women were excluded from clinical trials and most pregnant women diagnosed with COVID-19 terminated their pregnancies due to possible malformations or preferred to give birth prematurely [4,8].

There are not many studies that can be evaluated regarding the expression levels of *TLR4, NFKB1, TRPM2, IL-6, IL-1β* and *TNFα* genes that we analyzed depending on favipiravir administration. When we evaluated with the available information.

Kara., *et al*. reported that NF-κB-p65 and IL-6 immune reactivity increased with favipiravir administration in liver and kidney tissues [32]. It was revealed that oxidative stress (NF-κB-p65) and inflammation (IL-6) increased in rat liver and kidney tissues with favipiravir administration [33]. In our study, *IL-6* expression decreased in kidney tissues at all administration doses, whereas it increased in liver tissues at high doses. Although decreased *IL-6* levels in the kidneys are generally associated with decreased inflammation, in patients with advanced renal failure, decreased overall function of the kidney tissue may also decrease the *IL-6* production capacity and this may mean suppression of the overall inflammatory response. In our study, it is possible that the *IL-6* level was low due to the damage that high dose may have caused in the kidney during the embryonic period. Interleukin 1 beta (IL-1β)

is a potent proinflammatory cytokine and an important regulator of various inflammatory processes and immune responses. The cytokine interleukin-1β (IL-1β) is a key mediator of the inflammatory response. It is essential for host response and resistance against pathogens, but also exacerbates damage during chronic disease and acute tissue damage [34]. High levels of *IL-1β* in the liver generally indicate increased inflammation and immune response. High *IL-1β* levels increase inflammation in liver tissue and may cause cellular damage. In our study, while *IL-1β* levels were low in kidney tissues, there was a significant increase in the liver after high dose favipravir administration.

Low levels of *TNFα* in the liver and kidneys usually indicate low inflammation or suppression of the inflammatory response. This may be a sign of healthy organ functions or it may indicate that the treatment of inflammatory diseases is effective, but gene expressions may also be affected by tissue damage. In our study, *TNFα* gene expression levels were found to be low in both tissues. *NF-κB* plays a critical role in the regulation of inflammatory responses [35]. Decreased *NF-κB* gene expression in the liver may indicate that inflammatory responses and cellular stress responses are suppressed or at a low level. *NF-κB* is associated with metabolic stress and inflammation [36]. Low *NF-κB* activity may indicate that the liver is under low metabolic stress. In our study, *NF-κB* gene expression levels in the liver were significantly lower in all dose administrations. However, *NF-κB* gene expression levels in the kidney increased at high doses. Increased oxidative stress in kidney cells may trigger *NF-κB* activation. Oxidative stress may have increased inflammation by damaging kidney cells. *TLR4* plays an important role in the initiation of inflammatory responses after contact with pathogens [37]. The antiviral effect of favipiravir may reduce TLR4 gene expression by inhibiting the replication of viruses and reducing inflammatory responses. *TLR*4 has an important role in the initiation of inflammatory responses. The anti-inflammatory effect of favipiravir may reduce signalling through *TLR*4, which may result in decreased gene expression. In our study, *TLR4* gene expression levels were decreased in both liver and kidney tissues. Recent scientific investigations have revealed that TRPM2 channel plays a pivotal role in modulating autophagy by influencing the intracellular calcium levels and subsequent downstream signaling pathways [38,39]. Recent scientific investigations have revealed that reduced expression or activity of TRPM2 channel leads to impaired autophagic flux, resulting in accumulation of damaged cellular components and disruption of cellular balance [40]. In our study, *TRPM2* gene expression levels were increased in kidney but decreased in the liver. This may be due to impaired liver function and increased organ damage.

In conclusion, there are obvious changes in inflammatory processes and tissue damage in the liver and kidney tissues of the fetuses of pregnant rats administered favipiravir compared to the control. In addition to significant changes in the expression levels of the relevant genes compared to the control, we think that favipiravir may negatively affect the processes in the embryonic period due to the different expression levels observed in the kidney and liver tissues due to the nature of the tissue.

Bibliography

1. Gavriatopoulou Maria., *et al*. "Emerging treatment strategies for COVID-19 infection". *Clinical and Experimental Medicine* 21.2 (2021): 167-179.

2. Hayden Frederick G and Nahoko Shindo. "Influenza virus polymerase inhibitors in clinical development". *Current Opinion in Infectious Diseases* 32.2 (2019): 176-186.

3. Kaptein Suzanne J F., *et al*. "Favipiravir at high doses has potent antiviral activity in SARS-CoV-2-infected hamsters, whereas hydroxychloroquine lacks activity". *Proceedings of the National Academy of Sciences of the United States of America* 117.43 (2020): 26955-26965.

4. Louchet Margaux., *et al*. "Placental transfer and safety in pregnancy of medications under investigation to treat coronavirus disease 2019". *American Journal of Obstetrics and Gynecology MFM* 2.3 (2020): 100159.

5. Okumuş Nurullah., *et al*. "Evaluation of the effectiveness and safety of adding ivermectin to treatment in severe COVID-19 patients". *BMC infectious diseases* 21.1 (2021): 411.

6. Zhao Hong., *et al*. "Favipiravir in the treatment of patients with SARS-CoV-2 RNA recurrent positive after discharge: A multicenter, open-label, randomized trial". *International Immunopharmacology* 97 (2021): 107702.

7. Hanna Catherine R., *et al*. "Glasgow Early Treatment Arm Favirpiravir (GETAFIX) for adults with early stage COVID-19: A structured summary of a study protocol for a randomised controlled trial". *Trials* 21.1 (2021): 935.

8. Delang Leen., *et al*. "Favipiravir as a potential countermeasure against neglected and emerging RNA viruses". *Antiviral Research* 153 (2018): 85-94.

9. Sissoko Daouda., *et al*. "Experimental Treatment with Favipiravir for Ebola Virus Disease (the JIKI Trial): A Historically Controlled, Single-Arm Proof-of-Concept Trial in Guinea". *PLoS Medicine* 13.3 (2016): e1001967.

10. Furuta Yousuke., *et al*. "Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase". *Proceedings of the Japan Academy. Series B, Physical and Biological Sciences* 93.7 (2017): 449-463.

11. Ozsurekci Yasemin., *et al*. "Favipiravir use in children with COVID-19 and acute kidney injury: is it safe?". *Pediatric nephrology (Berlin, Germany)* 36.11 (2021): 3771-3776.

12. Tırmıkçıoğlu Zeynep. "Favipiravir exposure and pregnancy outcome of COVID-19 patients". *European Journal of Obstetrics, Gynecology, and Reproductive Biology* 268 (2022): 110-115.

13. Joshi Shashank., *et al*. "Role of favipiravir in the treatment of COVID-19". *International Journal of Infectious Diseases: IJID* 102 (2021): 501-508.

14. Li Chang., *et al*. "Antiviral mechanisms of candidate chemical medicines and traditional Chinese medicines for SARS-CoV-2 infection". *Virus Research* 286 (2020): 198073.

15. Pilkington Victoria., *et al*. "A review of the safety of favipiravir - a potential treatment in the COVID-19 pandemic?". *Journal of Virus Eradication* 6.2 (2020): 45-51.

16. Belrose Jillian Corinne and Michael Frederick Jackson. "*TRPM2*: a candidate therapeutic target for treating neurological diseases". *Acta pharmacologica Sinica* 39.5 (2018): 722-732.

17. Vaure Céline and Yuanqing Liu. "A comparative review of toll-like receptor 4 expression and functionality in different animal species". *Frontiers in Immunology* 5 (2014): 316.

18. Lin Shu-Chun., *et al*. "Areca (betel) nut extract activates mitogen-activated protein kinases and NF-kappaB in oral keratinocytes". *International Journal of Cancer* 116.4 (2005): 526-535.

19. Hayden Matthew S and Sankar Ghosh. "Shared principles in NF-kappaB signaling". *Cell* 132,3 (2008): 344-362.

20. Naugler Willscott E and Michael Karin. "NF-kappaB and cancer-identifying targets and mechanisms". *Current Opinion in Genetics and Development* 18.1 (2008): 19-26.

21. Mukhopadhyay T., *et al*. "Altered expression of the p50 subunit of the NF-kappa B transcription factor complex in non-small cell lung carcinoma". *Oncogene* 11.5 (1995): 999-1003.

22. Bargou RC., *et al*. "High-level nuclear NF-kappa B and Oct-2 is a common feature of cultured Hodgkin/Reed-Sternberg cells". *Blood* 87.10 (1996): 4340-4347.

23. Kalliolias, George D, and Lionel B Ivashkiv. "TNF biology, pathogenic mechanisms and emerging therapeutic strategies". *Nature Reviews Rheumatology* 12.1 (2016): 49-62.

24. Tulotta Claudia and Penelope Ottewell. "The role of IL-1B in breast cancer bone metastasis". *Endocrine-Related Cancer* 25,7 (2018): R421-R434.

25. Bilir Abdulkadir., *et al*. "Investigation of developmental toxicity of favipiravir on fetal bone and embryonic development". *Birth Defects Research* 114.17 (2022): 1092-1100.

26. Iwashita Yoshiaki., *et al*. "Thrombomodulin protects against lung damage created by high level of oxygen with large tidal volume mechanical ventilation in rats". *Journal of Intensive Care* 2.1 (2014): 57.

27. Le Mandat Schultz Aurelie., *et al*. "Expression of TLR-2, *TLR4*, NOD2 and pNF-kappaB in a neonatal rat model of necrotizing enterocolitis". *PloS one* 2.10 (2007): e1102.

28. Kermanian Fatemeh., *et al*. "Effects of adenosine A2a receptor agonist and antagonist on cerebellar nuclear factor-kB expression preceded by MDMA toxicity". *Medical Journal of the Islamic Republic of Iran* 28 (2014): 120.

29. Cook Naomi L., *et al*. "Reference genes for normalising gene expression data in collagenase-induced rat intracerebral haemorrhage". *BMC Molecular Biology* 11 (2010): 7.

30. Pfaffl Michael W., *et al*. "Relative expression software tool (REST) for group-wise comparison and statistical analysis of relative expression results in real-time PCR". *Nucleic Acids Research* 30.9 (2002): e36.

31. Favimol. "Favimol prescribing information". Istanbul: Neutec Ilaç San. Tic. A.S (2020).

32. Kara Adem., *et al*. "Evaluation of the toxicological effects of favipiravir (T-705) on liver and kidney in rats: biochemical and histopathological approach". *Drug and Chemical Toxicology* 46.3 (2023): 546-556.

33. Chen Fa., *et al*. "A functional haplotype of *NFKB1* influence susceptibility to oral cancer: a population-based and in vitro study". *Cancer Medicine* 7.5 (2018): 2211-2218.

34. Carrascal Livia., *et al*. "Role of Melatonin in the Inflammatory Process and its Therapeutic Potential". *Current Pharmaceutical Design* 24.14 (2018): 1563-1588.

35. Ma Yue., *et al*. "Reduction of NF-κB (p65) in Scrapie-Infected Cultured Cells and in the Brains of Scrapie-Infected Rodents". *ACS Chemical Neuroscience* 8.11 (2017): 2535-2548.

36. de Lima Enzo Pereira., *et al*. "Glycolipid Metabolic Disorders, Metainflammation, Oxidative Stress, and Cardiovascular Diseases: Unraveling Pathways". *Biology* 13.7 (2024): 519.

37. Kawasaki Takumi and Taro Kawai. "Toll-like receptor signaling pathways". *Frontiers in Immunology* 5 (2014): 461.

38. Jang Yongwoo., *et al*. "Trpm2 Ablation Accelerates Protein Aggregation by Impaired ADPR and Autophagic Clearance in the Brain". *Molecular Neurobiology* 56.5 (2019): 3819-3832.

39. Jiang Quan., *et al*. "Nitration of *TRPM2* as a Molecular Switch Induces Autophagy During Brain Pericyte Injury". *Antioxidants and Redox Signaling* 27.16 (2017): 1297-1316.