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REVIEW ARTICLE

SARS-CoV-2 Infection and Transmission Inhibitor

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Abstract:

As of December 2019, there has been an outbreak of severe respiratory syndrome coronavirus-2 (SARS-CoV-2) in China. Around 16% of patients developed acute respiratory distress syndrome, and 1%–2% died. There is no specific treatment reported. A pandemic related to Coronavirus is one of the most significant health crises in human history. In spite of a massive influx of cases, SARS-CoV-2 is still untreatable. Both old and novel virologic medicines were tested in order to develop a novel drug or vaccine. In advanced clinical trials in the US, favipiravir is currently approved for treating influenza infections in Japan, and it has been approved for treating SARS-CoV-2 or COVID-19 infections in Japan. Studies have shown that favipiravir can treat mild to moderate COVID-19 infections. The present review examines the role and use of favipiravir in the treatment of COVID-19. The purpose of this review is to provide evidence obtained from a variety of authentic sources. Current research is evaluating favipiravir for treating Coronavirus infections.

1. INTRODUCTION

COVID-19 consists of long polymers bounded by nucleocapsids, and it spreads through a variety of routes, including aerosolized transmission, fecal-oral transmission, droplets, and surface transmission. The disease affects multiple organs including the lungs, heart, and kidneys. There is a possibility of respiratory failure, pneumonia, or even death due to infections. It is common to suffer from acute lung and renal injuries and shock. The virus is detected by PCR testing from nasopharyngeal swabs. The virus and illness that Covid-19 causes are unknown, and there are no treatments available. There is no specific treatment available without symptomatic treatment [1].

The drug favipiravir is used to stop SARS-CoV-2 signs. A spike in research occurred after COVID-19 broke out to find a cure or medication. In order to combat COVID-19 (Coronavirus disease), triggered by the SARS-CoV-2 virus, a variety of drugs may be used, including favipiravir and others [2]. The drug favipiravir obstructs RNA-dependent RNA polymerase (RdRp) in RNA viruses in a broad-based and

potent manner. Since January 12, 2021, more than 88 million cases along with 1.9 million mortality cases have been reported worldwide [3]. Despite the difficulty of predicting the threshold [4], SARS-CoV-2 spread is unlikely to stop until at least 50% of the population is immune, either through vaccination or after recovering from a naturally acquired infection [5]. There are now some promising vaccine candidates approved by the FDA [6] in an emergency situation. It is, however, anticipated that global access to the necessary level will be delayed until the pandemic reaches the population impact level.

As shown in Table **1**, Coronavirus causes disease in humans and their cellular receptors.

The covid-19 pandemic has led to few effective treatments being developed to cope with this disease. Initially, favipiravir was applied to SARS-CoV-2 in Wuhan, where the epicenter of the pandemic was located. Italian authorities approved the prescription of the drug for emergency purposes after the pandemic spread to Europe. The drug is currently being marketed in Japan, Russia, Ukraine, Uzbekistan, Moldova, and Kazakhstan. Regions like Saudi Arabia and the United Arab Emirates have also delivered the respective approval to the said drug. Afterward, Turkey, Bangladesh, and most recently Egypt launched this agent for commercial use category. In the year

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2020 during the month of June approval of favipiravir was received for mild and moderate cases of COVID-19 infections in India from the DCGI. On Clinical Trials Gov, there were 32 studies registered as of the 23rd of July, 2020; three are complete, and 12 (twelve) are recruiting [7].

According to the Japanese Pharmaceuticals and Medical Devices Agency, favipiravir (AVIGAN®) was approved for the treatment of acute and re-emerging influenza virus infections in 2014 [8]. The majority of studies have reported its effectiveness against other RNA viruses, such as Ebola viruses [8, 9] or rhinoviruses and respiratory syncytial viruses [10]. The 50% effective concentration (EC50) of favipiravir against SARS-CoV-2 was reported to be 61.88 μM/L in Vero E6 cells *in vitro* studies. Therefore, favipiravir is highly effective at treating COVID-19 patients. Despite this, there is very limited research examining the safety as well as efficacy aspects of favipiravir in COVID-19 patients.

The viral inhibitory activity of favipiravir (T-705) was first identified during the study of chemical agents that can neutralize influenza viruses in the chemical library of Toyoma chemicals [11]. There were antiviral activities linked with the first compound, A/PR/8/34, which was later, named asT-1105, and it's their associated derivatives. The pyrazine moiety in the structure of T-1105(2) was chemically modified to yield the drug favipiravir.

Table 1. An overview of Coronaviruses, their hosts, their diseases, and their receptors.

Group	Virus	Host	Disease Caused	Cellular Receptor
I	229E	Human	An infection of the respiratory system	Human APN
	NL-63	Human	An infection of the respiratory system	ACE-2
II	OC43	Human	Enteric and respiratory infections	Neu-5,9-Ac-2-containing moiety
	HKU1	Human	Asthma	-
	SARS-C0V	Human	SARS (severe acute respiratory syndrome)	ACE-2

2. STRUCTURE
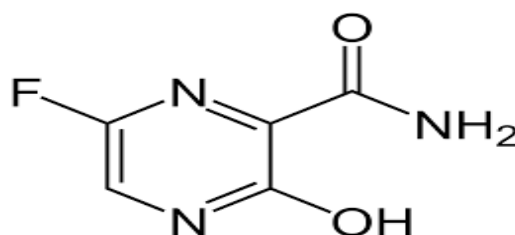
Chemical properties

1. - Name as assigned by IUPAC

-5-fluo-2-oxo-1-H-pyrazine-3-carboxamide

2. - Molecular formula

-C5H4FN3O2

3. - Synonyms

-6-fluoro-3-hydroxy-2-pyrazine carboxamide

-Avigan

-Favipiravir

-T-705-CPD

4. – Melting Point

-187°C to 193°C

5. - Solubility

-Slightly soluble in water

3. PHARMACOKINETICS AND PHARMACO-DYNAMICS

According to studies conducted on healthy Japanese volunteers, the maximum plasma concentration of favipiravir occurred 2 hours after oral administration, and then the concentration decreased rapidly with a half-life of 2 to 5.5 hours [12]. Favipiravir is administered as a prodrug. In addition to its excellent bioavailability (>94%), it is 52 percent protein bound and has a low volume of distribution (10–20 liters). It reaches C-max within 2 hours after a single dose. As a result of multiple doses, both T-max and half-life increase. Due to the short half-life (2.5-5 h) of favipiravir, its hydroxylated form is rapidly eliminated through the kidneys. In addition to aldehyde oxidase, xanthine oxidase plays a marginal role in the elimination process. The pharmacokinetics of favipiravir is dose-dependent and time-dependent. The compound is not metabolized by cytochrome P-450, but it inhibits one of its components (CYP2C8). The medication should be used with caution when combined with drugs that are converted by CYP2C8 [13, 14]. Fig. (**1**) illustrates Favipiravir's intracellular activation.

4. ASSESSMENT METHOD

Favipiravir has a novel mechanism of action in comparison to existing influenza antivirals that prevent the virus from entering and exiting cells [14]. As a result of its selective RNA inhibition properties, favipiravir-RTP inhibits RNA when activated. The polymerase prevents replication of the viral genome [15]. There is evidence that favipiravir-RTP interacts with RNA-dependent RNA polymerase (RdRp) under multiple hypotheses [16]. In spite of the fact that favipiravir was originally intended to treat influenza, the RdRp catalytic domain (favipiravir primary target) is expected to have similarities to other RNA viruses [9]. When the drug is administered into the body, it undergoes phosphoribosylation to become favipiravir-RTP. The following mechanisms are responsible for its antiviral effect:

A - This molecule serves as a substrate for RNA-dependent RNA polymerase (RdRp), which mistakes it for a purine nucleotide [7], thus inhibiting its activity.

B - The RNA strand is incorporated into the viral strand, preventing further expansion of the virus. Several RNA viruses retain the catalytic domain of the RdRp enzyme, allowing this drug to have a broad spectrum of activity.

According to recent findings, favipiravir causes lethal mutations during influenza virus infection *in vitro* [17]. Similar activity has not yet been demonstrated against SARS-CoV-2. Figs. (**1** and **2**) show Favipiravir's overall mechanism of action in its active and inactive forms, as well as how it interacts with the body's cell surface. In Fig. (**2**), we see a more detailed demonstration of how the drug interacts with living organisms.
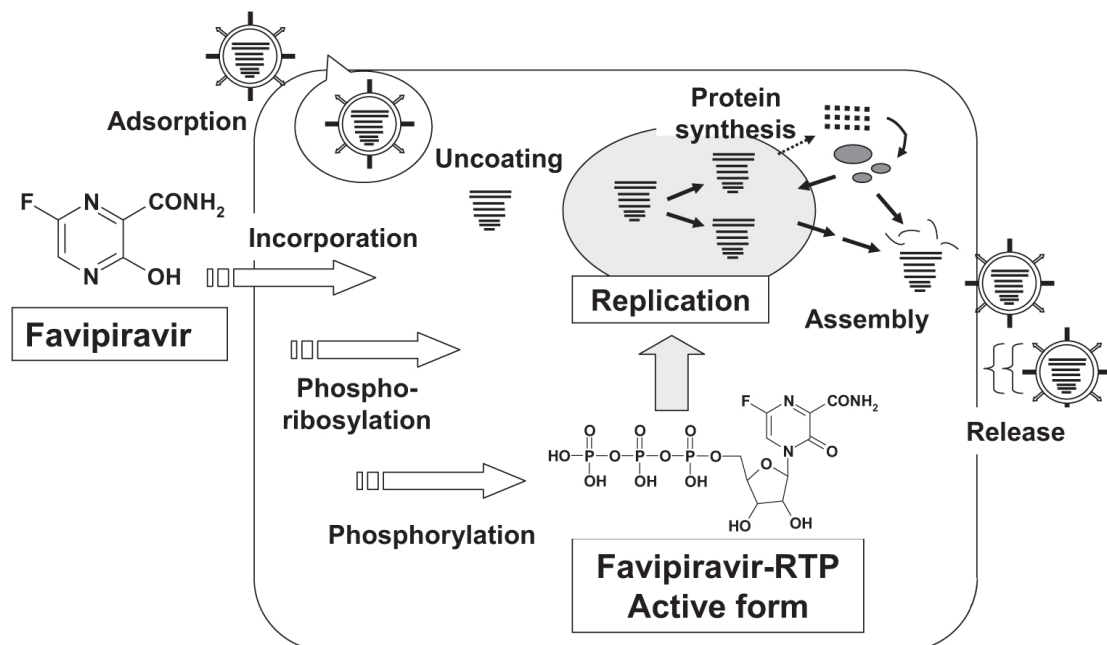

Fig. (1). Favipiravir's mechanism of action and intracellular activation are illustrated.
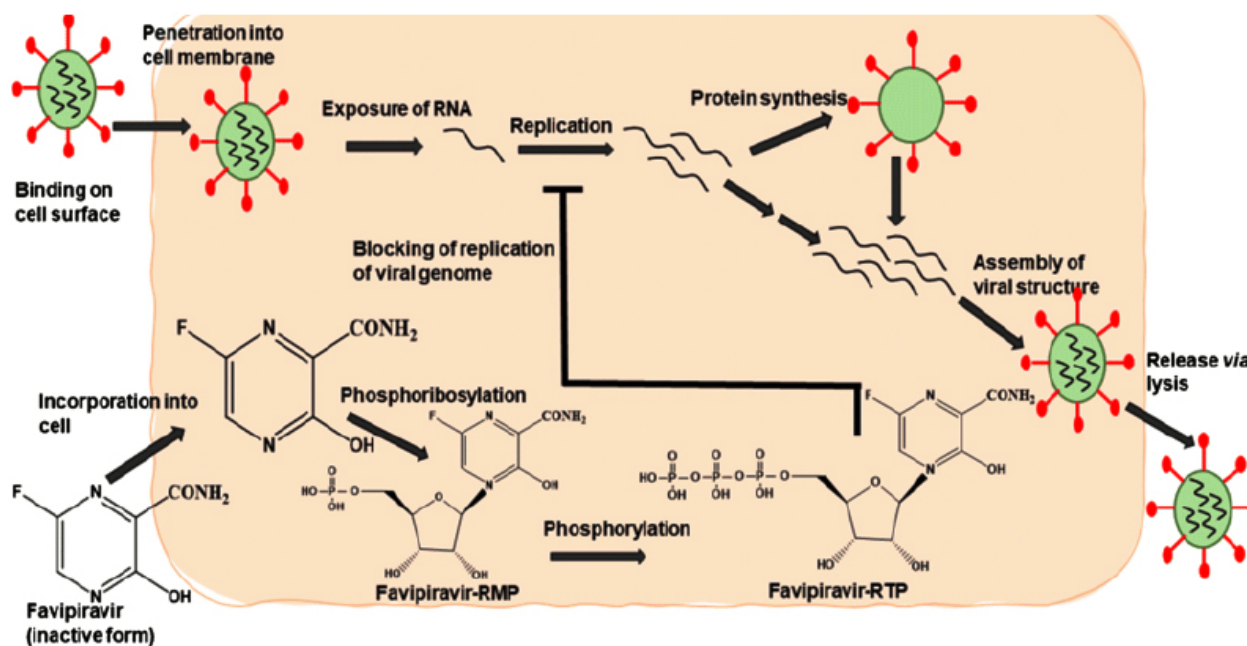
Fig. (2). An overview of the mechanism of action of favipiravir.

5. THE PHARMACOLOGICAL IMPLICATIONS

There are several RNA viruses that are resistant to favipiravir.

5.1. Influenza

The favipiravir molecule was discovered by chemically modifying pyrazine analogs in cells that exhibited anti-influenza virus activity [18]. There is an antiviral medicine called FAVIPIRAVIR. As a selective and powerful inhibitor of influenza viral RNA polymerase, the drug works well against many influenza virus strains and subtypes. A study found that favipiravir was also effective against influenza viruses resistant to neuraminidase inhibitors, which included oseltamivir [19].

5.2. COVID-19

Several clinical trials with favipiravir are currently being conducted to assess its efficacy and safety against SARS-CoV-2 [20]. Several countries, including India, have now approved the drug. According to DCGI, this drug is approved for use in cases of mild to moderate severity in India. The medication can only be prescribed once the patient or their representative has given informed consent for emergency use. During Day 1, it is recommended to take 1800 mg or 9 tablets of 200 mg twice a day. Then, for a maximum of 14 days, you can take 800 mg or four 200 mg tablets twice daily.

5.3. Ebola

In 2014, the World Health Organization shortlisted favipiravir for trial during the Ebola outbreak. Clinical studies have indicated that this drug may enhance survival, based on *in vitro* results [21]. Insufficient evidence was found to support the claim of benefit.

5.4. Clinical Trials

Over the past few months, clinical studies have been performed all over the world to assess the efficacy of favipiravir in the management of COVID-19. The major clinical studies are summarized here [22]. According to Table **2**, favipiravir exhibits a number of pharmacological indications backed by scientific evidence and clinical trials.

Table 2. An overview of Favipiravir pharmacological properties.

Study Type	Trial Outcome and Design	Conclusion
Exploratory Randomized, Controlled Trial	29 confirmed cases of COVID-19 were randomized (1:1:1) to Favipiravir for 14 days, Baloxavir-Marboxil (80 mg once daily orally on Days 1 and 4), or a control group. Lopinavir/ritonavir (400 mg/100 mg, bid, orally) and darunavir/cobicistat (800 mg/150 mg, qd, orally) as well as arbidol (200 mg, tid, PO) were administered to all patients. Interferon was required in all of them. The PCR levels were undetectable in all control groups on day 14 and 77% and 70% respectively in the Baloxavir and Favipiravir groups. Moreover, clinical improvements were similar between all groups. The baloxavir-marboxil and favipiravir groups both had one patient transferred to the ICU within seven days of the start of the trial. Among the 29 patients, there were no deaths.	The study results fail to support the hypothesis that adding baloxavir or favipiravir to COVID-19 patients' existing standard treatment would benefit them [22].

(Table 2) contd.....

Study Type	Trial Outcome and Design	Conclusion
Trial of prospective, randomized, controlled, open-label nature.	The study randomized 236 moderate/severe COVID-19 cases: 116 received Favipiravir for 10 days, and 120 took Umifenovir (Arbidol) for 10 days. All patients received conventional treatment. Clinical improvements at day 7 (the primary endpoint) were not significant between groups. Despite this, posthoc analysis for moderate COVID-19 patients showed significant enhancement in the Arbidol group (62/111, 55.86%) than in the Favipiravir group (70/98, 71.43%). Both pyrexia and cough were relieved faster with favipiravir. The rate of auxiliary oxygen therapy (AOT) and non-invasive mechanical ventilation (NVM) did not differ significantly between the groups.	A comparison of Favipiravir and Arbidol did not significantly improve clinical recovery rates. Pyrexia and cough relief were significantly improved by favipiravir [22].
Control study with open-label.[35]	For 14 days, 80 mild to moderate severity cases of COVID-19 were assigned to either Favipiravir (n = 35) or Lopinavir / Ritonavir (n = 55) (control group). In addition, both groups received aerosolized interferon (IFN). It was seen that favipiravir led to improved outcomes compared to the control arm, such as a shorter viral clearance period of 4 (2.5–9) days vs 11 (8–13) days, P = 0.001, and significant improvements in chest imaging (91.43% vs 62.22%, P = 0.004).	COVID-19 was significantly better treated with favipiravir in terms of disease progression and viral clearance [22].
Involvement-oriented, randomized, open-label phase 3 trial	In this study, 100 patients with COVID-19 were recruited. After receiving 3200 mg of favipiravir on day 1, the patients received 600 mg twice (days two through ten). In 50 patients, hydroxychloroquine was administered at 800 mg on day 1, 200 mg twice (days 2–10), and oral oseltamivir at 75 mg/12 h/day for ten days. A significant difference between the HCQ arm and the favipiravir arm was not observed in terms of the detection of SARS-CoV-2 by PCR (p = 0.7). However, favipiravir more frequently induced fevers and dry coughs (24% and 30%, respectively) than HCQ-based therapy (p > 0.05). Favipiravir caused elevated liver transaminases in 4 patients (8%) between Days 7 and 14, but they improved within two weeks after stopping the drug. As a result of myocarditis, one person died on Day 8 in the HCQ-based arm.	-

Table 3. There are adverse effects associated with Favipiravir.

-	≥ 1%	0.5- < 1%	< 0.5%
Hypersensitivity	-	Resh	Eczema, Proteus
Hepatic	AST (GOT) increased A/T (GPT) increased γ GTP increased	-	Blood ALP increased, blood half-life increased
Gastrointestinal	Dantoe	Nausea, vomiting abdominal pain	Abdominal discomfort, ulcer, haematochatis, goiter
Hematologic	Neutrophil count decreased, white blood cell count decreased	Glucose urine present	White blood cell count increased, reticulocyte count decreased, monocyte increased
Metabolic disorder	Uric acid increased, and Blood triglyceride increased	-	Blood potassium decreased
Respiratory	-	-	Asthma, oropharyngeal pain, rhinitis, nasopharyngitis
Others	-	-	CPK increased blood urine present, tonsil, vision blurred, eye pain, vertigo

6. IMPACTS OF ADVERSE EVENTS

Despite its adverse effects, favipiravir is generally considered safe, as confirmed by a large systematic review [23]. Here are some brief details about this drug's adverse effects. It is associated with an increase in total uric acid in the blood, diarrhea, a decreased white blood cell count (neutrophils), higher liver enzyme levels, and higher triglyceride levels in the blood.

- Symptoms of diarrhea
- Elevated uric acid levels (hyperuricemia).
- Neutrophil count reduced
- Having nausea
- Ingestion of vomit
- Pain in the abdomen

We are all aware of the risks associated with each drug. However, any drug should be used only if it has a minimal number of adverse effects and a high therapeutic effect. According to Table **3** , some adverse effects of favipiravir are minor, negligible, or less severe. Based on a large systematic review, this drug is effective in treating COVID-19 and safe in treating antiviral infections.

CONCLUSION

The COVID-19 infection is unlikely to disappear in the near future. Multiple clinical trials have been conducted on favipiravir against the devastating SARS-CoV-2 virus because of its novel antiviral activity and broad spectrum of activity. A recent study suggests that favipiravir can minimize viral clearance time and improve chest symptoms. The drug is considered relatively safe when used for a short period of time. Aside from being administered orally, in symptomatic patients not sick enough to require hospitalization, favipiravir is preferred. Due to the fact that most COVID-19 patients (85%) have mild to moderate disease and can be treated at home, this

drug could potentially be beneficial for many patients. Additionally, favipiravir is being studied in combination with umifenovir to see if they complement one another or act synergistically [22, 23]. As for the side effects of the drug, asymptomatic hyperuricemia and slight, reversible elevations in transaminases are reported most frequently. Consequently, Favipiravir appears to be effective in treating mild to moderate symptoms associated with SARS-CoV-2 infection. A comprehensive review of the antiviral research conducted over the course of the last decade describes how favipiravir has shown to be experimentally useful against COVID-19 and describes how it has been compared to other antiviral drugs. It is possible to clarify the antiviral properties of this drug using bioinformatics databases and tools. Clinical and experimental studies have demonstrated that this drug can cure COVID-19 disease.

LIST OF ABBREVIATIONS

μM/L	=	Micromole
AAS	=	Antiphospholipid Antibody Syndrome
ACE	=	Angiotensin-converting Enzyme
AOT	=	Auxiliary Oxygen Therapy
APN	=	Access Point Name
BBB	=	Blood Brain Barrier
CDC	=	Centre For Disease Control
CNS	=	Central Nervous System
COVID-19	=	Corona Virus Disease 19
CYP-2C-8	=	cytochrome P450 family 2 subfamily C member 8
DCGI	=	Drug Controller General of India
DPPH	=	2,2-Diphenyl -1 Picrylhydrazyl
EC-50	=	Effective Concentration
FDA	=	Food & Drug Administration
HCQ	=	HCQ = Hydroxychloroquine
HIV	=	Human Immunodeficiency Virus
ICU	=	Intensive Care Unit
IFNs	=	Interferons
IL	=	Interleukin
IMD	=	Immunological Diseases
IUPAC	=	International Union of Pure and Applied Chemistry
LDL	=	Low-Density Lipoprotein
LPS	=	Lipopolysaccharide
NIH	=	National Institute of Health
NVM	=	Non-invasive Mechanical Ventilation
PCR	=	Polymerase Chain Reaction
PCT	=	Porphyria Cutanea Tarda
PDCs	=	Plasmacytoid Dendritic Cells
PLE	=	Polymorphic Light Eruption
RA	=	Rheumatoid Arthritis
RdRp	=	RNA-dependent RNA polymerase
RNA	=	Ribonucleic Acid
RTP	=	Real-time Transport Protocol
SARS-CoV-2	=	Severe Acute Respiratory Syndrome- Corona Virus 2
UAE	=	United Arab Emirates
US	=	United States of America
USCDC	=	United States Centers for Disease Control and Prevention
WHO	=	World Health Organization

AUTHOR CONTRIBUTIONS

The review is outlined by Subhash Chandra and Sakshi. The manuscript was prepared by SC. SC and ANC edited and reviewed the article. The review and editing process was completed by SC, SS, and ANC, with the approval of all authors.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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REFERENCES

[1]   Chandra S, Saklani S, Aboul-Enein HY. Hydroxychloroquine Sulfate (Plaquenil): A possible candidate for pandemic SARS-CoV-2 or (COVID-19)? Coronaviruses 2021; 2(10): e170821190015.
[http://dx.doi.org/10.2174/2666796701666210108115614]

[2]   Chandra S, Palai S, Fagner Ferreira-Matias E, *et al.* Indian medicinal plants are effective in the treatment and management of COVID-19. Biocell 2023; 47(4): 677-95.
[http://dx.doi.org/10.32604/biocell.2023.026081]

[3]   Vicenti I, Zazzi M, Saladini F. SARS-CoV-2 RNA-dependent RNA polymerase as a therapeutic target for COVID-19. Expert Opin Ther Pat 2021; 31(4): 325-37.
[http://dx.doi.org/10.1080/13543776.2021.1880568]   [PMID: 33475441]

[4]   Rubin R. Difficult to determine herd immunity threshold for COVID-19. JAMA 2020; 324(8): 732.
[http://dx.doi.org/10.1001/jama.2020.14778] [PMID: 32840583]

[5]   Fontanet A, Cauchemez S. COVID-19 herd immunity: Where are we? Nat Rev Immunol 2020; 20(10): 583-4.
[http://dx.doi.org/10.1038/s41577-020-00451-5] [PMID: 32908300]

[6]   WHO. Coronavirus disease (COVID-19): Vaccines. 2022. Available From:
https://www.who.int/news-room/q-a-detail/coronavirus-disease-(covid-19)-vaccines

[7]   Furuta Y, Gowen BB, Takahashi K, Shiraki K, Smee DF, Barnard DL. Favipiravir (T-705), a novel viral RNA polymerase inhibitor. Antiviral Res 2013; 100(2): 446-54.
[http://dx.doi.org/10.1016/j.antiviral.2013.09.015] [PMID: 24084488]

[8]   Lee JS, Adhikari NKJ, Kwon HY, *et al.* Anti-Ebola therapy for patients with Ebola virus disease: A systematic review. BMC Infect Dis 2019; 19(1): 376.
[http://dx.doi.org/10.1186/s12879-019-3980-9] [PMID: 31046707]

[9]   Oestereich L, Lüdtke A, Wurr S, Rieger T, Muñoz-Fontela C, Günther S. Successful treatment of advanced Ebola virus infection with T-705 (favipiravir) in a small animal model. Antiviral Res 2014; 105: 17-21.
[http://dx.doi.org/10.1016/j.antiviral.2014.02.014] [PMID: 24583123]

[10]   Smither SJ, Eastaugh LS, Steward JA, Nelson M, Lenk RP, Lever MS. Post-exposure efficacy of Oral T-705 (Favipiravir) against inhalational Ebola virus infection in a mouse model. Antiviral Res 2014; 104: 153-5.
[http://dx.doi.org/10.1016/j.antiviral.2014.01.012] [PMID: 24462697]

[11]   Shiraki K, Daikoku T. Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. Pharmacol Ther 2020; 209: 107512.
[http://dx.doi.org/10.1016/j.pharmthera.2020.107512] [PMID: 32097670]

[12]   Eloy P, Solas C, Touret F, *et al.* Dose rationale for Favipiravir use in patients infected with SARS-CoV-2. Clin Pharmacol Ther 2020; 108(2): 188.
[http://dx.doi.org/10.1002/cpt.1877] [PMID: 32350860]

[13]   Agrawal U, Raju R, Udwadia ZF. Favipiravir: A new and emerging antiviral option in COVID-19. Med J Armed Forces India 2020; 76(4): 370-6.
[http://dx.doi.org/10.1016/j.mjafi.2020.08.004] [PMID: 32895599]

[14]   Madelain V, Nguyen THT, Olivo A, *et al.* Ebola virus infection: Review of the pharmacokinetic and pharmacodynamic properties of drugs considered for testing in human efficacy trials. Clin Pharmacokinet 2016; 55(8): 907-23.
[http://dx.doi.org/10.1007/s40262-015-0364-1] [PMID: 26798032]

[15]   Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proc Jpn Acad, Ser B, Phys Biol Sci 2017; 93(7): 449-63.
[http://dx.doi.org/10.2183/pjab.93.027] [PMID: 28769016]

[16]   Zhao L, Zhong W. Mechanism of action of favipiravir against SARS-CoV-2: Mutagenesis or chain termination? Innovation 2021; 2(4): 100165.

[17]   [http://dx.doi.org/10.1016/j.xinn.2021.100165] [PMID: 34518821]

[17]   Baranovich T, Wong SS, Armstrong J, *et al.* T-705 (favipiravir) induces lethal mutagenesis in influenza A H_1N_1 viruses *in vitro*. J Virol 2013; 87(7): 3741-51.
[http://dx.doi.org/10.1128/JVI.02346-12] [PMID: 23325689]

[18]   Jomah S, Asdaq SMB, Al-Yamani MJ. Clinical efficacy of antivirals against novel coronavirus (COVID-19): A review. J Infect Public Health 2020; 13(9): 1187-95.
[http://dx.doi.org/10.1016/j.jiph.2020.07.013] [PMID: 32773212]

[19]   Goldhill DH, te Velthuis AJW, Fletcher RA, *et al.* The mechanism of resistance to favipiravir in influenza. Proc Natl Acad Sci USA 2018; 115(45): 11613-8.
[http://dx.doi.org/10.1073/pnas.1811345115] [PMID: 30352857]

[20]   Sissoko D, Laouenan C, Folkesson E, *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 Med 2016; 13(3): e1001967.
[http://dx.doi.org/10.1371/journal.pmed.1001967] [PMID: 26930627]

[21]   Mishima E, Anzai N, Miyazaki M, Abe T. Uric acid elevation by Favipiravir, an antiviral drug. Tohoku J Exp Med 2020; 251(2): 87-90.
[http://dx.doi.org/10.1620/tjem.251.87] [PMID: 32536670]

[22]   Final express. 2020. Available From: https://www.financialexpress.com/lifestyle/health/covid-19

[23]   Hassanipour S, Arab-Zozani M, Amani B, Heidarzad F, Fathalipour M, Martinez-de-Hoyo R. The efficacy and safety of Favipiravir in treatment of COVID-19: A systematic review and meta-analysis of clinical trials. Sci Rep 2021; 11(1): 11022.
[http://dx.doi.org/10.1038/s41598-021-90551-6] [PMID: 34040117]