

## **Review on Favipiravir Application Uses and Adverse Effect During Covid-19**

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### **ABSTRACT**

The global outbreak of the COVID-19 pandemic, caused by the SARS-CoV-2 virus, has spurred an urgent search for effective antiviral medications. Favipiravir (FVP), an antiviral medicine, has emerged as a promising solution to halt the replication and spread of the virus within the human body. In this comprehensive review, we delve into the molecular mechanisms of FVP, exploring its ability to combat the coronavirus family, with SARS-CoV-2 as the primary focus. The coronavirus family, notorious for causing respiratory illnesses ranging from the common cold to severe acute respiratory syndrome (SARS), poses a significant threat to global public health. FVP, known for its anti-viral properties, has garnered attention for its potential to address the COVID-19 crisis. This review meticulously examines the harmful effects associated with FVP, shedding light on its safety margins and the evolving understanding of its deteriorating state. Despite its popularity as a go-to anti-COVID-19 drug, it is crucial to understand the nuances surrounding FVP to optimize its usage and mitigate potential risks. As the world grapples with the ongoing pandemic, understanding the intricacies of FVP's efficacy and safety profile becomes paramount. This review aims to contribute to the growing body of knowledge surrounding FVP, providing insights that are vital for healthcare professionals, researchers, and policymakers in their collective efforts to combat the global health crisis.

**Keywords:** Covid-19, Anti-viral, Favipiravir , Viral disease, SARS-CoV-2, Favi-pill.

### **INTRODUCTION**

SARS-CoV-2 is an extremely contagious strain of the COVID-19 virus that produces severe respiratory symptoms. This family of viruses contains a large diversity of viruses. After circulating rapidly from its December 2019 origin in Wuhan, China, the COVID-19 virus was proclaimed a pandemic in March 2020. The global spread of the COVID-19 pandemic has caused major economic losses and strained healthcare systems around the world. Previous pandemics include SARS and MERSA; the present COVID-19 outbreak began in China; and the two pandemics that came before it have followed. It is believed that the virus can be contracted from a

zoonotic source and spreads through close personal contact.<sup>[1]</sup>

There are no antiviral medications that specifically target COVID-19 at this time. Nevertheless, scientists are looking into the possibility of using antiviral drugs that are already on the market or in the works for other types of viruses. With any luck, this strategy will lead to the rapid development of a cure for this unusual viral infection. Fever, lethargy, muscular pains, sore throat, runny nose, diarrhea, olfactory and gustatory loss, headache, and eye pain are common symptoms of the coronavirus. We set out to learn more about Favipiravir's (FVP) toxicity, safety margins, and degradation products so that we can better understand the effects of this breakthrough anti-COVID-19 drug, which has changed the course of

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human history. We mainly looked at how it behaved when subjected to different degradation scenarios. Clinical trials of favipiravir in Japan, China, and Russia have shown promising results. The United States, the United Kingdom, and India are just a few of the countries where a plethora of trials are presently underway. Favipiravir has recently been included in treatment protocols in several Indian states and in many international guidelines.<sup>[2-3]</sup>

### Mechanism of COVID-19 Infection

Coronavirus has been able to infect humans for a long time because it is quite similar to other viruses that cause the common cold. Coughing, sneezing, or touching a contaminated surface are the main ways it can be transmitted because of how contagious it is. Remember that virus droplets can potentially be swallowed or inhaled. About 30,000 nucleotides make up the coronavirus genome. It includes a number of non-structural proteins as well as four structural proteins: nucleocapsid (N), membrane (M), spike (S), and envelope (E). Within the capsid, the protective protein encasing the virus, is the nuclear capsid, otherwise called the N-protein.<sup>[4]</sup> By binding to the virus's single-stranded positive RNA, it enables the virus to infiltrate and multiply within human cells. Finding a way to block the N-terminal of the N-protein from interacting with the one positive strand of RNA remains an important unsolved scientific question. Doing so will prevent the virus from replicating and transcribe its genes. Some research suggests that theophylline and pyrimidone may be able to block coronavirus N protein N terminal domain RNA binding. Potentially novel avenues for in vitro validations may emerge as a result of this finding. Since the M-protein is more abundant on the surface of the coronavirus, it is thought to have a critical function in coordinating the virus's assembly.<sup>[5]</sup>

Merging the viral and host cell membranes and linking the virus to receptors on host cell surfaces are also responsibilities of the S-protein. As a result, the virus is able to infiltrate the host cell without any problems. With an approximate amino acid sequence of 76–109, the E-protein is a tiny membrane protein. It is a small portion of the viral

particle that helps regulate the permeability of host cell membranes and allows the virus to interact with host cells. The DNA is protected by a lipid bilayer.<sup>[6-7]</sup>

It has been found that the surface of the virus contains a hemagglutinin-esterase dimer (HE). While the HE protein isn't required for replication, it is essential for virus entry and infection of the natural host cell. The most recent cryo-electron microscopy (EM) studies have solved the mystery of the Spike (S) protein's closed and open (prefusion) conformations. Three identical chains, each with 1273 amino acids, make up this glycoprotein. The S1 and S2 subunits make up its two separate domains of protein. Cell recognition is carried out by the S1 subunit, while the fusion of viral and cellular membranes is facilitated by the S2 subunit. In the second step, a number of protein conformational changes occur, the exact nature of which is yet unclear. How viruses replicate, package their RNA, and infect human cells. There are ACE2 receptors on the surface of some human cells, primarily those in the lungs. Invasion of the body is made possible when the spike (S) protein of the coronavirus binds to these receptors. Here, at the boundary between the S1 and S2 subunits, proteases from the host body, such as trypsin and furin, cleave the coronavirus S protein. After the S2 domain (S2' site) is cleaved, the fusion peptide is released at a later stage. The process of membrane fusion will be activated as a result of this.<sup>[8-10]</sup>

### Therapeutic validation target:

The epidemic prompted extensive research into several potential treatment medicines. A variety of medications were employed, each with its unique mechanism of action. Antivirus medications can prevent viruses from infecting cells. One such drug is recombinant neutralizing monoclonal antibodies (rNEMs). Medications such as anti-inflammatory and antithrombotic treatments target the immune response. Drugs that target the RAAS (renin-angiotensin-aldosterone system) are also available.<sup>[11]</sup> A number of RCTs have looked at the efficacy and safety of both brand-new and recycled drugs. Some treatments have been approved or given emergency-use authorization (EUA) by

regulatory agencies such as the FDA and the EMA. There was a positive association between burnout from COVID-19 and stress from the coronavirus and emotions of melancholy, worry, and stress, but a negative correlation between resilience and these variables. Along with age, gender, and resilience, researchers found that COVID-19-related burnout and stress were associated with elevated levels of depression, anxiety, and stress. Based on the findings, it appears that the COVID-19-BS and the Polish CSM are valid measures of COVID-19-related burning out and stress. The results also showed that the stress and exhaustion brought on by the COVID-19 epidemic in its latter phases may affect mental health in the future.<sup>[12]</sup>

### **Favipiravir as Treatment approach:**

Favipiravir is a medicine with an existing license; it is an oral, broad-spectrum Rd-Rp inhibitor. A therapeutic dosage of favipiravir is effective against SARS-CoV-2 infection, according to in vitro investigations. The oral formulation of favipiravir is anticipated to address the unfulfilled treatment requirements of a significant portion of the COVID-19 group. Roughly 80% of individuals with mild to moderate COVID-19 fall into this category, and the majority of them can be treated as outpatients.<sup>[13-14]</sup>

Based on a readiness score that takes into account the following: the formulation method's clarity and certainty, the availability of human safety data, the strength of preclinical results, the significance of the target and mechanism of action, the certainty of manufacturing, and the progress of COVID-19 clinical trials, this ranking is derived. The efficacy of the formulation process is also considered. Favipiravir is effective against several influenza viruses, including those that infect birds. Ebola, noroviruses, hantaviruses, arenaviruses, and flaviviruses are among the RNA viruses that it may impede the replication of.<sup>[15-18]</sup>

### **Mechanism of Action of Favipiravir:**

The active favipiravir ribofuranosyl-5B-triphosphate, or favipiravir-RTP, is formed when the purine base analogue prodrug favipiravir is phospho-ribosylated within the cell. It is highly effective against RNA viruses and selectively

inhibits RNA-dependent RNA polymerase (Rd-Rp). The viral error-prone Rd-Rp inserts favipiravir into the developing viral RNA, leading to mutations in the virus and the end of the replication chain. The antiviral activities of favipiravir are enhanced by the presence of Rd-Rp in certain RNA virus types.<sup>[19-20]</sup>

Following RNA viral integration, favipiravir-RTP can mutate and evade coronavirus repair mechanisms. The initial percentage of cytosine in the SARS-CoV-2 genome is only approximately 17.6%. Adding favipiravir-RTP puts further strain on the CoV nucleotide content. In most cases, favipiravir-RTP is effective against SARS-CoV-2, despite the fact that it raises the mutation rate. The cytopathic effect is a result of the decrease in viral RNA and infectious particle levels. Favipiravir has a high affinity for Rd-Rp, as shown by its docking score of -6.252. Favipiravir thus aims at the Rd-Rp complex.<sup>[21-22]</sup>

### **Role of Favipiravir in Covid-19:**

No other viral Rd-Rp is as active as the SARS-CoV-2-RD-Rp complex. By inhibiting the viral Rd-Rp enzyme, favipiravir facilitates its insertion into viral RNA and so protects human DNA from damage. Researchers found that nucleoside analogs, including favipiravir, work well against COVID-19. It is challenging to determine the ideal dose of favipiravir due to the paucity of preclinical in vitro data. In the case of Ebola, for example, the dosage of favipiravir was increased since preclinical studies demonstrated that the target concentrations needed to suppress the virus were higher than those in influenza.<sup>[23-25]</sup> This medicine supports a faster rate of recovery and clears the virus more rapidly than lopinavir/ritonavir (LPV/RTV) and umifenovir, according to clinical trials on COVID-19. Clinical trials conducted in Russia, China, and Japan have demonstrated encouraging outcomes for favipiravir. Several other nations, such as the United States, the United Kingdom, and India, are also conducting new trials. The use of favipiravir to treatment regimens has lately been suggested by a number of international organizations and specific Indian states. This study sheds light on the growing significance of favipiravir in the therapy of COVID-19 infection

and emphasizes the benefits of starting antiviral treatment early. Also included are favipiravir's in vitro and clinical data, pharmacokinetic and pharmacological properties, and its function in COVID-19 treatment regimens.<sup>[26]</sup>

### Pharmacology:

Toyoma chemicals' chemical library was the first to yield the synthetic prodrug favipiravir (T-705), which was found during an investigation of chemical compounds active against the influenza virus. It was demonstrated that the lead chemical A/PR/8/34 (now called T-1105) and its derivatives had antiviral properties. T-1105 undergoes chemical modifications to its pyrazine moiety to produce favipiravir. In 2014, Japan approved its use to treat newly emerging pandemic influenza infections. The medication favipiravir is administered in the form of a prodrug. Approximately 94% of it is bioavailable, it has a volume of distribution of 10–20 liters, and 54% of it binds to proteins. A single dose takes two hours to reach C<sub>max</sub>. The half-life and T<sub>max</sub> both grow with each dosage.<sup>[27]</sup> The short half-life (2.5-5 hours) of hydroxylated favipiravir causes the kidneys to speed up its clearance. Aldehyde oxidase is the enzyme responsible for elimination, while xanthine oxidase is more of a supporting actor. The pharmacokinetic properties of favipiravir demonstrate a dose- and time-dependent response. It inhibits CYP2C8, however this cytochrome P450 system component does not metabolize it. So, it's important to be careful when taking medications that the CYP2C8 system metabolizes.<sup>[28]</sup>

### Adverse effect:

The aforementioned Japanese study found that over 20% of individuals who got favipiravir at a dose below the COVID-19 threshold experienced adverse effects. Moderate adverse effects, such as diarrhea and hyperuricemia, affected 5% of individuals, and transaminitis and a decreased neutrophil count affected 2%. One study found that favipiravir use was associated with an increase in mental health issues. When looking at the impact of favipiravir on QTc prolongation, the results are mixed. Some pharmacodynamic studies have

shown a favorable association, while research conducted in Japan has found the opposite.<sup>[29]</sup> There is a very low chance of adverse effects with favipiravir, according to a comprehensive analysis. The medication's side effect profile is summarized below:

The frequency of hyperuricemia increases as the dosage of favipiravir increases. But there are no clinical indications associated with this. Longer periods of follow-up are necessary to properly evaluate the risk of favipiravir-induced hyperuricemia resulting in clinical symptoms, regardless of the absence of evidence for this.

Favipiravir has the potential to cause teratogenic and embryotoxic consequences, according to the available evidence. After receiving approval from the Japanese Drug Safety Bureau, favipiravir should be distributed with a stern warning to pregnant or potentially pregnant women, together with cautious packaging and prescription notifications. Favipiravir is not recommended by the FDA since there are other medicines that may be more effective. Counseling on effective methods of birth control should be provided to males who have received this surgery during and for seven days after treatment finishes. A negative urine pregnancy test must be done before favipiravir is given to pregnant women in order to eliminate the potential of pregnancy.<sup>[30]</sup>

### CONCLUSIONS:

There is little evidence to support the use of favipiravir, an oral drug that is similar to remdesivir but has weaker data. But it's still a treatment option to think about for mild to moderate cases. An intriguing two-day reduction in viral shedding duration and a slight but obvious improvement in the time to clinical recovery were noted in the preliminary results of the first Indian trial utilizing this drug. To put things in perspective, the commonly used drug oseltamivir decreased the time it took for clinical symptoms to become better by 16.8 hours, according to 20 trials, one of which included influenza. One of the main advantages of favipiravir is that it may be taken orally, making it suitable for patients who are sick but not yet critically sick enough to need

hospitalization. Most people infected with COVID-19 have mild to moderate symptoms, making home treatment a viable option; so, this medicine has the potential to be used by many patients. Furthermore, a present investigation is investigating the potential of favipiravir as a prophylactic strategy in contacts who have been exposed but are otherwise healthy. The most common side effects of the medicine, which include asymptomatic hyperuricemia and minor, temporary elevations in transaminases, appear to be manageable. The fact that it causes birth defects means that pregnant women should never use it. Users are expected to take eight tablets daily for the duration of the term, in addition to eight pills on day one, which is a significant burden. Another possible drawback is that the prescribed treatment program lasts for two weeks. Favipiravir has the potential to alleviate mild to severe symptoms in patients infected with SARS-CoV-2.

**Conflicts of Interest:** The authors declare that there are no conflicts of interest.

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