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# A Review: Favipiravir-Antiviral Drug for the Treatment of COVID-19

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**ABSTRACT:**
The Coronavirus disease - 2019 ( COVID -19 ) outbreak worldwide has led to research to develop drugs or vaccines to prevent it. Severe acute respiratory syndrome coronavirus 2 ( SARS-CoV-2) is an enveloped, single-stranded RNA virus. Favipiravir is an oral antiviral drug that effectively inhibits RNA-dependent RNA polymerase. In this article, we provide a comprehensive, evidence-based review of the favipiravir drug in the context of the pandemic to elucidate its role in the treatment of COVID-19.

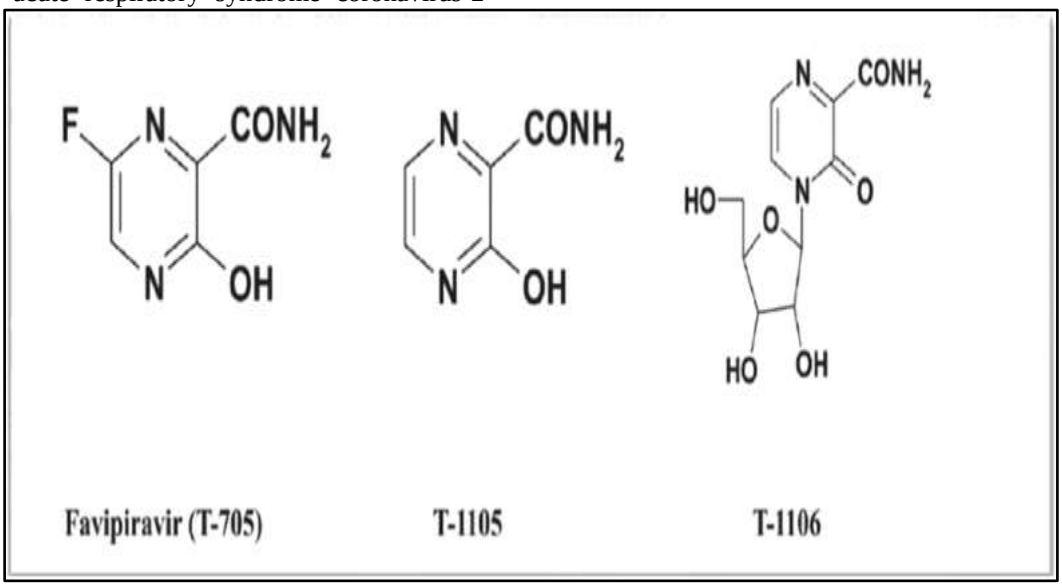
**KEYWORDS :**
Antiviral, COVID-19, Favipiravir, SARS-CoV-2, Pharmacology, RNA, Pharmacokinetics, In Vitro, Dose.

## I . INTRODUCTION :

The Coronavirus disease -2019 ( COVID-2019 ) pandemic that originated in 2019 in China's Hubei province has walloped every continent. COVID-19 is an infectious disease associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is positive-sense single-stranded ribonucleic acid (RNA) virus, the discovery of a new and specific antiviral agent against the SARS-CoV-2 would involve a long and arduous timeline. One such drug is Favipiravir, initially marketed as an anti-influenza agent in Japan. Favipiravir was first used against SARS-Cov-2 in Wuhan at the very epicenter of the pandemic in June 2020. Favipiravir shows results in China, Japan, and India. Favipiravir also received DCGI approval in India for mild and moderate COVID-19 infections.

## II. PHARMACOLOGY :

Toyama chemical co. Ltd. in Japan discovered Favipiravir. Favipiravir is a modified pyrazine analog that was initially approved for therapeutic use in resistant cases of influenza. The antiviral targets RNA-dependent RNA polymerase (RdRp) enzymes, which are necessary for the transcription and replication of viral genomes. Favipiravir is derived by chemical modification of the pyrazine moiety of T-1105.




Favipiravir (T-705) T-1105 T-1106

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## III. DRUG PROFILE : FAVIPIRAVIR

**Category:** Antiviral agent
**IUPAC Name:** 6-fluro -3-hydroxy pyrazine-2-carboxamide
**Molecular Formula :** C5H4FN3O2
**Molecular Weight:** 157.1 g/mol
**Description:** A Crystalline Solid
**Solubility:** Soluble in Water, Organic solvents such as Ethanol, DMSO, and Dimethylformamide and highly solubility in aqueous buffer
**pKa Value:** 5.1
**Melting Point:** 187 to 193 0C
**Half-Life:** 2 to 5.5 hours
**Stability :** ≥2 years
**Mode of Action:** Favipiravir binds to and inhibits the RNA-dependent RNA polymerase, ultimately preventing viral genome RNA transcription and replication. FVP has also used some life-threatening infections such as Ebola, Lassa Fever and rabies.
**Side Effects:** Diarrhea, Increased uric acid level, Decreased white blood cells count, Increased liver enzymes, Psychiatric symptoms

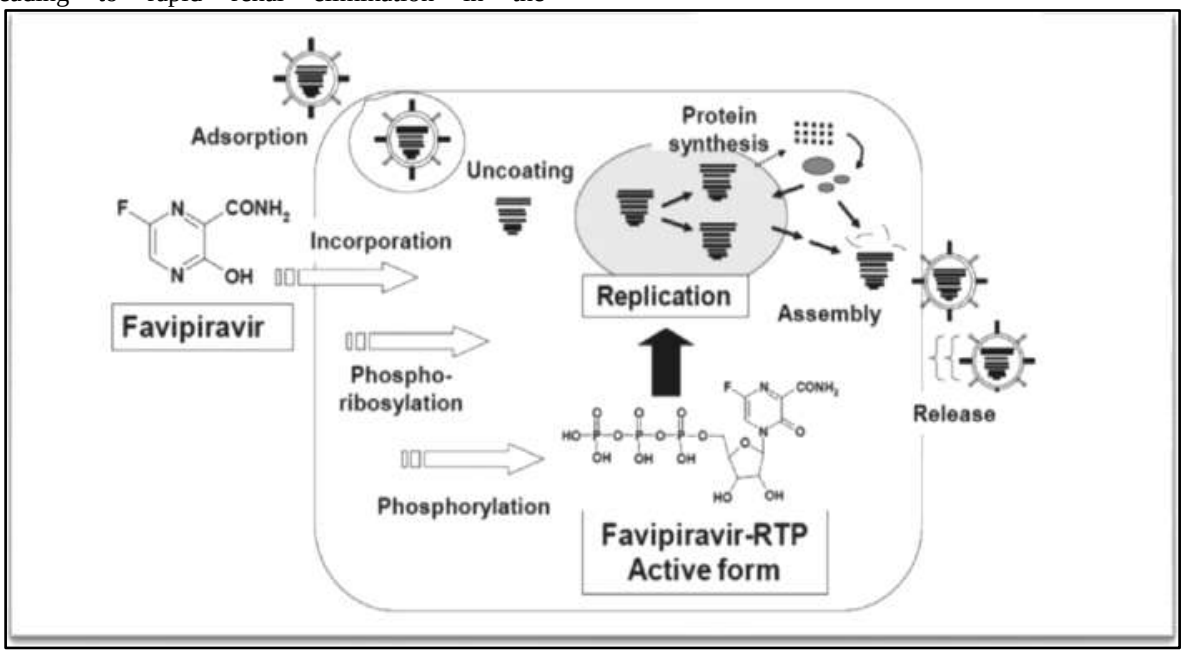
## IV. PHARMACOKINETICS AND PHARMACODYNAMICS :

Favipiravir is administered as a prodrug. It has excellent bioavailability (～94%), 54% protein binding, and a low volume of distribution (10–20 L). It reaches Cmax within two h after a single dose and both Tmax and half-life increase after multiple doses. Favipiravir has a short half-life (2.5–5 h), leading to rapid renal elimination in the hydroxylated form. Elimination is mediated by aldehyde oxidase and marginally by xanthine oxidase. Favipiravir exhibits both dose-dependent and time-dependent pharmacokinetics. It is not metabolized by the cytochrome P450 system but inhibits one of its components (CYP2C8). Thus, it must be used cautiously when coadministered with drugs metabolized by the CYP2C8 system.

## V. MECHANISM OF ACTION :

Within the tissue, the molecule undergoes phosphor ribosylation to favipiravir-RTP, which is the active form of this drug. It exerts its antiviral effect through the following mechanisms:

- This molecule acts as a substrate for the RNA-dependent RNA-polymerase (RdRp) enzyme, which is mistaken by the enzyme as a purine nucleotide, thus inhibiting its activity and leading to the termination of viral protein synthesis
- It gets incorporated into the viral RNA strand, preventing further extension. This mechanism of action, along with the preservation of the catalytic domain of the RdRp enzyme across various RNA viruses, explains this drug's broad spectrum of activity.
- It has recently been shown that favipiravir induces lethal mutagenesis in vitro during influenza virus infection, making it a virucidal drug. Whether a similar activity is demonstrated against SARS-CoV-2 or not is uncertain.



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## VII. ROLE IN SARS-CoV-2 :

Based on the mechanism of action and safety of the favipiravir, the drug may be a promising candidate for use against the SARS-CoV-2 infection. Favipiravir has a range of activity against many single-stranded RNA viruses, is well tolerated in humans and has a high barrier to resistance. Favipiravir is a teratogen in pregnant women and is associated with hyperuricemia. Therefore, the administration of the drug is well-controlled. Investigating the prophylactic antiviral potency of favipiravir and searching for its pro-drugs and analogs showing improved activity or safety is critical.

A recent in vitro study by Wang et al., 2020a, and Wang et al., 2020b reported the efficacy of favipiravir in reducing SARS-CoV-2 infection. Favipiravir has a half-maximal effective concentration (EC50) of 61.88 μM, a half-cytotoxic concentration (CC50) >400 μM, and a selectivity index (SI) >6.46. The EC50 is similar to its EC50 against Ebola (67 μM). It justifies the need for a high dose to achieve a pharmacologically relevant target through a concentration of 40–80 μg/mL in COVID-19 (Du and Chen, 2020a). The wide gap between CC50 and EC50 gives a comfortable safety margin for a high dose of favipiravir.

## VII. DOSE AND COST :

The recommended dosage of favipiravir for adults is 1800 mg orally twice daily on 1st day, followed by 800 mg orally twice daily, up to a maximum of 14 days. The 14-day course in India costs Rs 10,200

## VIII. DCGI APPROVAL :

Considering the emergency and unmet medical need in COVID-19, Glenmark was granted permission to manufacture and market favipiravir for restricted emergency use in the country on June 19, 2020, for the treatment of mild to moderate COVID-19 disease. This approval is contingent on providing the complete report of the ongoing clinical trial within three months of support.

## IX. DRUG INTERACTIONS :

**Pyrazinamide**: Concomitant use of pyrazinamide with favipiravir increases uric acid levels. Regular uric acid level monitoring is mandatory when these drugs are used together.

**Repaglinide:** Favipiravir inhibits the metabolism of repaglinide through the CYP2C8 pathway, thus increasing its potential to cause toxicity (hypoglycemia, headache, increased incidence of upper respiratory tract infections, etc.). Cautious concomitant use is recommended.

**Theophylline**: Theophylline increases the blood levels of favipiravir, and adverse reactions to favipiravir may occur.

**Famciclovir, sulindac:** The efficacy of these drugs may be reduced when coadministered with favipiravir.

**Acyclovir**: Acyclovir may delay the conversion of favipiravir into the active moiety, thus reducing its antiviral efficacy.

## X. CONCLUSION :

In our real-world study, favipiravir was found to have a clinical cure rate of more than 90% in mild-to-moderate COVID-19 patients. This supports the use of favipiravir in the treatment of COVID-19. Favipiravir was well tolerated, with only minimal side effects, which were transient in nature. The main advantages of favipiravir are that it is administered orally and that it can be given to patients who are symptomatic but not ill enough to be hospitalized. As most COVID-19 patients (85%) have mild to moderate disease and can be treated at home, this drug could be used in many patients. As with any antiviral, it should be stressed that favipiravir should be administered early after the onset of symptoms to reduce viremia effectively. Its role in shortening the duration of viral shedding could also have an epidemiological impact as it could minimize viral transmission at home and in the community. The role of favipiravir in prophylaxis in exposed but healthy contacts is also being examined in an ongoing trial. Favipiravir is also being evaluated with other antiviral drugs, such as umifenovir, to see if these drugs act in a complementary or synergistic manner.

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