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Favipiravir: A Critical Review of Pharmacology, Pre-Clinical Data, and Emerging Clinical Uses in COVID-19

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Abstract: ***Since last two years, whole world is going through the pandemic situation of Corona Virus Disease-19 (COVID-19). It caused more than 43 lakhs deaths worldwide. COVID-19 outbreak all over the world has led the researchers and Scientists to develop drugs or vaccines to prevent the spreading of this virus. Due to the unavailabity of proper drug treatment, various veterinary drugs are trying in humans. It is one of such type of antiviral drug which was previously used in treatment of viral infection in animals and birds. In this article, we have tried to provide a comprehensive, evidence-based review of this drug in the context of the present pandemic to elucidate its role in the management of COVID-19.***

Keywords: Favipiravir; Pharmacology; COVID-19; Antiviral; Clinical trials.

I. INTRODUCTION

Favipiravir (5-fluoro-2-oxo1H-pyrazine-3-carboxamide) **(Fig. 1)**, an antiviral drug that was initially introduced in the treatment of treat influenza in Japan. In Feb., 2020 post the outbreak of novel corona virus (covid-19). Favipiravir was studied in China and several other countries as an experimental treatment of Covid-19. In late December 2019, Chinese health authorities reported an outbreak of pneumonia of unknown origin in Wuhan, Hubei Province [1].

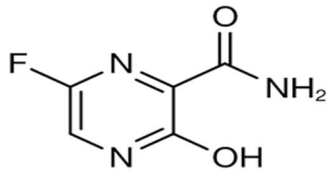


Fig. 1: Chemical structure of favipiravir.

As COVID-19 incidence and mortality rapidly climb, treatment options are limited. Repurposing existing pharmaceuticals provides an immediate treatment opportunity. While there is no licensed treatment that specifically acts against COVID-19, medications such as broad-spectrum antiviral are being employed as experimental adjuncts to supportive care. Potential drugs that may be repurposed include antimalarial hydroxychloroquine, antiretrovirals lopinavir/ritonavir and darunavir/ritonavir, and influenza drugs oseltamivir, remdesivir and favipiravir (FP). These drugs are now being trialed globally in different combinations for the treatment of COVID-19 [2-4].

II. INVENTION OF NEWER DRUGS

Invention of a new and specific antiviral agent against the SARS-CoV-2 would involve a long and arduous timeline. Hence, by default, repurposed drugs, already in use against other viral infections, have been pressed into quick service. One such drug is favipiravir, initially marketed as an anti-influenza agent in Japan. It is derived by chemical modification of the pyrazine moiety of T-1105. This drug has just received emergency approval by the *Drug Controller General of India* and hence this comprehensive review of favipiravir comes at a timely juncture [5]. Hydroxychloroquine, remdesivir, ritonavir, Favipiravir, etc are some existing drugs being explored for treatment. The results of repurposing prevailing antiviral were not acceptable level in COVID-19 patients especially with diabetes mellitus, hypertension, CVS, renal failure, liver cirrhosis, stroke, etc [6-7].

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III. MECHANISM OF ACTION

Favipiravir is 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 leading to termination of viral protein synthesis. It gets incorporated in the viral RNA strand, preventing further extension [8].

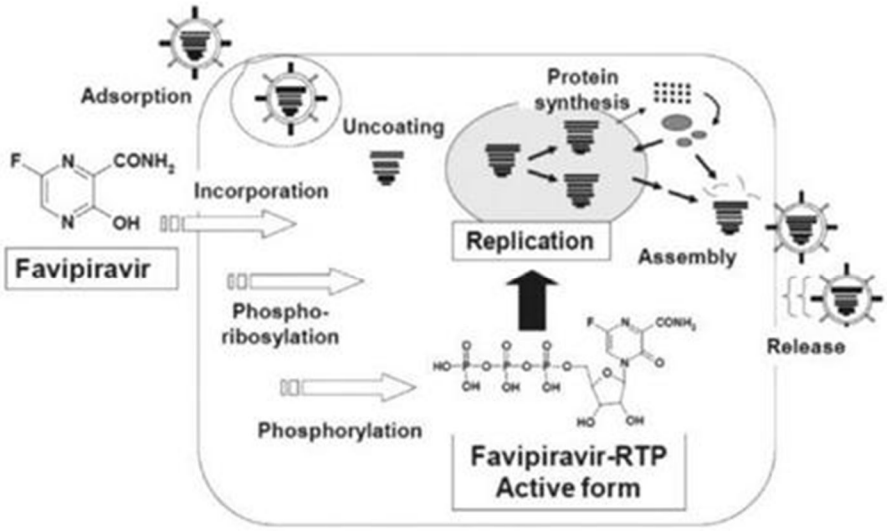


Fig. 2: Mechanism of anti-viral action (www.google.com).

IV. PHARMACOKINETICS STUDY

Favipiravir is administered orally as a prodrug. It has an excellent bioavailability (~94%) plasma protein binding 54%. It has a short half-life (2.5-5h) leading to rapid renal elimination in the hydroxylated form. Elimination is mediated by aldehyde oxidase and marginally by xanthine oxidase. Prophylaxis 1600 mg orally twice daily on day 1 followed by 800 mg orally twice a day on days 2–25. It exhibits both, dose-dependent and time dependent pharmacokinetics. It is not metabolized by the cytochrome P450 system but inhibits one of its components (CYP2C8) [9-10].

V. SPECTRUM OF ACTIVITY

RNA viruses, including West Nile virus, yellow fever virus, foot-and- mouth disease virus, enterovirus, and rift valley fever [11].

VI. SAFETY PROFILE

Favipiravir has an established and well-characterized safety profile from 4000+ patients (Pilkington et al., 2020). The common adverse events (AEs) include gastrointestinal AEs, uric acid elevations, decrease of neutrophil count, increase of aspartate aminotransferase (SGOT), increase of alanine transaminase (SGPT), psychiatric symptom reactions, and increase in blood triglycerides. The proportion of serious AEs was 0.4% and 1.1% discontinuation due to AEs (Fabiflu Prescribing Information). Similar proportions of AEs were reported between low and high doses of favipiravir. It demonstrates a favorable safety profile with respect to total and serious AEs [12-15].

VII. PRECAUTIONS & CONTRAINDICATIONS

Precautions and contraindications are discussed bellow [16]

A. It is contraindicated in pregnant and lactating women. Due to its teratogenic potential, it is contraindicated in pregnant and suspected pregnant women.
B. It is distributed in sperms; hence, it is advised to use effective contraceptive methods by both women and men of reproductive age during the course and 7 days post-therapy.
C. It is contraindicated in patients with hypersensitivity, severe hepatic impairment, and severe renal impairment.
D. It should be administered with care in patients with gout or a history of gout, with hyperuricemia.

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VIII. CLINICAL TRIALS

Various clinical trials studies are carried out for the drugs in various countries. The details of study are discussed bellow.

A. Japan

Japan hospitalized COVID-19 patients in Japan to assess the safety and efficacy of favipiravir.18 From February to May 2020, a total of 2158 cases were registered from 407 hospitals. In more than 90 percent of cases, favipiravir was administered at a dose of 1800 mg orally on day 1 followed by 800 mg twice daily on subsequent days. The median duration of therapy was 11 days. Rates of clinical improvement at 7 and 14 days were 73.8% and 87.8%, 66.6% and 84.5%, and 40.1% and % for mild, moderate, and severe disease, respectively [17]. Favipiravir in combination with nafomostat (transmembrane protease serine 2 inhibitor, previously used successfully in MERS-CoV-2 infection, acute pancreatitis and DIC) was found to be useful in a small case series consisting of 11 serious patients with COVID-19 in Japan [18].

B. Russia

The Russian Government approved favipiravir for the treatment of COVID-19, on the basis of encouraging early readouts from ongoing open-label randomized adaptive design clinical trial [COVID-FPR-01] in a 390-patient population. Results from 60 patients (40 on favipiravir and 20 on SOC) showed faster fever resolution (3 days vs. 6 days), rapid viral elimination (4 days vs. 9 days), and RT-PCR negativity up to 87.5% by day 10 [19].

C. China

An open-label control study in Chinese (N = 80) patients with mild to moderate COVID-19 was conducted to examine the effects of favipiravir vs. LPV/RTV for the treatment of COVID-19. It also showed a significant improvement rate in chest imaging (CT) (91.43% vs. 62.22%; p = 0.004) and higher improvement rates of chest CT in the group with viral clearance within 7 days of treatment were observed.

Multivariate logistic regression showed that the antiviral therapy independently affected the CT changes. Multivariable Cox regression showed that favipiravir was significantly (p = 0.026) associated with faster viral clearance, additionally the timing of antiviral therapy reached near significance (p = 0.055). Favipiravir was better (p < 0.001) tolerated than LPV/RTV. The major limitation of this study was that it was not randomized, doubleblinded, and placebo- controlled [20-21].

D. India

Recently, a phase 3, open label, randomized, multicenter study (CTRI/2020/05/025114, Glenmark Pharmaceuticals) was initiated in India to determine the efficacy of favipiravir in patients infected with mild to moderate COVID-19 in line with the global trials ongoing for this drug. The study enrolled patients with both mild (N = 90) and moderate (N = 60) COVID-19 by stratified randomization based on baseline disease severity. The primary objective of this study was to evaluate the clinical efficacy and safety of favipiravir combined with standard supportive care. The primary endpoint was time until the cessation of oral shedding of SARS-CoV-2 virus.

The secondary endpoints included— time from randomization to clinical cure based on clinician assessment, rate of clinical cure at day 4/7/10/14, rate of SARS-CoV2 RT-PCR negativity at day 4/7/10/14, time from randomization to first time use of high flow supplemental oxygen/noninvasive ventilation/ mechanical ventilation/extracorporeal membrane oxygenation, and time from randomization to hospital discharge. The total duration of study participation had been a maximum of 28 days from the day of randomization. The results from this study will be pivotal in the further substantiation of global evidence on the efficacy and safety therapy against COVID-19 [22].

E. Saudi Arabia

An ongoing open-labeled randomized controlled trial from Saudi Arabia is evaluating the efficacy of favipiravir and hydroxychloroquine combination therapy Identifier: NCT04392973] in the management of moderate to severe COVID-19. The experimental arm consists of favipiravir (dose: 1800 mg twice daily on day 1 followed by 800 mg twice daily for a total period of 10 days or till hospital discharge) plus hydroxychloroquine (400 mg twice daily on day 1 followed by 200 mg twice daily for next 4 days). The control arm includes the SOC treatment in COVID 19. The primary endpoint of the trial is time to clinical improvement and time to a negative PCR test.21 Results of this trial are eagerly awaited [23].

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F. USA

The research team at Stanford Medicine have recently commenced a double-blind, placebo- controlled trial (favipiravir vs placebo for 10 days) to assess the utility of favipiravir in reducing symptoms and the duration of viral shedding in outpatients with COVID-19.About 120 patients are expected to be enrolled beginning July 6, 2020 [24].

IX. SIDES EFFECTS

The adverse effects were relatively minor and included hyperuricemia and diarrhea in 5% of the participants and reduced neutrophil count and transaminitis in 2% of the participants. One study showed occurrence of psychiatric symptoms in association with favipiravir. Effect of favipiravir in QTc prolongation is still uncertain, with some pharmacodynamic studies suggesting a positive association, but a Japanese study suggesting otherwise. Overall, favipiravir has a good safety profile, as was confirmed by a large systematic review [25].

A. Hyperuricemia

Favipiravir use results in a dose-dependent increasing trend in the prevalence of hyperuricemia. This is however not associated with clinical manifestations. There has been no evidence that hyperuricemia caused by favipiravir leads to clinical manifestations; however, longer follow-up periods would be required to fully assess this risk [26-27].

B. Teratogenicity

There is evidence that favipiravir has a teratogenic potential and embryotoxicity. The Japanese drug safety bureau approval advises that favipiravir be given a strong warning against use in women of reproductive age and recommends precautionary statements on packaging and prescription alerts. The bureau also recommends that favipiravir should be avoided where alternative drugs could be used [28].

X. DRUG INTERACTIONS

Drug interactions are discussed bellow.

A. Concomitant use of pyrazinamide with favipiravir increases the levels of uric acid. Regular uric acid level monitoring is mandatory when these drugs are used together.
B. Favipiravir inhibits the metabolism of repaglinide through the CYP2C8 pathway, thus increasing its potential to cause toxicity (hypoglycemia, headache, increase incidence of upper respiratory tract infections, etc). Cautious concomitant use is recommended.
C. Theophylline increases the blood levels of favipiravir and adverse reactions to favipiravir may occur.
D. Famciclovir, sulindac: Efficacy of these drugs may be reduced when coadministered with favipiravir.
E. Acyclovir may delay the conversion of favipiravir into the active moiety, thus reducing its antiviral efficacy [29].

XI. ASSAY OF DRUG

There are many analytical tools that are used for the analysis of various pharmaceutical drugs, formulations, herbal formulations, crude drugs and their extracts [30-54]. These methods includes Uv-spectrophotometry, gas chromatography, HPLC, HPTLC, etc [55- 75].

XII. CONCLUSION

Thus, it is conclude that Favipiravir, can be a best option to remdesivir in the treatment of COVID-19.

XIII. DISCLOSURE OF CONFLICT OF INTEREST

The author declares no conflict of interest.

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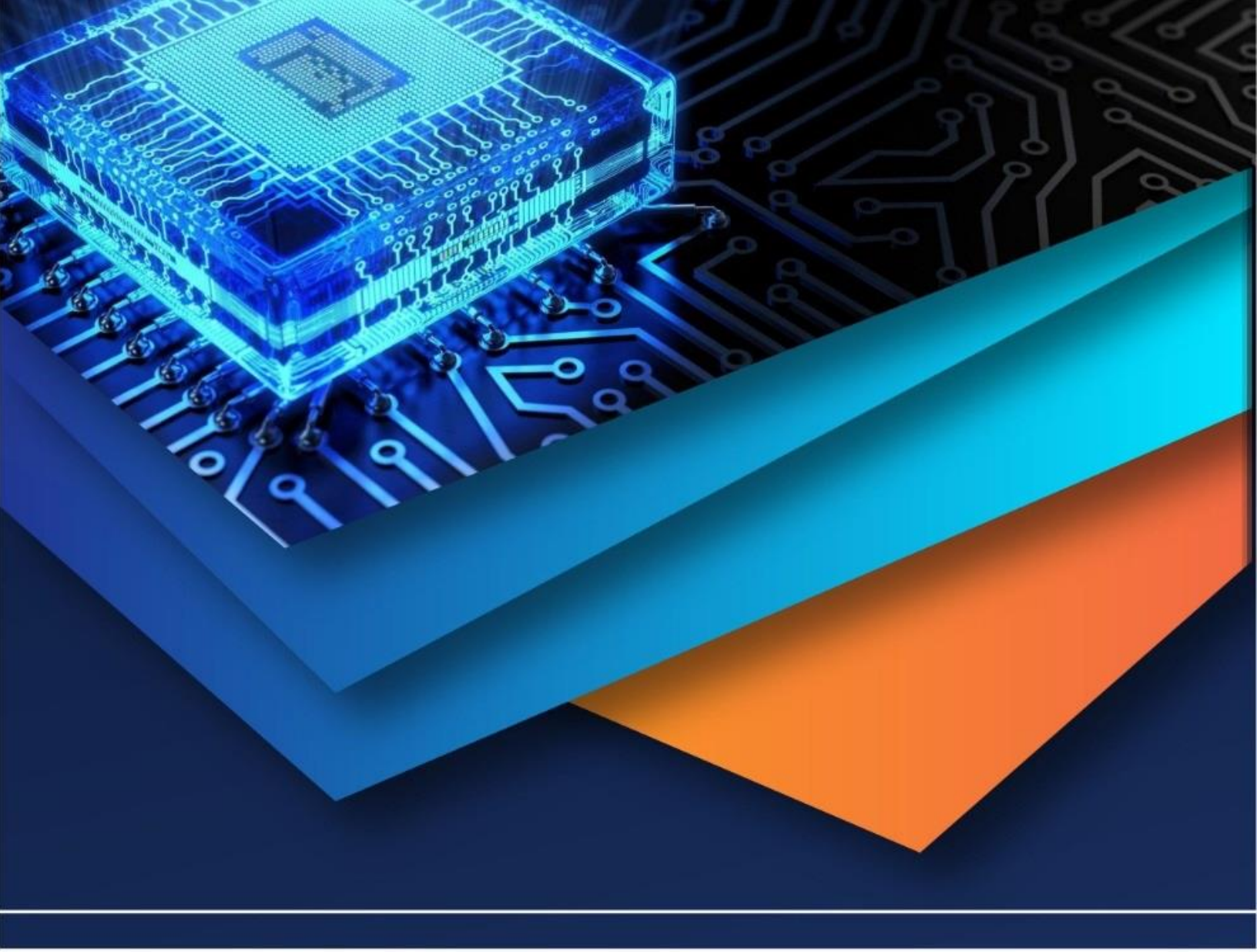
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