Indian Journal of Biotechnology and Pharmaceutical Research
Journal homepage : www.ijbpr.in
ISSN: 2347-3266
2021, 9(2): 1 – 8

Review Article

Therapeutic Use of Favipiravir in COVID-19: A Narrative Review

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ABSTRACT

The novel coronavirus (2019-nCoV) or COVID 19 has rapidly become the pandemic responsible for the global health crisis and thousands of dead and millions of suspected cases around the world. This review article includes the characteristics of COVID 19 and use of Favipiravir in the management of COVID 19. The RNA dependent RNA polymerase also named as nsp12 is the central component of viral replication and transcription machinery of coronavirus. And this appears to be the primary target for the antiviral drug Favipiravir. Favipiravir is an antiviral agent, which gets phosphorylated to Favipiravir RTP (active form) intracellularly, which inhibits viral replication by interacting with viral RNA polymerase. Favipiravir is effective against a wide range of influenza viruses, including strains which are resistant to the existing anti-influenza drugs. They have also shown effectiveness against other RNA viruses like arenavirus, filoviruses etc. This antiviral profile can make Favipiravir a potentially promising drug for the present pandemic of COVID 19. Pharmacokinetic profile of Favipiravir was generated from pkcsm online server.

KEY WORDS: COVID-19, Favipiravir, Influenza, Anti-viral, pandemic, nsp12

Introduction

The novel coronavirus (2019-nCoV) or coronavirus infectious disease 2019 (COVID-19) is a highly transmissible and deadly viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV- 2). [1],[2],[3] COVID-19 causes severe respiratory complications, followed by targeted organ damage [4],[5].

Received: 05.05.2021, Revised: 17.05.2021, Accepted: 24.05.2021

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According to recent reports, Glenmark describes the antiviral activity of Favipiravir against SARS-CoV-2 in *in vitro* model that has led to its arrival in the agenda of the potential candidate for COVID-19 treatment. This small stimulus gave good hope to the researchers who are screening drugs that can be repurposed for the treatment of COVID 19. Current pandemic situation and expected outcome is illustrated in Figure 1. This short review discovers a current understanding of the antiviral activity of Favipiravir against COVID 19.

Favipiravir overview

Favipiravir is chemically 6-fluoro-3-hydroxy-2-pyrazinecarboxamide. Its antiviral activity is attenuated to selective inhibition of the RNA-

dependent RNA polymerase of influenza virus. In addition to its antiviral activity against influenza viruses, it has also proved to have excellent efficacy against other RNA viruses like arenavirus, phleboviruses, hantavirus, flavivirus, enterovirus etc. [6] With such a unique mechanism of action and such a broad spectrum of antiviral activity, Favipiravir is a promising drug for many RNA viral diseases, including those for which there is no approved treatment pattern.

Favipiravir: Mechanism of Action

Favipiravir inhibits the Replication process of virus by incorporating into cells and gets converted into Favipiravir ribofuranosyl-5'-triphosphate (the active form) by host cells through phosphoribosylation process of favipiravir. The active form of Favipiravir further inhibits the RNA Dependent RNA Polymerase activity of SARS CoV-2 which in turn inhibits the replication of virus. [7]

Side effects/ Adverse Events

Fever associated with favipiravir use was observed in 19 of 2,970 cases. Thus, fever is not a rare side effect of favipiravir administration. [8] In repeated-dose toxicity studies, adverse effects like Decrease in RBC production, increase in liver function parameters (Alanine aminotransferase, alkaline phosphatase, Aspartate aminotransferase, and Total bilirubin), and increased vacuolization in hepatocytes. [9] Chemical properties, Pharmacokinetic and Toxicity profile of Favipiravir is illustrated in Figure 2. The pharmacokinetic profile of Favipiravir was observed from the PKCSM online server. [Table 1]

Toxicity prediction & drug-likeness was performed using OSIRIS Property Explorer program. Toxicity is accountable for the withdrawal and failure of new chemical entities. The toxicity profile of selected drugs was analyzed through the OSIRIS® Property Explorer program. This tool is accessible through cheminformatics.ch and chemistry.org. It is a freely available online software program that forecasts potential side effects such as mutagenicity, tumorigenicity, irritant, reproductive effects, drug-likeness and physicochemical properties analogous with a compound in a colour-coded format. The green colour indicates drug conform behaviour, yellow indicates medium risk, whereas the red colour shows a high risk for mutagenicity or low intestinal absorption. [Figure 2] [10], [11], [12].

1. ANTIVIRAL ACTIVITY OF FAVIPIRAVIR:

The antiviral activity of Favipiravir is unique from other antiviral agents like amantadine (Inhibits the virion M2 ion channel) or Oseltamivir (inhibits viral neuraminidase) since it directly inhibits the viral replication and transcription. [13] Favipiravir is a prodrug which gets phosphorylated by cellular enzymes to its active form favipiravir- ribofuranosyl-5-triphosphate (RTP). Its antiviral effect is attenuated by the addition of purine nucleic acids, indicating the viral RNA polymerase mistakenly recognizes Favipiravir-RTP as a purine nucleotide. RNA dependent RNA polymerase domains are not present in human cells, thus the action of favipiravir is specific to RNA viruses. According to data the inhibition of human DNA polymerase α and β by favipiravir (inhibition rates at 1 mM: −9.12 to 13.5%) is appreciably low. [14] These excellent characteristics of the drug make it one of the leading medicines of choice for RNA viral infections.

2. ACTION OF FAVIPIRAVIR ON COVID 19.

COVID-19 caused by SARS-CoV represent a diverse family of positive-sense RNA viruses capable of causing respiratory and enteric disease in human. The emergence of this virus from the CoV family necessitates the trial of antiviral agents that target the conserved elements of viral life such as replication and transcription of the positive-strand viral RNA genome. Upon infecting host cells, coronaviruses assemble a multi-subunit RNA-synthesis complex of viral non-structural proteins (nsp) responsible for the replication and transcription of the viral genome. [15] The key component of which is the non-structural protein 12 (nsp12). The nsp12 RNA-dependent RNA polymerase possesses some minimal activity on its own, but the addition of the nsp7 and nsp8 co-factors greatly stimulates polymerase activity. [16] SARS-CoV-2 nsp 12(RNA dependent RNA polymerase, RDRP) SWISS-MODEL expressed in Figure 3.

As of February 2020, 90 genome sequences of SARS-CoV-2 have been published and analysed in the Nexstrain repository (Nextstrain.org). The alignment of nsp 12 of the whole CoV family shows that the SARS-CoV-2 nsp 12 is nearly 96% identical to that of SARS-CoV. [17] Since Favipiravir acts on rdrp of RNA viruses, thus it's action on nsp12 rdrp of SARS-CoV-2 can be used as the basis to evaluate the efficacy of this drug in the light of this pandemic.

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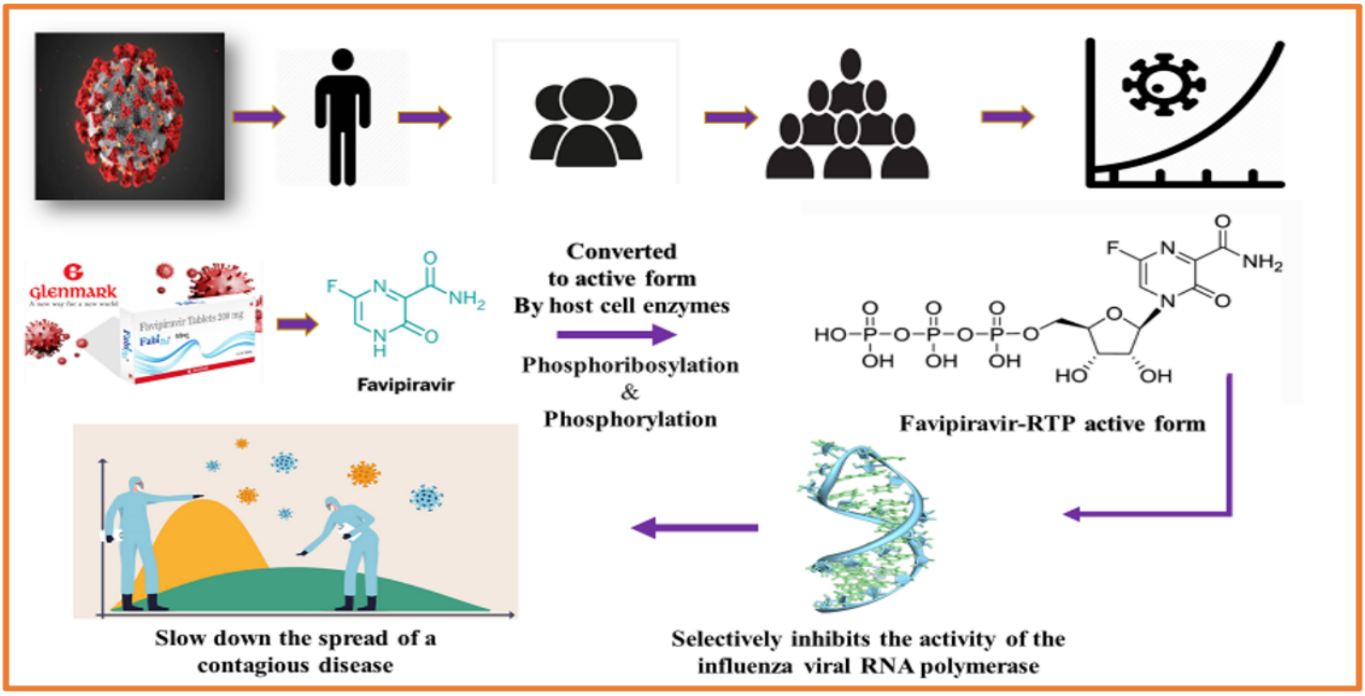

Figure 1: Current pandemic situation and expected outcome

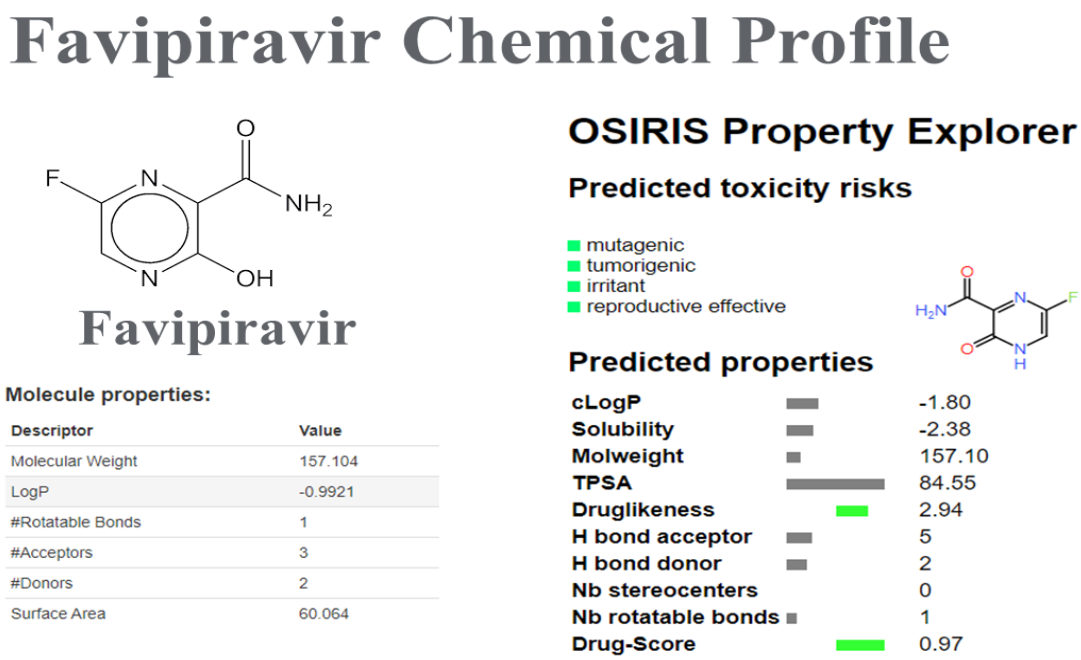

Figure 2: Chemical properties, Pharmacokinetic and Toxicity profile of Favipiravir

Completed clinical trials for the use of favipiravir in COVID-19.

S.No	Study title and design	References	Intervention	Outcomes
	Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study.	[18]	Control group- N=45 Lopinavir/Ritonavir Day 1-14 400mg/100mg BD Treatment group- N= 35 Favipiravir Day 1: 1600mg BD Day 2-14: 600mg BD	COVID-19 positive patients who were treated with favipiravir had faster viral clearance and better CT changes compared to that of the control group

	Safety and efficacy of favipiravir versus hydroxychloroquine in management of COVID-19: A randomised controlled trial	[19]	Group 1 N=50 Oseltamivir 75mg BD for 10 days and hydroxychloroquine 400mg BD on 1st day followed by 200mg BD from day 2-10. Group 2 N=50 Favipiravir Day 1: 1600mg BD Day2-10: 600mg BD	i. 90% patients in both groups attained viral clearance by the end of the study. ii. Raised transaminase levels due to favipiravir was resolved without withdrawal iii. Worldwide concern about hydroxychloroquine safety. iv. Favipiravir is safe and effective alternative for hydroxychloroquine in patients with mild or moderate COVID-19.
	A Prospective, Randomized, Open-Label Trial of Early versus Late Favipiravir Therapy in Hospitalized Patients with COVID-19	[20]	Group 1- N=44 Early treatment group Start favipiravir one day 1 Group 2- N=45 Late treatment group Start favipiravir on day 6	i. Reduction in time of defervescence ii. Significant improvement with fever.

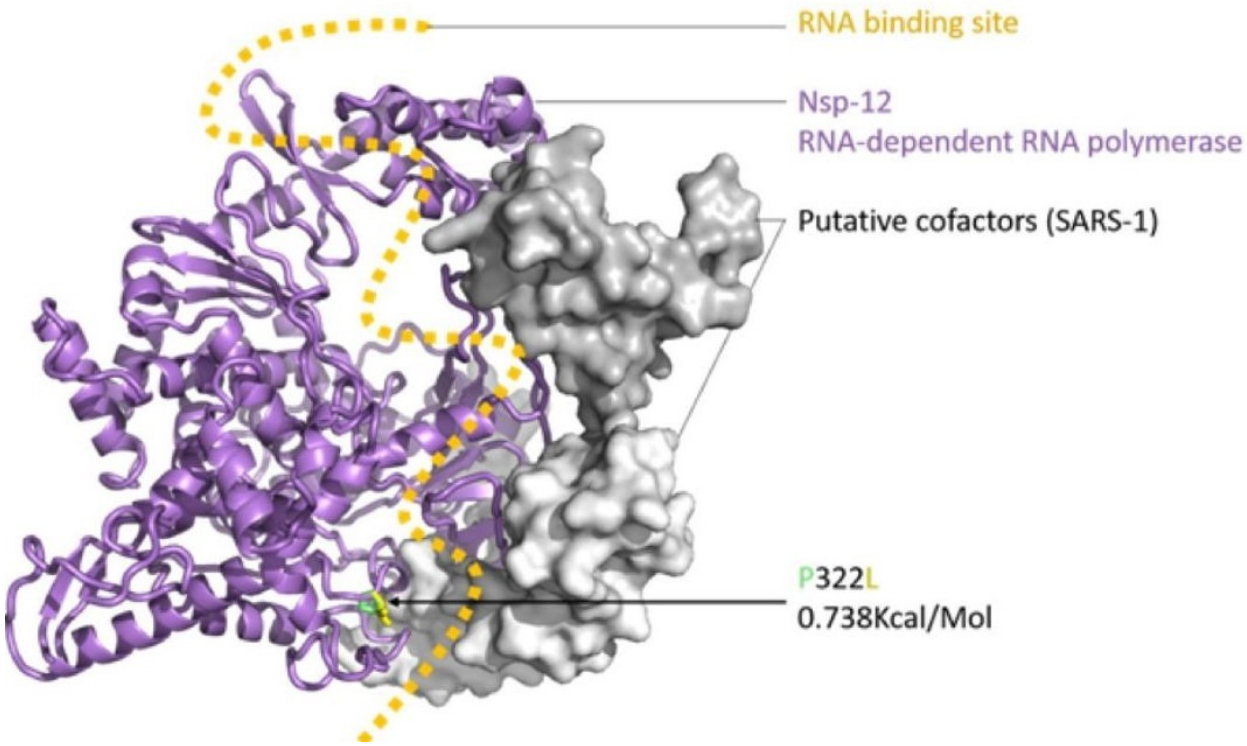

Figure 3: SARS-CoV-2nsp 12(RNA dependent RNA polymerase, RDRP) SWISS-MODEL expression

Conclusions

Antiviral activity of Favipiravir is specific and conserved to the viral life cycle such as replication, transcription and addition of purine nucleotide to RNA dependent RNA polymerase which are absent in humanss making it the right choice of drug. Favipiravir RTP does not exhibit any kind of activity against DNA dependent RNA polymerase or DNA polymerase. It proves that Favipiravir favours RNA virus more than a DNA virus and mammalian cells. Thus, the broader spectrum of Favipiravir drives our attention to pursue clinical trials for devastating infections. We strongly believe that Favipiravir will be a promising therapeutic agent for the present pandemic of COVID 19.

Acknowledgements

We would like to thank all the Health care professionals.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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How to Cite This Article:

Preethi L, Alexander Ravikumar, Ankul Singh S and Sarvesh Sabarathinam. Therapeutic use of Favipiravir in COVID-19: A narrative review. Indian J. Biotech. Pharm. Res. 2021; 9(2): 1 – 8.