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# Favipiravir - From Lungs to Liver and Beyond

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## Abstract

*Favipiravir is a purine nucleoside precursor, which was initially found to be effective against influenza. Favipiravir has subsequently shown to be effective against an array of human RNA viruses including SARS-CoV-2, Ebola and hepatitis C virus, to name a few. However, despite its broad-spectrum antiviral potential, the drug did not receive the type of attention it deserved, possibly often due to the lack of randomized, clinical trials involving this drug. While this shortfall may not be denied, it must also be borne in mind that favipiravir is often used in such viral infections where having a control group is not only challenging, but may also be unethical.*

***Keywords:*** *Favipiravir, influenza, COVID-19, Ebola, human RNA virus.*

## Introduction

Favipiravir (FPV) is a purine nucleoside precursor which acts by competitive inhibition of RNA-dependent RNA polymerase (RdRp). FPV was discovered and synthesized by Toyama Chemical. Co. Ltd., Tokyo, Japan. In 2014, FPV was approved in Japan for treatment for nivel epidemic influenza strains unresponsive to standard antivirals [1].

FPV is a prodrug that is metabolically activated into FPV-ribofuranosyl-5'-triphosphate in tissues by ribosylation and phosphorylation [2, 3]. FPV prevents transcription and replication of RNA viral genome by binding to and inhibiting RdRp [4, 2, 3]. RdRp is conserved only in RNA viruses and not in human cells, which makes FPV an excellent antiviral candidate [5]. The precise mechanism of the broad-spectrum antiviral action of FPV is yet to be understood. It has been postulated that FPV terminates nascent viral RNA strand and inhibits viral RNA synthesis [6]. It may also be that FPV becomes incorporated into nascent viral RNA strand preventing it's further extension [7].

There are also reports of induction of lethal viral mutagenesis by FPV [8]. A highly conserved lysine residue of the viral polymerase may also be the key to the broad-spectrum antiviral effect of FPV against positive-sense single-stranded RNA viruses [9].

FPV is well tolerated. Adverse events include increase in serum uric acid level, the reason FPV should be used with caution in the presence of hyperuricemia and gout or history of gout [10]. Patients may also experience mild to moderate diarrhea, an asymptomatic rise of serum transaminases and reduced neutrophil count [11].

Patented FPV was produced by Fujifilm Group, Tokyo, Japan under license from Toyama Chemical Co. Ltd., Tokyo, Japan. Initially the oral form was FPV was available, but subsequently intravenous preparations were developed to improve the efficacy of oral FPV. Generic FPV became widely available, including in Bangladesh, during the COVID-19 pandemic.

## Influenza

FPV inhibits the growth of all types (A, B and C) of influenza viruses (IV) in vitro [12, 13].

FPV also protects mice against lethal infection with different strains of IV [14]. It has also been demonstrated that administration FPV up to 72 hours following infection with seasonal IV strains like H1N1, H5N1 and H7N9 results in dose-dependent reduction of viruses in the lungs as well as mortality in mice [2, 12, 14, 15]. In humans, FPV results in faster alleviation of influenza symptoms and viral load reduction compared to placebo [16]. FPV, in combination with oseltamivir, yields better clinical improvement and viral RNA negativity, compared to oseltamivir monotherapy in critically ill influenza patients. However, no significant improvement in mortality was noted [17].

**COVID-19**

A randomized, comparative, open-labelled, phase-3 clinical trial established that when added to standard supportive care in patients with polymerase chain reaction (PCR) confirmed COVID-19 patients with mild to moderate symptoms, FPV results in early cessation of viral shedding and improvement in median time to clinical symptoms, with fewer adverse events compared to standard supportive care only [18]. Another prospective, multi-centre, clinical trial of FPV in COVID-19 in Japan also demonstrated a trend towards earlier virus clearance with zero mortality or disease progression in patients with mild-COVID-19 [19]. A systemic review has also shown significant clinical and radiological improvement in COVID-19 patients following administration of FPV compared to standard supportive care [20].

Our group also conducted a small study during the COVID-19 pandemic. This observational, prospective, single-centre study included 32 patients who were positive for SARS-CoV-2 by PCR. They received hydroxychloroquine and doxycycline in addition to standard of care. Besides, 9 patients also received oral favipiravir. They were followed up till they tested negative for SARS-CoV-2 by PCR on 2 consecutive occasions taken within 2 days. All of them had improvement of COVID-19 symptoms at discharge [21].

**Ebola**

In mouse model, FPV has been shown to effective both in post-exposure prophylaxis and as a therapeutic option in Ebola virus infection (EVD), when started at the initiation liver injury and detection of the virus in blood [22, 23]. A systematic review revealed 2 clinical trials of FPV in EVD from West Africa. In both these studies, reduced mortality was observed in EVD with low viral load following administration of FPV when compared with historical control groups [24].

**Scope Against Other Human RNA Viruses**

FPV is likely to be effective against an array of RNA viruses due to the conserved RdRp catalytic domain and it's ability to induce lethal mutagenicity. It has shown to induce lethal mutagenesis of the hepatitis C virus (HCV). Lethal mutagenesis refers to the elimination of a virus by inducing excess mutations during it's replication by a mutagenic agent, which is often a nucleotide analogue.

A study revealed that FPV in combination with ribavirin induces synergistic lethal mutagenesis of HCV. These 2 drugs do not induce mutations in same sites in the NS5B-coding region of HCV, which possibly explains this synergistic lethal mutagenesis, which potentiates their antiviral efficacy by 3-6 folds [8].

FPV in combination with ribavirin was administered in 2 patients diagnosed with Lassa fever. Both patients survived having only mild derangement of serum transaminases [25]. Yellow fever virus (YFV) infected hamsters have shown significant improvement with FPV [26]. Similarly, FPV reduced infectivity of Rift Valley fever virus in cell cultures as well as in animal models [27]. Promising results were obtained in a study using FPV to treat Punta Toro virus-infected rodents [28]. FPV was also found to be protective when administered to Sin Nombre virus (SNV) and Andes virus (ANDV) infected hamsters before the onset of viremia, suggesting role of FPV in post-exposure prophylaxis against these 2 viruses, which are main causes of Hantavirus pulmonary syndrome 9HPS) in the Americas [29]. FPV has also been shown to be highly effective in mice infected with Congo hemorrhagic fever (CCHF) virus [30].

**Conclusion**

Review of literature suggests that FPV is a highly promising antiviral agent effective against an array of human RNA viruses. However lack of robust, randomized controlled clinical trials remains the main obstacle for widespread use of this wonderful agent. While the need of double-blind, multi-centre, randomized clinical trials with FPV cannot be denied, it also has to be kept in mind that the drug has shown promise against many deadly human RNA viruses, against which such studies are difficult to conduct and in many cases having control arms may not be ethically permissible.

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