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Overview of Favipiravir in Devastating Covid 19

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ABSTRACT: Background: The global pandemic of Coronavirus disease 2019 (COVID-19) which lead to respiratory illness cases firstly in Wuhan city, Hubei province, China.

Main body: Generally, there is no drug so far developed specifically to treat the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2). The Covid-19 is caused by the coronavirus which is enveloped and this RNA virus replicates using an enzyme RNA dependent RNA polymerase. So, in order to treat this deadly virus, an eye focused on Favipiravir which is originally an Anti-viral drug developed for treatment of influenza.

Conclusion: This article furnishes the basic information on the development and make use of Favipiravir in the treatment of COVID-19.

Keywords: Favipiravir, COVID-19, SARS-COV-2, Anti-Viral agents.

I. BACKGROUND

Coronaviruses are a large family of RNA viruses; which show discrete point-like projections on their surface. In 2020, the WHO stated COVID-19 as a pervasive disease. The South china morning has reported first case can be tracked on Nov 17, 2019. While WHO stated first confirmed case on Dec 8, 2019 [1]. From December 2019 to March 2021, more than 121 million of COVID-19 cases have been recorded in more than 210 countries[2]. So far,the cases reported are 156,709,488 and 3,269,840 people died from COVID 19 as of 7 May,2021[3].

CORONA VIRUS

Evolution-

Human coronaviruses were first identified in 1965 which caused common cold. Later the decades the scientists come across various human and animal viruses and named accordingly based on their crown like appearance [4].

II. INTRODUCTION

The spell “coronavirus” is come from the “crown”-like morphology. Coronaviruses show prospectivedeadly human respiratory infections and tent to various diseases in animals and birds [5]. The investigation of this disease was then assigned to a new virus that is affiliated to the coronavirus family called coronavirus disease 2019 (COVID-19). It is also entitled SARS-CoV-2 as it is close to SARS-CoV. This hardback virus is very communicable and it has been spread very quickly and widely across the world[6].

The CoVs are positive-stranded RNA viruses secluded from variety of animal species. They arepassed on to humans where they spread illness that fluctuate from common cold to deadly diseases like MERS and SARS.

The virus classification is as follows- They belong to the Coronaviridae family, which is the largest family in the order Nidovirales comprising of subfamily Orthornavirae which includes four genera: alphacoronavirus, betacoronavirus, gammacoronavirus, and delta coronavirus. The viruses SARS-CoV, MERS-CoV, and COVID-19 are beta coronaviruses [7].

The variants of SARS-COV-2 according to US government interagency include variant of interest (B.1.526, B.1.526.1, B.1.525, B.1.617, B.1.617.1, B.1.617.2, B.1.617.3, and P.2), variant of concern (B.1.1.7, B.1.351, P.1, B.1.427, and B.1.429), and no variants of high consequence are so far identified in US [8].

MAIN TEXT

Introduction:

As the development ofa new drug is a cumbersome process, the foremost option in front of us is to concentrate on repurposing the existing drugs to vanquish this pandemic. One such development includes the happening of Favipiravir, which is an anti-influenza marketed earlier in Japan.

FAVIPIRAVIR

Favipiravir chemical structure –

Favipiravir is a pyrazine analogue with chemical formula $C_5H_4FN_3O_2$ and possess average

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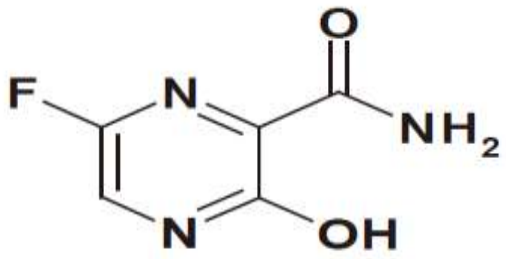
weight of 157.104 and synonyms include – Fapilavir, Favilavir, Favipiravir [9].
IUPAC name – 6-Fluoro-3-oxo-3,4-dihydro-2-pyrazinecarboxamide (French) [10]
When coming to the stereochemistry of the Favipiravir it is achiral and optical activity is unspecified with zero charge and zero stereo centres [11]

The chemical structure of Favipiravir mentioned below is taken from the reference [12]



Chemical structure of favipiravir (T-705).

Discovery of Favipiravir –

Favipiravir was discovered by Toyama Chemical Co., Ltd. Located in Japan by modifying the pyrazine analogue which was initially approved for clinical use in the cases which developed resistant to influenza. Favipiravir has been discovered for the treatment of life-threat viruses such as virus Lassa, virus Ebola, and it's now COVID 19[13].

Structure activity relationship of Favipiravir-

- Modification at 2'C-methyl-NTP leads to chain termination immediately
- Pyrazine ring containing smaller compounds are deeply docked with relatively smaller pocket of VP35
- Pyrrolidinone scaffold and benzene rings are essential for the appropriate binding with that of VP35 IID

The above data is taken away from the reference [14]

Mechanism of action of Favipiravir-

Favipiravir also defined as Avigan or T-705is a viral RNA dependent RNA polymerase inhibitor and it causes chain termination and prevent elongation of RNA in the cell. It also shows anti-viral activity against arenaviruses, bunyaviruses and filoviruses which are all RNA viruses causing fatal haemorrhagic fever and has no activity against DNA viruses [15]
The following pictorial representation of mechanism of action of Favipiravir is obtained from the reference [16]

Properties of Favipiravir-

- Favipiravir possess a high rate of absorption which is of 97.6%
- It possesses 54% of plasma protein-binding activity

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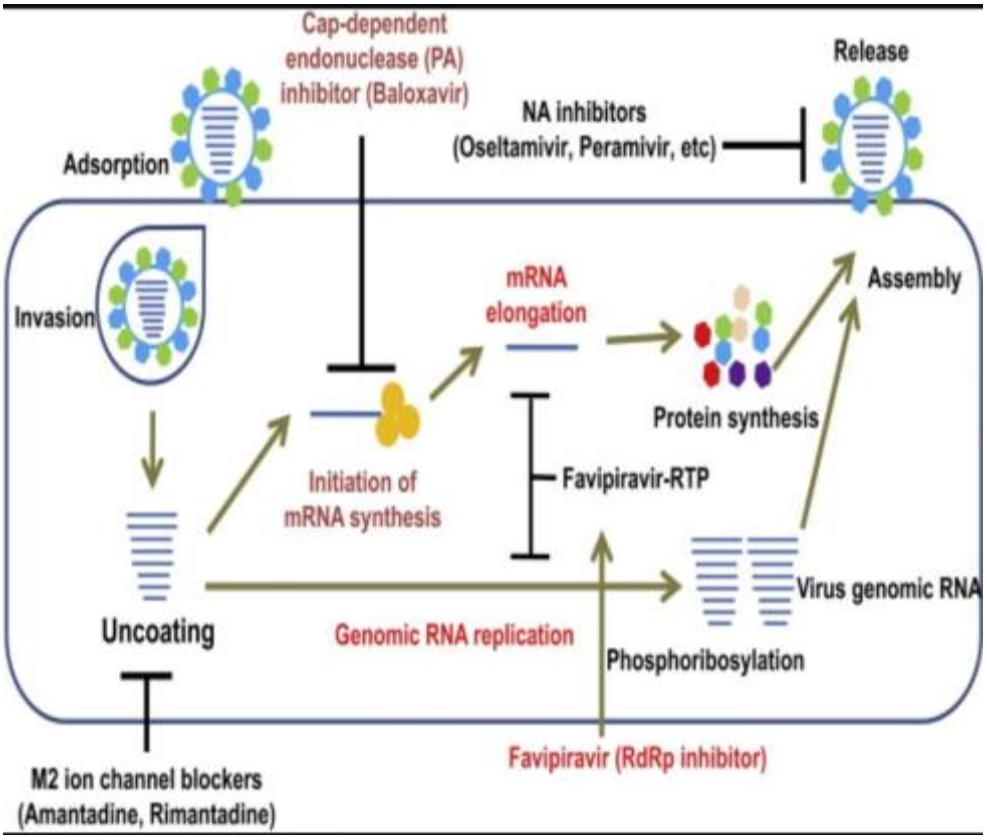

- Favipiravir being a prodrug metabolizes to favipiravir-RTP i.e., favipiravir-ribofuranosyl-5' -triphosphate
- Renal excretion is the mode of elimination of metabolites of Favipiravir

The above data is collected from the reference [17]

Method of Synthesis of Favipiravir-

1. Methyl 3-amino-6-bromopyrazine-2-carboxylate when reacted with sodium nitrite leads to production of 6-bromo-3-methoxypyrazine-2-carboxylate and reaction takes place in presence of acid.
2. The product obtained above upon reaction with diphenyl methenamine produce methyl 6-amino-3-methoxypyrazine-2-carboxylate.
3. This upon reacting with ammonia water produce 6-amino-3-methoxypyrazine-2-carboxamide.
4. In presence of Olahs reagent the above obtained compound reacts with sodium nitrite to give 6-fluoro-3-methoxypyrazine-2-carboxamide.
5. This compound undergoes reaction with sodium iodide in TMSCI to produce Favipiravir.

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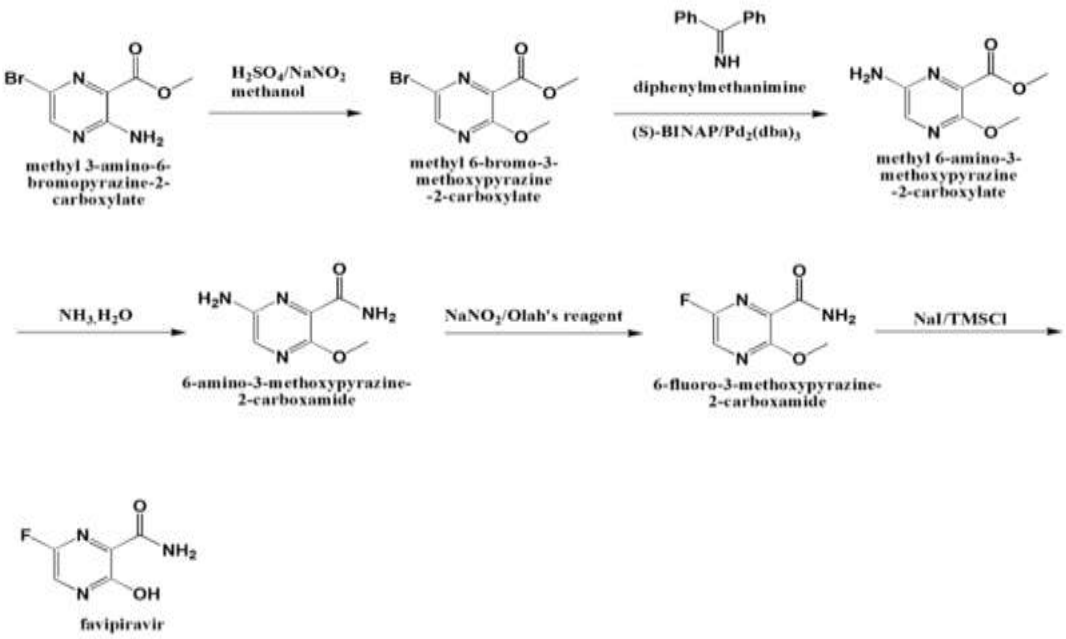
The above method of synthesis and the reaction mentioned below is referred from [18]

Favipiravir in Influenza and COVID 19

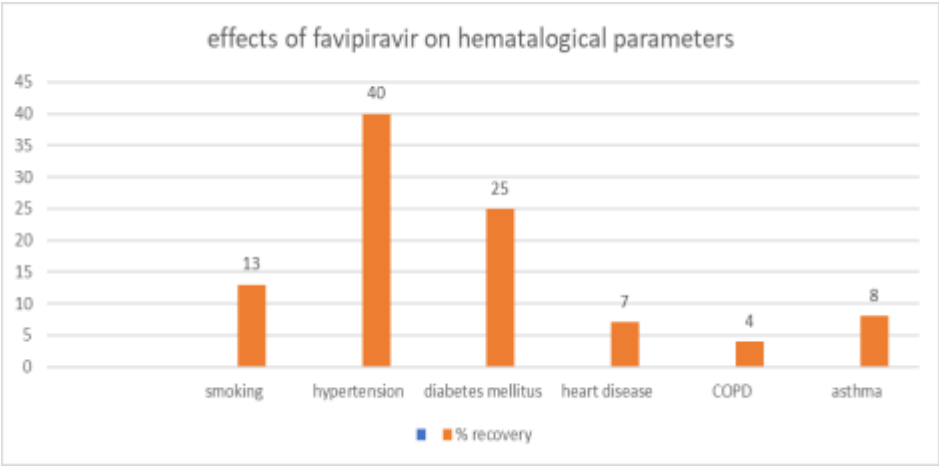


In influenza,favipiravir is found to lower the TNF-alpha levels and pulmonary viral load in the lungs. And also used in case of post exposure prophylaxis and in treatment of various RNA virus infections (like rabies, Ebola, Lassa fever and Norovirus). The approved dose for influenza is 1600 mg two times a day on first day and next four days 600 mg is given two times a day [19].

According to non-linear pharmacokinetics using a PK model 2,400 mg twice daily of favipiravir is given as loading dose one day one and for next nine days 1600 mg is given as maintenance dose to treat SARS-COV-2 which is similar to the dose given in Ebola [20]

Effectiveness of Favipiravir in discrete conditions –

wwThe percentage recovery using Favipiravir in various conditions like smoking, hypertension, diabetes, heart disease, COPD, asthma is represented in the below bar graph and the obtained from the reference [21]



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Adverse events-

- Liver enzyme abnormalities
- Psychiatric symptoms
- Gastrointestinal symptoms
- Serum uric acid elevations
- QT prolongation and teratogenic effects [22]

Contraindications-

- In case of hypersensitivity to favipiravir
- Severe renal impairment
- Severe hepatic impairment
- Pregnancy and breastfeeding

The above data is gathered from the reference [23]

Clinical uses-

- In the treatment of re-emerging viral infections due to influenza virus
- In case of not responding to the antiviral agents that are in exist [24]

CLINICAL DATA

The clinical efficacy of Favipiravir in COVID 19 has been studied using phase2 and phase3 clinical trials. In a trial involving randomized, prospective, controlled and open label multi-centre trials on 240 patients with COVID 19 suffering from critical illness the favipiravir showed to decrease the time

III. CONCLUSION

These results suggest that favipiravir can induce mutagenesis in the virus, providing a proof of principle for the use of favipiravir derivatives or mutagenic nucleosides in clinical treatment of SARS-cov-2(covid-19).

Abbreviations:

COVID-19: Coronavirus disease 2019; SARS-CoV: Severe acute respiratory syndrome coronavirus; MOA- mechanism of action; SAR-structure activity relationship

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Declarations

Ethics approval and consent to participate:

It is not applicable.

Consent for publication:

It is not applicable.

Competing interests:

The authors declare that they have no competing interests.

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