Review Article

Molnupiravir and Favipiravir in the therapeutics of SARS-CoV-2 - A review

Ayush Singh[1, 2], Riya Sehgal[1], Karamjit Kaur[1], Manju[1], Jatin Isher[1, 3], Neeru Kumari[1, 4]

From, [1]Department of Pharmacy, Global Group of Institutes, [2]Department of Production, Alkem Laboratories Limited, Baddi, Solan, Himachal Pradesh, [3]Department of Quality Assurance, Kwality Pharmaceuticals Ltd., [4]Department of Quality Control, Kwality Pharmaceuticals Ltd., Amritsar, Punjab, India

Correspondence to: Ayush Singh, Department of Production, Alkem Laboratories Limited, Baddi, Solan, Himachal Pradesh - 173205 and Department of Pharmacy, Global Group of Institutes, Amritsar, Punjab, India-143501. **Email:** ayushsingh28659@gmail.com

ABSTRACT

SARS-CoV-2 led to several unwanted deaths all across the globe since 2020. High mortality rates are seen by this virus. As per the various theories, numerous variant and deadly strains are come into existence in the world due to COVID-19 pandemic. To treat deadly strains of this virus, various anti-viral are drugs that are utilized in the therapeutics of COVID-19. Few antivirals are molnupiravir, favipiravir, remdesivir, alisopirivir and many more. Molnupiravir was originally developed to treat influenza at Emory University but also reports abandoned for mutagenicity concerns. Favipiravir is a prodrug has been approved to treat the influenza rather than the seasonal influenza and this medication selectively inhibition of RdRp. This review generally covers the two potent oral antiviral molnupiravir and favipiravir investigation.

Key words: Molnupiravir, Favipiravir, COVID-19, SARS-CoV-2, Clinical data, Chemical.

Coronavirus disease 2019 (COVID-19), the illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had a devastating effect on the world's population resulting in more than 5.4 million deaths worldwide and emerging as the most significant global health crisis since the influenza pandemic of 1918. Since being declared a global pandemic by the World Health Organization (WHO) on March 11, 2020, the virus continues to cause devastation, with many countries continuing to endure multiple waves of outbreaks of this viral illness [1]. COVID-19 outbreak in China, led to tremendous breakdown in the healthcare sector. With emerging therapies including vaccines and anti-viral therapies, it is necessary to research on their clinical effects on treatment. Most of the drugs used in clinical practice have limited clinical experience [2].

With the vast expanding knowledge of the SARs-CoV-2 virology, newer potential targets are being identified. We have summarized the clinical picture of two anti-virals Molnuoiravir and Favipiravir. Molunipiravir is the first oral antiviral medicine to show considerable and convincing antiviral activity in vitro and in animal models. Shreds of evidence suggest that molnupiravir reduces hospitalization and mortality among unvaccinated individuals [3]. Favipiravir is also one such drug with a crucial role in treating mild to moderate COVID-19. With its oral form it can be easily administered and meant for treatment in mildly ill COVID-19 patients [4].

Variants of SARS-CoV-2

Since the COVID-19 pandemic first began in December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus has continuously evolved with many variants emerging across the world. These variants are categorized as the variant of interest (VOI), variant of concern (VOC), and variant under monitoring (VUM). As of September 15, 2021, there are four SARS-CoV-2 lineages designated as the VOC (alpha, beta, gamma, and delta variants). VOCs have increased transmissibility compared to the original virus, and have the potential for increasing disease severity [5]. All the variant of SARSCoV-2 are enlisted in the Table No. 1.

Molnupiravir

Molnupiravir is the drug that came into existence worldwide for the treatment of COVID-19. Molnupiravir (Emory Institute of Drug Development-2801 [EIDD-2801]/MK-4482) is one of the upcoming oral drugs which is promising. This oral agent was developed by Drug Innovation Ventures at Emory University, and later acquired by Ridgeback therapeutics in partnershipwith Merck & Co, USA. In general, antiviral drugs tested so far usually terminate the elongation of RNA-chain by targeting the viral polymerases but such anti-virals have not shown a very promising role in the treatment of SARS-CoV-2

infections [14]. This drug affects the RNA-dependent RNA-Polymerase enzyme used by the coronavirus for transcription and replication of its viral RNA genome [15].

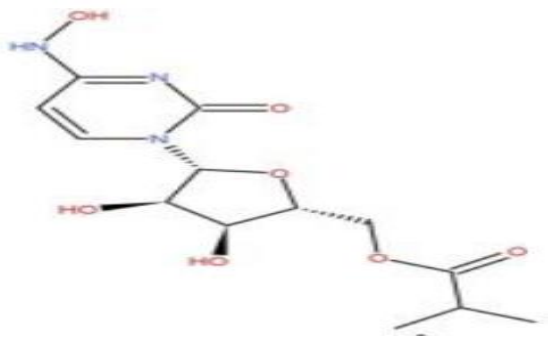


Figure 1: Chemical Structure of Molnupiravir

Molnupiravir is an isopropyl ester prodrug of the nucleoside analogue β-d-N4–hydroxycytidine (NHC or EIDD-1931). Molnupiravir interferes with the replication of various viruses, including SARS-CoV-2. It inhibits SARS-CoV-2 replication in human lung tissue, blocks SARS-CoV-2 transmission in ferrets and reduces SARS-CoV-2 RNA in patients [15].It is β-D-N4-hydroxycytidine (EIDD-1931) is an orally bioavailable ribonucleoside analogue and has broad-spectrum activity against numerous RNA viruses in animal models [16-18]. Molnupiravir (EIDD-2801), is a prodrug of β-D-N4-hydroxycytidine (EIDD-1931) and is rapidly converted into EIDD-1931 in the plasma by the host's esterase. After entering host cells, EIDD-1931 is intracellularly transformed into its active form, β-D-N4-hydroxycytidine-triphosphate, which inhibits viral replication through its incorporation into the viral genome. Consequently, the accumulation of mutations results in the viral error catastrophe.

Mechanism of action

Previously, it was developed to treat influenza and was recognized as another candidate for antiviral drugs. Understanding the mechanism of molnupiravir at the molecular level is critical to the further development of antiviral drugs. The drug is activated through metabolism in the body. Once inside the cell, it becomes an RNA-like component. In the first step, RNA polymerase incorporates these components into the RNA genome of the virus. In the next step, RNA-like components are paired with viral genetic material components.

Viral RNA contains several mutations when it multiplies to produce new viruses, preventing the reproduction of the pathogen. This viral drug causes mutations in other RNA viruses and prevents them from expanding. Molnupiravir, a promising drug, is in the third phase of studies. When molnupiravir enters the cell, the active molnupiravir forms N-hydroxycytidine hydrate (NHC triphosphate (MTP), which can be replaced by CTP or UTP by RdRp of SARS-CoV-2.

Initially, when RdRp uses positive-strand genomic RNA for the synthesis sub-genomic RNA and negative-strand genomic RNA as a template, it regularly substitutes M for U or C. In the next step, +gRNA or +sgmRNA can be used from RNA including M as a template. Then mutations are formed in positive-stranded genomic RNA products due to the presence of M in negative strand genomic RNA, and these products prevent the formation of healthy new viruses.

At the end of this two-step mechanism, the mechanism of molnupiravir and its activated type were shownto result in RNA mutations through polymerases of other viruses. According to previous studies, molnupiravir-induced lethal mutagenesis was determined by a relatively high selectivity of MTP for incorporation as a CTP analogue and the indiscriminate incorporation of either ATP or GTP when MNP is centralized in the template strand [19].

Favipiravir

Favipiravir (6-fluoro-3-hydroxypyrazine-2-carboxamine) which is a prodrug, is an anti-influenza drug that has shown broad-spectrum antiviral activity against a variety of other RNA viruses. This antiviral drug metabolized intracellularly into its active ribonucleoside 5′-triphosphate form that acts as a nucleotide analogue to selectively inhibit RdRp and induce lethal mutagenesis. Recently, several studies reported in vitro inhibitory activity of favipiravir against SARS-CoV-2 with 50% EC50. Based on these results, more than 20 clinical trials on the management of COVID-19 by favipiravir are ongoing.

Table 1: Variant of SARS-CoV-2

VARIANT	STRAIN	DESCRIPTION	REFERENCES
VOC	Alpha	Detected in Oct 2020 and correlated with a significant increase in the rate of COVID-19 infection.	[11]
VOC	Beta	Detected in 18 December 2020 in South Africa.	[12]
VOC	Gamma	Detected in Tokyo on 6 January 2021 by National Institutes of Infectious Diseases	[13]
VOC	Delta	Detected in 6 May 2021 and it is globally dominant variant	[14]
VOC	Omicron	Detected in 26 November 2021 in South Africa.	[15,16]
VOI	Lambda	Detected in Peru in August 2020	[17]
VOI	Mu	Detected in Colombia in January 2021.	[18]

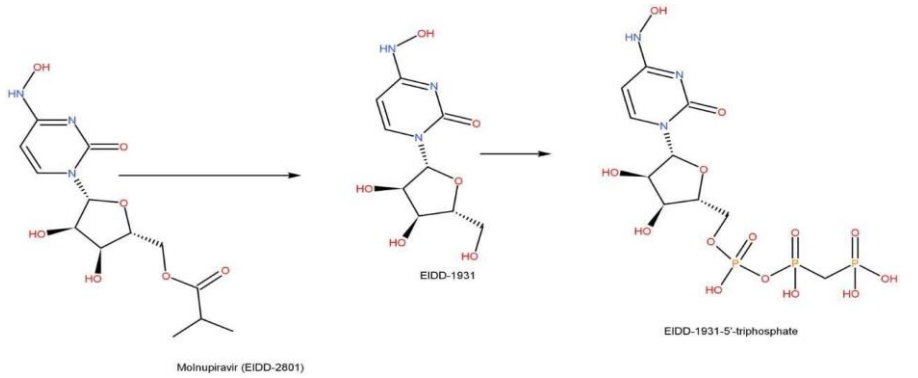


Figure 2: Mechanism of action of Molnupiravir

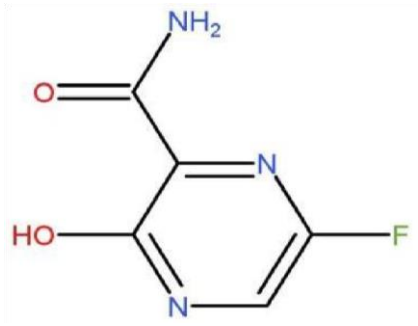


Fig 3: Chemical Structure of Favipiravir

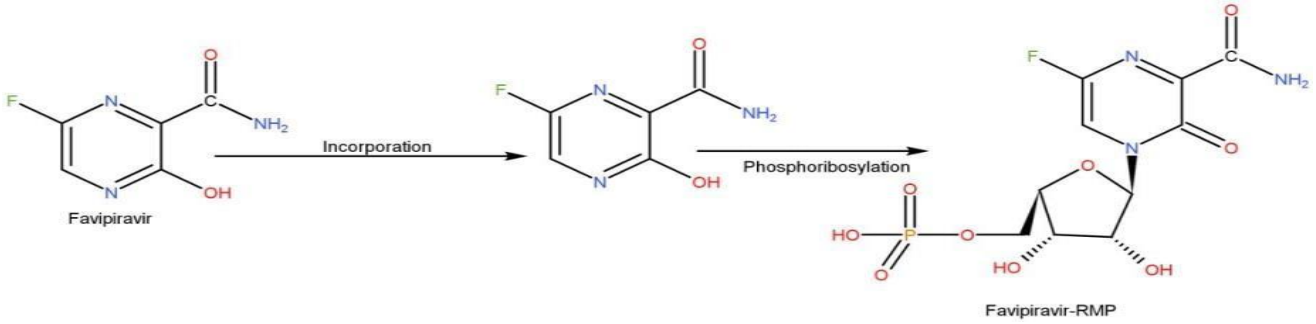


Figure 4 (a): Mechanism of Favipiravir

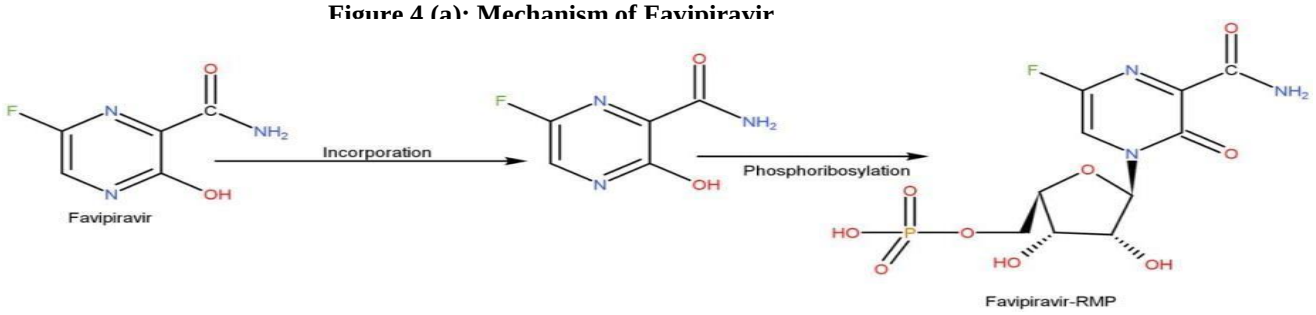
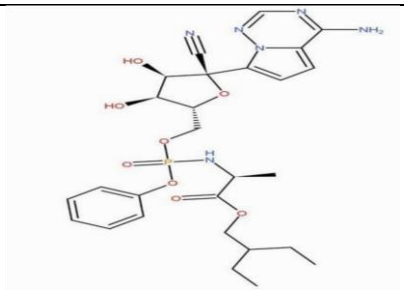
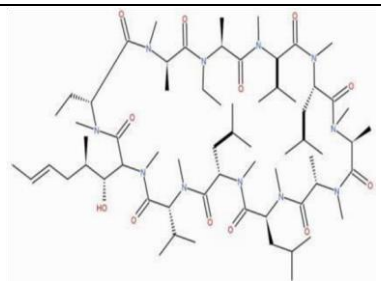


Figure 4(b): Mechanism of action of Favipiravir (Favipiravir-RMP phosphorylates and produce Favipiravir-RTP in active form)

Table 2 - Miscellaneous Anti-viral drugs used in the treatment of Covid-19 and their respective deadly strains

Drug	Structure	Mechanism of Action
Remdesivir		The active metabolite of this drug interferes with the action of RdRp and evades profeeding by viral exoribonucleaases causing a reduction in the synthesis of RNA
Alisopirivir/ Debio 025/ UNIL-025		Abolish cyclophilin A or rotamase A

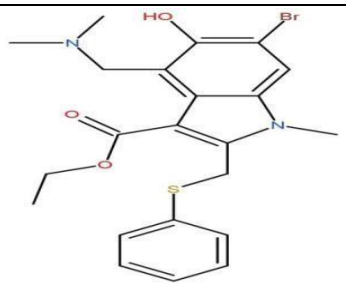
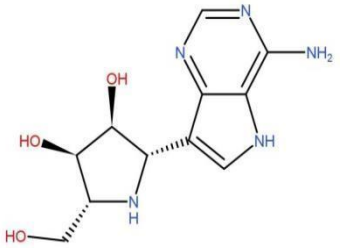
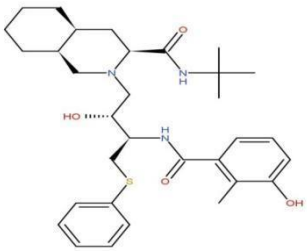
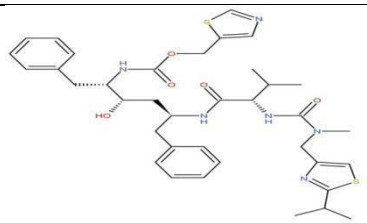
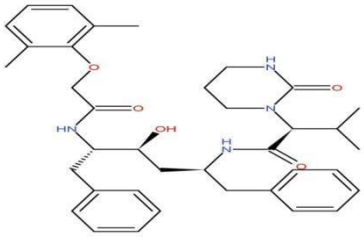
Umifenovir		It suppress the membrane fusion of influenza virus and orifice impinging betwixt the virus and target host cell.
Galidesivir/ BCX4430/ Immucillin-A		This is under Phase 1 human trail in Brazil for SARS-CoV-2 and possess broad spectrum antiviral potency against virus belongs to RNA families involving Bunyaviruses, Marburg virus disease, Zika virus, Ebola virus, Arenaviruses, Flaviviruses, Phleboviruses, Paramyxoviruses
Nelfinavir		This medication is a competitive inhibitor and protease inhibitor with activity against HIV-1.
Lopinavir		This drug also inhibit the HIV protease enzyme by producing an enzyme inhibitor complex, thus preventing the segmentation of the gag-pol polyproteins
Ritonavir		Generally, this medication abolishes the HIV viral proteinase enzyme that normally breaks the structural and replicative proteins that arises from major HIV genes.

Table 3: clinical trial of several medications that are utilized in the therapeutics of SARS-CoV-2

Identifier number	Drug	Sponsor Sponsor	Status	Enrollment
NCT04323527	Chloroquine Diphosphate	Fundação de Medicina Tropical Dr. Heitor Vieira Dourado	Completed	278
NCT04343729	Methylprednisolone	Fundação de Medicina Tropical Dr. Heitor Vieira Dourado	Completed	416
NCT04853199	Quercetin	Hôpital Universitaire Sahloul	Recruiting	200
NCT04334148	Hydroxychloroquine	Adrian Hernandez	Completed	1360
NCT04510493	Canakinumab	University Hospital, Basel, Switzerland	Completed	116
NCT04842747	VERU-111	Veru Inc.	Recruiting	300
NCT04602000	CT-P59	Celltrion	Completed	1642
NCT04978025	Colloidal silver	Hôpital Universitaire Sahloul	Recruiting	50
NCT04646044	Bempegaldesleukin	Nektar Therapeutics	Completed	30
NCT04560231	Remdesivir	Lahore General Hospital	Recruiting	30

NCT04477993	Ruxolitinib	Vanderson Geraldo Rocha	Terminated	5
NCT04780581	Dexamethasone	Fundación Instituto de Estudios de Ciencias de la Salud de Castilla y León	Recruiting	290
NCT04406246	Nitazoxanide	Materno-Perinatal Hospital of the State of Mexico	Completed	150
NCT04473274	Pioglitazone	Samaritan Health Services	Completed	10
NCT04668209	CX4549	University of Arizona	Recruiting	40
NCT04414618	Opaganib	RedHill Biopharma Limited	Completed	42
NCT04409509	CSL312	CSL Behring	Completed	124
NCT04341116	TJ003234	I-Mab Biopharma Co. Ltd.	Recruiting	384
NCT04632381	Zotatifin	Effector Therapeutics	Recruiting	36
NCT04672564	Carrimycin	Shenyang Tonglian Group CO., Ltd	Recruiting	300

Mechanism of action

Favipiravir-RTP binds to and inhibits RdRp, which ultimately prevents viral transcription and replication. Favipiravir is a purine base analogue that is converted to active favipiravir-RTP by intracellular phosphoribosylation. It is a selective and potent inhibitor of RdRp of RNA viruses. Favipiravir is incorporated into the nascent viral RNA by error-prone viral RdRp, which leads to chain termination and viral mutagenesis [20].

The RdRp existing in various types of RNA viruses enables a broader spectrum of antiviral activities of favipiravir. After RNA viral incorporation, favipiravir-RTP works as a mutagen, which is capable of fleeing coronavirus repair machinery. The favipiravir-RTP adds to the pressure on CoV nucleotide content, which already has a low cytosine in the SARSCoV-2 genome. In total, along with the increased frequency of mutation, favipiravir-RTP has a positive effect on SARSCoV-2 by a cytopathic effect, which is induced by the virus, reduction in the number of viral RNA, and infectious particles. Favipiravir has a strong binding affinity to RdRp with a docking score of 6.925. Hence, targets the Achilles heel (RdRp complex) of SARS-CoV-2.

Miscellaneous Anti-Viral agents in the therapeutics of SARS-CoV-2

We have also elaborated the list of other drugs that are being employed in the treatment of COVID-19. There are several kinds of anti-viral drugs other than molnupiravir and favipiravir for the treatment of COVID-19.

Clinical data

Major drugs that are under clinical trial of various drugs under several phases for the development of new pharmaceutical medicament for the treatment of SARS-CoV-2 from different genera (or different classes of drugs) are entitled in the Table 3.

Conclusion and Future Scope

The review concludes that antivirals used in the treatment of coronavirus can serve excellent in treatment. Anti-viral drugs prevent viral replication through several kinds of mechanisms or physiology. This review justifies that molnupiravir (MK-4482) is a prodrug used to treat mild-to-moderate COVID-19. MK-4482 is the first oral, direct-acting antiviral that shows highly effective at reducing nasopharyngeal SARS-CoV-2 infection. Favipiravir act as a prodrug and undergoes ribosylations and phosphorylation intracellularly to become active favipiravir-RTP. This drug inhibits RdRp at long last prevent viral transcription and replication. Both drugs are not preferred in pregnancy because several studies and evidence show that molnupiravir causes fetal harm. During clinical treatment, these newer generation drugs serve as a potential drug for the therapeutics of COVID-19. Intensive investigations related to antiviral drugs that are utilized in the therapeutics of SARS-CoV-2 for specific pharmacological actions, and their mechanism of action, safety, and efficacy could be the future research interest to explore the drugs exhaustively. There is still an ever-increasing need for high quality evidence to investigate newer and effective therapies for COVID-19.

Abbrevatons

+sgmRNA: Positive-strand Subgenomic mRNA; **ATP:** Adenosine triphosphate; **CTP:** Cytidine triphosphate; **EC:** Effective concentrations; **EIDD:** Emory Institute for Drug Development; **Favipiravir-RTP:** Favipiravir ribofuranosyl-5B-triphosphate; **GTP:** Guanosine-5'-triphosphate; **HIV:** Human immunodeficiency virus; **RdRp:** RNA-dependent RNA polymerase; **SARS-CoV-2:** Severe Acute Respiratory Syndrome Corona virus 2; **UTP:** Uridine triphosphate; **VOC:** Variant of Concern; **VOI:** Variant of Interest.

REFERENCES

1. Singh AK, Singh A, Singh R, et al. Molnupiravir in COVID-19: A systematic review of literature. Diabetes Metab Syndr [Internet]. 2021; 15(6): 102329.
2. Zarenezhad E, Marzi M. Review on molnupiravir as a promising oral drug for the treatment of COVID-19. Med Chem Res [Internet]. 2022; 31(2): 232-43.
3. Kabinger F, Stiller C, Schmitzová J, et al. Mechanism of molnupiravir-induced SARS-CoV-2 mutagenesis. Nat Struct Mol Biol [Internet]. 2021; 28(9): 740-6.

4. Baranovich T, Wong S-S, Armstrong J, et al. T-705 (favipiravir) induces lethal Mutagenesis in influenza A H1N1 virusesin vitro. J Virol [Internet]. 2013; 87(7): 3741-51.
5. Reynard O, Nguyen X-N, Alazard-Dany N, et al. Identification of a new ribonucleoside inhibitor of Ebola virus replication. Viruses [Internet]. 2015; 7(12): 6233-40.
6. Toots M, Yoon J-J, Hart M, et al. Quantitative efficacy paradigms of the influenza clinical drug candidate EIDD-2801 in the ferret model. Transl Res [Internet]. 2020; 218: 16-28.
7. Urakova N, Kuznetsova V, Crossman DK, et al. B-d -N4-hydroxycytidine is a potent anti-alphaviru compound that induces a High Level of mutations in the viral genome. J Virol [Internet]. 2018; 92(3).
8. Painter, George R, Bluemling, et al. N4-hydroxycytidine and derivatives and anti-viral uses related there to published 2020-09-03, assigned to Emory University.
9. ClinicalTrials.gov NCT04405739. The Safety of Molnupiravir (EIDD-2801) and its Effect on Viral Shedding of SARS-CoV2 (END-COVID)
10. Clinicaltrails.gov NCT04402203. Study on Safety and Efficay of Favipiravir (Favipira) for COVID-19 Patient in selected Hospitals of Bangladesh.
11. New evidence on VUI-2020/2021 and review of the public health risk assessment. 15 December 2020.
12. Lowe D, “The new mutations” American Association for the Advancement of Science 22 December 2020.
13. Faria NR, Claro IM, Candido D, et al, “Genomic Characterisation of an emergent SARS-CoV-2 lineage in Manaus: prelimary findings.March 2021.
14. Cutler S. “Nepal variant”: what we’ve learned so far. The Conversation [Internet]. 2021 Jun 16 [cited 2022 15. Aug 1];
15. Torjesen, Ingrid, 2021. COVID-19; Omicron may be more transmissible than other variants.
16. Callaway, Ewen. Heavily mutated corona virus 2021.
17. COVID-19 coronavirus: Ultra-contagious Lambda variant. 2021; 6(7).
18. O’Neill L. Mu: everything you need to know about the new coronavirus variant of interest. The Conversation [Internet].

How to cite this article: Ayush Singh, Riya Sehgal, Karamjit Kaur, Manju, Jatin Isher, Neeru Kumari. Molnupiravir and Favipiravir in the therapeutics of SARS-CoV-2 - A review. Indian J Pharm Dug Studies. 2022: 1(3) 73-78.

Funding: None *Conflict of Interest: None Stated*