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REVIEW ARTICLE

Molnupiravir: A new candidate for COVID-19 treatment

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Abstract

The novel coronavirus disease 2019 (COVID-19) emerged in late December 2019 in china and has rapidly spread to many countries around the world. The effective pharmacotherapy can reduce the mortality of COVID-19. Antiviral medications are the candidate therapies for the management of COVID-19. Molnupiravir is an antiviral drug with anti-RNA polymerase activity and currently is under investigation for the treatment of patients with COVID-19. This review focuses on summarizing published literature for the mechanism of action, safety, efficacy, and clinical trials of molnupiravir in the treatment of COVID-19 patients.

KEYWORDS
antiviral drugs, COVID-19 treatment, EIDD-2801, MK-4482, molnupiravir, novel coronavirus disease 2019

1 | INTRODUCTION

In December 2019, novel coronavirus disease 2019 (COVID-19) was recognized to cause a cluster of pneumonia cases in Wuhan, China.[1,2] It has rapidly spread to other areas of the world.[2–4] In March 2020, the World Health Organization (WHO) declared COVID-19 as a global pandemic.[5] As of December 23, 2021, there have been 276 436 619 confirmed cases of COVID-19, including 5 374 744 deaths, reported to WHO.[6] Person-to-person contact and respiratory droplets are the two major routes of transmission of COVID-19 infection to humans. The usual incubation period for COVID-19 is 14 days.[7] The Final diagnosis of COVID-19 is based on the real-time reverse-transcriptase-polymerase chain reaction method.[8,9] Clinical manifestations of COVID-19 are fever, dry cough, sore throat, shortness of breath, fatigue, headache, loss of taste or smell, diarrhea, and nausea.[2,3,10,11] Based on the epidemiologic data, COVID-19 has a lower mortality rate with a higher degree of infectivity than the Severe Acute Respiratory Syndrome coronavirus and the Middle East Respiratory Syndrome coronavirus.[12,13] But, underlying disease (i.e., hypertension, diabetes, and cancer) could increase mortality in COVID-19 patients.[14] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, and positive single-stranded RNA virus and belongs to the *Coronaviridae* family of viruses.[15] Currently, different types of COVID-19 vaccines such as mRNA-based vaccine and viral vector vaccine have been developed for the prevention of COVID-19. The vaccine is the best way for the protection against COVID-19 but disadvantages of COVID-19 vaccines include:

- Short-term immunization
- Need for booster doses
- Severe allergic reactions such as anaphylaxis (occurs rarely)
- Unknown long-term side effects

Also, the rate of vaccination is still low in many low- and lower-middle-income countries. On the other hand, oral agent is usually

Abbreviations: Cmax, maximum plasma concentration; COVID-19, coronavirus disease 2019; CoVs, coronaviruses; DAIDS, division of acquired immunodeficiency syndrome; IL, interleukin; LoM, lung-only mice; RdRp, RNA-dependent RNA polymerase; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; Tmax, time of Cmax; WHO, World Health Organization.

preferred for patients due to its ease of use. The RNA-dependent RNA polymerase (RdRp) is a key enzyme for the replication of SARS-CoV-2 and plays a central role in the pathophysiology of COVID-19.[16] Molnupiravir (EIDD-2801, MK-4482), an oral ribonucleoside analog with broad-spectrum antiviral activity, is an isopropyl ester prodrug of ′B-D-N4-hydroxycytidine (known, EIDD-1931 or NHC) and targets RdRp.[17] It blocks the SARS-CoV-2 replication in cell lines, animal infected models, and culture media containing airway epithelial cells[18–20] and has been suggested as a candidate treatment for COVID-19.[16] One of the advantages of this drug target is that the RNA-dependent polymerase has no equivalent in the human. This drug is currently under review by the United States Food and Drug Administration. We aimed to review the clinical evidence about the safety and efficacy of the molnupiravir administration in the treatment of patients with COVID-19.

2 | PATHOPHYSIOLOGY OF COVID-19

Coronaviruses (CoVs) have four main structural proteins, including spike, membrane, envelope, and nucleocapsid proteins. CoVs enter the host cell through the interaction between the spike protein and the host cell receptors such as angiotensin-converting enzyme 2 and CD147.[21–23] RdRp is responsible for the CoVs replication in host cells which leads to the production of CoVs with high mutagenicity and diversity.[24] After initial exposure, the immune system is triggered via cytotoxic cells, antibodies, and interferons. In the advanced stages of COVID-19, the alveolar infiltration of T cells, neutrophils, and macrophages contribute to cytokine production such as interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha. Cytokine storm results in acute respiratory distress syndrome (ARDS), and multi-organ dysfunction.[25] Hyperinflammatory is also associated with the hypercoagulable state via overexpression of tissue factor in the coagulation cascade.

3 | MECHANISM OF ACTION OF MOLNUPIRAVIR IN COVID-19

In plasma, molnupiravir is converted to the active nucleoside analog (EIDD-1931) by host esterases. EIDD-1931 has been shown to inhibit a range of viruses including Chikungunya virus, Venezuelan equine Encephalitis virus, Respiratory Syncytial virus, Norovirus, Influenza A and B viruses, Ebola virus, and human Coronaviruses. EIDD-1931 diffuse in several tissues and converts to triphosphate form. RdRp uses NHC triphosphate as a substrate instead of cytidine-triphosphate and uridine-triphosphate that leads to the production of a mutated RNA. Molnupiravir is a more desirable electron donor, which alters the conditions obliged for infectivity. EIDD-1931 appears to affect the mitochondrial function of viruses but in vitro studies show no significant toxicity effects on mitochondrial function.[26] Molnupiravir inhibits the RdRp enzyme of SARS-CoV-2, and causes several errors in the RNA virus replication.[27] In other words, molnupiravir-like remdesivir can reduce the pathogenesis and replication of coronaviruses. The results of the docking study showed that the limited space of mutations in the drug structure can cause the inhibitory effects of molnupiravir on the appearance of drug resistance-related mutations. Therefore, molnupiravir can be effective in treating patients with resistance to remdesivir.[28]

4 | CLINICAL CONSIDERATION, AND DRUG INTERACTIONS OF MOLNUPIRAVIR

Based on pharmacokinetic studies, molnupiravir should be administered twice daily to provide an adequate concentration in the respiratory tissues.[17] Based on the results of clinical trials, molnupiravir is well absorbed orally and shows linear pharmacokinetics between doses of 50–1600 mg. Administration of molnupiravir with food may significantly decrease the rate of absorption. However, the extent of absorption is similar in both with or without food. Therefore, the administration of molnupiravir with food is conflicting.[29] Headache, nausea, and diarrhea are the most common adverse effects of molnupiravir. Other adverse effects include influenza-like syndrome, back pain, rhinorrhea, hot flashes, and pain in extremity.[29,30] Trace amounts of molnupiravir found in the urine.[29] Molnupiravir is a mutagenic nucleotide analog that causes mutagenesis in the DNA of mammalian cells. Theoretically increases concerns about its interference with vaccination. Furthermore, that leads to potential carcinogenic and teratogenic effects on sperm precursors and embryonic growth. However, in the suggested dose, twice a day for 5 days is not commonly possible.[31,32] There are no comprehensive studies describing its metabolism in the body, blood carriers, and drug–drug interactions.[33] Indeed, no identified interaction with transporters, liver enzymes, and other drugs have been reported even by its active metabolite.[33,34] Therefore, more studies are needed to clarify the metabolism and drug–drug interactions of molnupiravir. Due to the potential of molnupiravir for teratogenicity, it should not be used during pregnancy until further studies clarify their teratogenicity risk.[17]

5 | MOLNUPIRAVIR IN COVID-19; PUBLISHED STUDIES

Several studies have investigated the inhibitory effects of molnupiravir on COVID-19 replication in animal models. In the study conducted by Wahl et al.[26] the effects of EIDD-2801 on lung infection were investigated in mice. In this study, lung-only mice (LoM) was used as an in vitro model to assess lung infection. To the creation of LoM model, human lung tissue was implanted subcutaneously in the back of male and female mice with 12–21 weeks old. Then, 8 weeks after surgery, these animal models were used for the experimental process. EIDD-2801 was started 12–48 h after infection and administered every 12 h. A significant reduction in the number of viruses in lung tissue is apparent 2 days after the start of treatment. For evaluating the prophylactic effects, molnupiravir was started 12 h before infection. The results

showed that molnupiravir is more effective in the prevention of COVID-19 infection if it is started earlier. Cox et al.[35] investigated the effects of EIDD-2801 in inhibiting COVID-19 transmission in ferrets. In this study, EIDD-2801 was used as BID, 12 and 36 h after infection by oral gavage. Also, the effect of molnupiravir on blocking contact transmission was investigated (in the control and drug groups). Based on the results, it blocks the virus transmission 24 h after administration. In another study, the evaluation of the inhibitory effects of EIDD-2801 on COVID-19 replication in Syrian hamster lung epithelial cells showed a significant reduction in virus replication.[36] In a study conducted by Abdelnabi et al.[16] the administration of molnupiravir reduced the virus titer and the RNA load of the virus in a dose-dependent manner compared with the control group. This study has also demonstrated that delaying therapy may not stop the virus replication. But, the progression of the infection in the hamster's lungs may have a delayed. In a similar study conducted by Abdelnabi et al.[20] the effect of combination therapy with favipiravir and molnupiravir on the COVID-19 infection was investigated. In this study, molnupiravir administered at doses of 75, 150, 200, and 500 mg/kg BID for 4 days with starting treatment 1 h before infection and showed a dose-dependent decrease in virus RNA copies and virus load into lung tissue. After the first 24 h of COVID-19 infection, the administration of molnupiravir may not reduce the virus replication effectively but, it can slow the progression of COVID-19. In this study, administration of high doses of favipiravir (300 and 500 mg/kg) showed a reduction in virus load. In addition, the combination therapy of molnupiravir and favipiravir increases the number of mutations in the RNA structure dramatically compared with favipiravir or molnupiravir alone, which in turn significantly reduces the RNA titer.[20] The details of these studies are given in Table 1.

6 | MOLNUPIRAVIR IN COVID-19; ONGOING CLINICAL TRIALS

Based on clinicaltrials.gov database until November 12, 2021, seven clinical trials are being conducted to evaluate the efficacy and safety of molnupiravir in COVID-19 patients (Table 2). Among them, two study is based in the United Kingdom, and five studies are multicountry. Study sample size ranges from 96 to 1450, with a cumulative sample size of 4116. Molnupiravir is administered orally at doses of 50 mg to 800 mg in each clinical trial. The severity of COVID-19 ranges from mild to severe. One clinical trial evaluates the efficacy and safety of molnupiravir, nitazoxanide, and monoclonal antibody VIR-7832 in COVID-19 infection. Other clinical trials compare the effectiveness of molnupiravir versus placebo or standard of care. The primary endpoints of studies are time-to-sustained recovery, determination of safety and tolerability of single and multiple ascending doses of molnupiravir, the occurrence of an adverse event, the occurrence of any adverse events as assessed by Kaplan–Meier approach, reduction in serious complications of COVID-19 such as hospitalization, reduction in oxygen saturation <92% or death, virologic clearance rates after oral administration of EIDD-2801, hospitalization rate and/or death, the occurrence of serious adverse events as assessed by division of acquired immunodeficiency syndrome (DAIDS). In a Phase 1 clinical trial,[29] healthy subjects with age between 18 and 60 years, and a body mass index between 18 and 30 kg/m^2 were randomized in a 3:1 ratio to receive a single dose of molnupiravir, multiple doses of molnupiravir, or placebo for 5.5 days. Subjects were followed-up for 14 days to assess the safety, tolerability, and pharmacokinetics of molnupiravir.

The pharmacokinetics study with single ascending doses of molnupiravir showed that concentrations were not quantifiable at doses less than 600 mg. At doses of 600 and 800 mg, concentrations of molnupiravir were quantifiable at the 0.25-hour time point in 5 and 4 subjects, respectively. At the 0.5-hour time point after a dose of 800 mg, concentrations of molnupiravir were quantifiable in all subjects. At doses of 1200 and 1600 mg, concentrations of molnupiravir were quantifiable at one or more time points between 0.25 and 1.5 h in all subjects. Following oral administration of molnupiravir at doses of 600 to 1600 mg, the maximum plasma concentration (Cmax), and time of Cmax (Tmax) were up to 13.2 ng/ml and between 0.25 and 0.75 h, respectively. EIDD-1931 is found in plasma approximately 1.00 h after oral administration of molnupiravir at doses up to 800 mg. However, at doses of 1200 and 1600 mg, Tmax is achieved in about 1.75 and 1.50 h, respectively. The concentrations of molnupiravir were quantifiable in plasma 24 h after receiving 1200 and 1600 mg molnupiravir with prolonged elimination half-lives with values of 1.81 and 4.59 h, respectively.

The pharmacokinetics study with multiple ascending doses of molnupiravir showed that concentrations of molnupiravir were under the limit of quantification at doses less than 400 mg BID, and pharmacokinetic parameters were not measurable. After receiving molnupiravir 600 mg BID, molnupiravir concentrations were assessable in four subjects at either 0.5 or 1 h post-dose on day 1 and 3 subjects at 0.5 h post-dose on day 6. Similar to single ascending doses, after receiving molnupiravir 600-mg BID, concentrations of molnupiravir were quantifiable in all patients except 1 subject at 0.5 h post-dose on days 1 and 6, but at no other time points. After oral administration of molnupiravir, EIDD-1931 emerged rapidly in plasma, with a Tmax in all dose cohorts of between 1.00 and 1.75 h post-dose across both days 1 and 6. For all doses, plasma concentrations deteriorated in a monophasic manner on day 1, with mean half-lives ranging from 0.918 to 1.18 h. Also, plasma concentrations declined in a monophasic manner on day 6 for the majority of subjects at doses ≤400 mg BID. However, for one subject at each dose of the 300- and 400-mg and all subjects with doses of 600- and 800-mg BID, biphasic elimination was observed on day 6 with a shorter mean half-live. Notably, administration of molnupiravir at a dose of 600 mg twice daily showed no definite terminal elimination phase, so it is not possible to evaluate the half-life for the majority of subjects. The mean half-live was 7.08 h when molnupiravir is given at a dose of 800 mg BID. For all doses of molnupiravir, the Cmax was between 0.843 and 1.10 and median Tmax is achieved up to 0.75 h after administration of the capsule formulation.

TABLE 1 Clinical studies published for the therapeutic effects of molnupiravir in COVID-19

Study, year	Infection model	Route of infection by SARS-CoV–2	Dose of molnupiravir	Other treatments	Follow-up time	Outcomes
Wahl et al., 2021	Mice	Direct injection into lung tissue on LoM	—	—	Days 2, 6, and 14 after infection	Reducing the replication and amount of infectious particles in lung tissue
Cox et al., 2021	Ferrets	Intranasal	5 or 15 mg/kg BID 12 h post infection And 5mg/kg BID 36 h post infection For blocking contact transmission: Control group: vehicle (methyl cellulose 1%) Drug group: EIDD-2801, 5 mg/kg BID	—	24 h after initiation of treatment	undetectable viral particles in the respiratory system and blocking contact transmission of the virus
Rosenke et al., 2021	Syrian hamster	Intranasal	250 mg/kg BID (12 h pre-infection and 12 h post- infection groups) Vehicle (control group)	—	Fourth day after infection	Reduction in the replication of SARS-CoV-2 viruses
Abdelnabi et al. 2020	Syrian Gold hamster	Intranasal	75 or 200 mg/kg BID(Start administration 24–48 h after infection) for 4 days	—	—	Dose-dependent reduction in viral RNA load and virus titer
Abdelnabi et al., 2021	Syrian Gold hamster	Intranasal	150 mg/kg BID	Favipiravir (300 mg/kg BID Intra-peritoneal injection)	—	Reduction in viral RNA load and virus titer Increasing the number of mutations in the RNA structure

TABLE 2 Summary of ongoing clinical trials investigating the therapeutic effects of molnupiravir for the treatment of COVID-19

ID	Status	Design	Country	Population (n = patients)	Intervention group(s)	Comparison group(s)	Primary outcomes
NCT04575584	Terminated	Randomized, double-blind, placebo-controlled trial	Multicounty	N = (304)	200 mg or 400 mg or 800 mg molnupiravir orally every 12 h for 5 days	Placebo administeredorally every 12 h for5 days	Time-to-sustained recovery Percentage of participants with an adverse event Percentage of participants who discontinued study intervention due to an adverse event
NCT04746183	Recruiting	Open-label, randomized clinical trial	United Kingdom	N = (600)	molnupiravir administered orally, twice daily for 10 doses or nitazoxanide administered orally, initially twice daily for 14 doses with starting dose 1500 mg BID or VIR-7832 administered IV infusion with starting dose 50 mg	Placebo or standardof care	Master protocol: Dose-finding /Phase I Master protocol: efficacy evaluation/Phase II – severe patients Master protocol: efficacy evaluation/Phase II – mild to moderate patients CST-2 Phase I: to determine the safety and tolerability of multiple ascending doses of molnupiravir to recommend dose for phase II. CST-2 Phase II: to determine the ability of molnupiravir to reduce serious complications of COVID-19 including hospitalization, reduction in SAO2<92%, or death.
NCT04405570	Completed	Randomized, double-blind, placebo-controlled trial	Multicounty	N = (204)	EIDD-2801 twice daily for 5 days	Placebo oral capsuletwice daily for 5 days	Virologic efficacy Number of participants with any adverse events as assessed by Kaplan–Meier approach
NCT04575597	Active, not recruiting	Randomized, placebo-controlled, double-blind clinical trial	Multicounty	N = (1450)	Molnupiravir administered orally in capsule form every 12 h for 5 days	Placebo matching molnupiravir administered orallyin capsule form every12 h for 5 days	Percentage of participants who are hospitalized and/or die Percentage of participants with an adverse event Percentage of participants who discontinued study intervention due to an adverse event
NCT04405739	Recruiting	Randomized, placebo-controlled, double-blind clinical trial	Multicounty	N = (96)	EIDD-2801 administered orally twice daily for 5 days	Placebo oral capsule twice daily for 5 days	Number of participants that achieve virologic clearance after oral administration of EIDD-2801 Number of participants with any serious adverse events as assessed by DAIDS
NCT04392219	Completed	Randomized, double-blind, placebo-controlled trial	United Kingdom	N = (130)	A single dose or two single doses of EIDD-2801 administered orally	Placebo matching molnupiravir administered orally	Number of participants with treatment emergent adverse events and severity of treatment emergent adverse events
NCT04939428	Recruiting	Randomized, double-blind, placebo-controlled trial	Multicounty	N = (1332)	Four molnupiravir 200 mg capsules taken orally	Placebo capsule matched to molnupiravir200 mg capsulestaken orally	Percentage of participants with COVID-19 through Day 14 Percentage of participants with ≥1 adverse event Percentage of participants who discontinued study intervention due to an adverse event

Abbreviations: CST, candidate-specific trial; DAIDS, division of acquired immunodeficiency syndrome; IV, intravenous.

Common adverse effects are headache and diarrhea, which was lower in the molnupiravir group (12.5%) compared to the placebo group (18.8%). 93.3 percent of adverse effects were mild. The results of this study showed that molnupiravir is well-tolerated. One subject was discontinued early due to skin rash. Subjects were randomized in a 1:1 ratio to evaluate the effect of food on the pharmacokinetics of molnupiravir. They received 200 mg molnupiravir in the fed state or 200 mg molnupiravir under fasting conditions. There was a reduction in the absorption rate but no decrease in overall exposure.

7 | LIMITATION

This review article might have some limitations. First, due to the limited published data about the use of molnupiravir in COVID-19, more data are needed to support the application of molnupiravir in the treatment of COVID-19. Second, like most review articles, some studies may be missed to come into our review.

8 | CONCLUSION

The RdRp is an essential enzyme for COVID-19 replication and seems to play a key role in the pathophysiology of COVID-19. Molnupiravir targets RdRp and is a candidate drug for COVID-19 treatment. Based on animal studies, molnupiravir can be effective in COVID-19, but well-designed randomized clinical trial studies are required in the future to confirm the therapeutic effects of molnupiravir in patients with COVID-19.

ETHICS APPROVAL STATEMENT

No ethical approval required for the review article.

DISCLOSURE

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

HR and SPA, devised the main conceptual ideas. FP, SPA, and HR, wrote the initial draft of the manuscript. FP and HR, reviewed the manuscript and edited it critically for important intellectual content. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

Not applicable.

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REFERENCES

1. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: the mystery and the miracle. *J Med Virol*. 2020;92(4):401-402.
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*. 2020;395(10223):497-506.
3. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *The Lancet*. 2020;395(10223):507-513.
4. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. *Lancet*. 2020;395(10223):470-473.
5. Baradaran H, Hamishehkar H, Rezaee H. NSAIDs and COVID-19: a new challenging area. *Pharm Sci*. 2020;26(Suppl 1):S49-S51.
6. World Health Organization Coronavirus disease (COVID-19) situation dashboard. CEST. Accessed December 23, 2021. https://covid19.who.int
7. Rezaee H, Pourkarim F, Pourtaghi-Anvarian S, et al. Drug-drug interactions with candidate medications used for COVID-19 treatment: an overview. *Pharmacol Res Perspect*. 2021;9(1).
8. Corman VM, Landt O, Kaiser M. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. *Eurosurveillance*. 2020;25(3):2000045.
9. Rubin EJ, Baden LR, Morrissey S, Campion EW. Medical journals and the 2019-nCoV outbreak. *N Engl J Med*. 2020;382(9):866.
10. National Center for Health Statistics, & Centers for Disease Control and Prevention. COVID-19 data from the National Center for Health Statistics. 2020. Accessed April 1, 2020. https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html
11. Lechien JR, Chiesa-Estomba CM, Hans S, Barillari MR, Jouffe L, Saussez S. Loss of smell and taste in 2013 European patients with mild to moderate COVID-19. *Ann Intern Med*. 2020;173(8):672-675.
12. World Health Organization Coronavirus disease (COVID-19) weekly epidemiological update. 2020. Accessed August 24, 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200824-weekly-epi-update.pdf?sfvrsn=806986d1_4
13. Gorbalenya AE, Baker SC, Baric RS, Coronaviridae Study Group of the International Committee on Taxonomy of Viruses, et al. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol*. 2020;5(4):536-544.
14. Nouri-Vaskeh M, Kalami N, Zand R, et al. Comparison of losartan and amlodipine effects on the outcomes of patient with COVID-19 and primary hypertension: a randomised clinical trial. *Int J Clin Pract*. 2021;75(6):e14124.
15. Ciotti M, Angeletti S, Minieri M. COVID-19 outbreak: an overview. *Chemotherapy*. 2019;64(5-6):215-223.
16. Abdelnabi R, Foo CS, Kaptein SJ, et al. The combined treatment of Molnupiravir and Favipiravir results in a potentiation of antiviral efficacy in a SARS-CoV-2 hamster infection model. *EBioMedicine*. 2021.
17. Toots M, Yoon J-J, Hart M, Natchus MG, Painter GR, Plemper RK. Quantitative efficacy paradigms of the influenza clinical drug candidate EIDD-2801 in the ferret model. *Transl Res*. 2020;218:16-28.
18. Vicenti I, Zazzi M, Saladini F. SARS-CoV-2 RNA-dependent RNA polymerase as a therapeutic target for COVID-19. *Expert Opin Ther Pat*. 2021;31(4):325-337.
19. Paymode DJ, Vasudevan N, Ahmad S, et al. Toward a practical, two-step process for molnupiravir from cytidine. *Org Process Res Dev*. 2021;25:1822-1830.
20. Abdelnabi R, Foo CS, Kaptein SJ, et al. The combined treatment of Molnupiravir and Favipiravir results in a marked potentiation of efficacy in a SARS-CoV2 hamster infection model through an increased frequency of mutations in the viral genome. *bioRxiv*. 2021; 2020–12.

21. Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature*. 2003;426(6965):450-454.
22. Jia HP, Look DC, Shi L, et al. ACE2 receptor expression and severe acute respiratory syndrome coronavirus infection depend on differentiation of human airway epithelia. *J Virol*. 2005;79(23):14614-14621.
23. Grass GD, Toole BP. How, with whom and when: an overview of CD147-mediated regulatory networks influencing matrix metalloproteinase activity. *Biosci Rep*. 2016;36(1):e00283.
24. Duffy S, Shackelton LA, Holmes EC. Rates of evolutionary change in viruses: patterns and determinants. *Nat Rev Genet*. 2008;9(4):267-276.
25. Khadke S, Ahmed N, Ahmed N, et al. Harnessing the immune system to overcome cytokine storm and reduce viral load in COVID-19: a review of the phases of illness and therapeutic agents. *Virol J*. 2020;17(1):1-8.
26. Wahl A, Gralinski LE, Johnson CE, et al. SARS-CoV-2 infection is effectively treated and prevented by EIDD-2801. *Nature*. 2021;591(7850):451-457.
27. Thakur S, Sarkar B, Ansari AJ, et al. Exploring the magic bullets to identify Achilles' heel in SARS-CoV-2: delving deeper into the sea of possible therapeutic options in Covid-19 disease: an update. *Food Chem Toxicol*. 2021;147:111887.
28. Padhi AK, Shukla R, Saudagar P, Tripathi T. High-throughput rational design of the remdesivir binding site in the RdRp of SARS-CoV-2: implications for potential resistance. *Iscience*. 2021;24(1):101992.
29. Painter WP, Holman W, Bush JA, et al. Human safety, tolerability, and pharmacokinetics of molnupiravir, a novel broad-spectrum oral antiviral agent with activity against SARS-CoV-2. *Antimicrob Agents Chemother*. 2021;65(5).
30. Painter WP, Holman W, Bush JA, et al. Human safety, tolerability, and pharmacokinetics of a novel broad-spectrum oral antiviral compound, molnupiravir, with activity against SARS-CoV-2. *medRxiv*. 2020.
31. Singh AK, Singh A, Singh R, Misra A. Molnupiravir in COVID-19: a systematic review of literature. *Diabetes Metab Syndr*. 2021;15(6):102329.
32. Menéndez-Arias L. Decoding molnupiravir-induced mutagenesis in SARS-CoV-2. *J Biol Chem*. 2021;297(1):100867.
33. Kumar D, Trivedi N. Disease-drug and drug-drug interaction in COVID-19: risk and assessment. *Biomed Pharmacother*. 2021;139:111642.
34. Miller SR, McGrath ME, Zorn KM, Ekins S, Wright SH, Cherrington NJ. Remdesivir and EIDD-1931 Interact with human equilibrative nucleoside transporters 1 and 2: implications for reaching SARS-CoV-2 viral sanctuary sites. *Mol Pharmacol*. 2021;100(6):548-557.
35. Cox RM, Wolf JD, Plemper RK. Therapeutically administered ribonucleoside analogue MK-4482/EIDD-2801 blocks SARS-CoV-2 transmission in ferrets. *Nat Microbiol*. 2021;6(1):11-18.
36. Rosenke K, Hansen F, Schwarz B, et al. Orally delivered MK-4482 inhibits SARS-CoV-2 replication in the Syrian hamster model. *Nat Commun*. 2021;12(1):1-8.

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