



Antiviral Pills against SARS-CoV-2 Virus to Combat Future Epidemic Threats in Pakistan

Ayesha Khan, Hadia Batool, and Shaheen Shahzad*

Department of Biological Sciences, International Islamic University, Islamabad, Pakistan

Abstract: Antiviral pills are oral medications that treat infections through the inhibition of the viral growth and replication cycle. Paxlovid by Pfizer and Molnupiravir by Merck are the two pills effective for high-risk SARS-CoV-2 patients. Paxlovid works by inhibiting the replication cycle of SARS-CoV-2 using cysteine residues in-vitro. These cysteine residues inhibit the main protease of the virus by functioning as reversible covalent inhibitors. Molnupiravir works by introducing a high rate of mutations in the viral RNA causing the virus to become biologically unstable and non-functional. Both antiviral drugs can bridge the gap in the preparedness for viral outbreaks in low-income countries like Pakistan by mitigating the chances of fatality and inpatient treatment in high-risk, unvaccinated individuals. Pakistan has been plagued by various epidemics over the years however SARS-CoV-2 outbreak caused many deaths along with an economic crisis. The country lacks the resources to endure high inpatient treatment rates in case of SARS-CoV-2 infections, which is why the need for antiviral pills like Paxlovid and Molnupiravir is empirical to overcome epidemics and viral outbreaks. This work outlines the antiviral pills and their efficacy against SARS-CoV-2 with a focus on how these drugs can overcome significant gaps in epidemic preparedness and response in Pakistan. We aim to highlight how antiviral pills against SARS-CoV-2 can ensure resilience to future epidemic threats in Pakistan.

Keywords: SARS-CoV-2, Antiviral pills, Paxlovid, Molnupiravir, Epidemic, Pakistan

1. INTRODUCTION

The Middle East Respiratory Syndrome, Severe Acute Respiratory Syndrome, and other viral breakouts in the past have been caused by viruses of the Coronaviridae family [1]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had been identified as the source of a group of pneumonia cases reported in Wuhan, China, in December 2019 [1, 2]. This viral infection quickly spread around the world and was shortly classified as a worldwide pandemic by World Health Organization (WHO) [2–5]. In Pakistan, this pandemic has posed serious concerns regarding the country's weak healthcare infrastructure as the frequency of SARS-CoV-2 patients rose significantly. In order to prevent SARS-CoV-2, various vaccine types, including mRNA-based vaccines and viral vector vaccines, have been developed. While appropriate vaccinations have been approved to combat severe SARS-CoV-2

infections, the immediate requirement for orally administered antiviral drugs particularly designed to target SARS-CoV-2 persists [6, 7].

Vaccinations provide optimal protection against SARS-CoV-2, however, it is a challenge to vaccinate highly populous low-income countries. It is also difficult to transport and store vaccines in remote villages with limited resources. The Food and Drug Administration (FDA) has granted emergency use authorizations (EUs) for a number of biological products & pharmaceuticals against SARS-CoV-2, such as Kineret, Evusheld, Actemra, Propofol-Lipuro 1 %, Baricitinib, and COVID-19 convalescent plasma, however, these authorizations are only allowed for inpatient treatments [8]. Following the outbreak, developing orally administered antivirals that can be consumed by outpatients became a top focus [7]. Two novel oral antiviral pills were approved by the US Food and Drug Administration (FDA)

in 2021 for the treatment of outpatients with minimal to severe COVID-19 symptoms [9]. These two antiviral pills are Paxlovid (Pfizer) and Molnupiravir (Merck) which aim to reduce the frequency of reported deaths and the need for inpatient treatments [10].

The ribonucleoside analogues Beta-D-N4-hydroxycytidine (NHC), which is then modified intracellularly to its activated state Molnupiravirtriphosphate (MTP), is the main component in Molnupiravir. It functions by targeting RNA-dependent RNA polymerase (RdRp), an important enzyme in SARS-CoV-2 RNA replication and translation machinery. Molnupiravir introduces mutations in the viral RNA causing the virus to become biologically unstable and non-functional. On the contrary, Pfizer developed the antiviral pill nirmatrelvir marketed under the name, Paxlovid [11]. Paxlovid inhibits SARS-CoV-2 replication using cysteine residues in vitro. The cysteine residues inhibit the main protease of the virus by functioning as reversible covalent inhibitors. The description of the different characteristics of Paxlovid and Molnupiravir are illustrated in Table 1.

2. MATERIALS AND METHODS

Electronic databases such as Google Scholar,

PubMed, and Science Direct had been browsed for publications dated between January 2020 to November 2022 with keyword phrases including “Paxlovid”, “Molnupiravir”, “COVID-19”, “SARS-CoV-2” “Antiviral pill”, “MK-4482”, “SARS-CoV-2”, “EIDD-280”, “nirmatrelvir plus ritonavir” “PF07321332”, “Efficacy”, “Safety” and “Pakistan”. The publications reporting the medical testing and experimental research on Molnupiravir and Paxlovid as antivirals against SARS-CoV-2 published between 2019 to 2022 met the criteria for inclusion. Non-relevant studies, non-English papers, and full-text unavailability were among the exclusion parameters. The process flow diagram for selecting publications for this article is given in (Figure 1).

3. PATHOPHYSIOLOGY OF SARS CoV-2

The four primary structurally important proteins found in coronaviruses are the spike, membrane, envelope, and nucleocapsid proteins. Extracellular matrix metalloproteinase inducer (EMMPRIN) and angiotensin-converting enzyme 2 are two examples of host cell surface receptors coronaviruses can use for entering human cells. RNA-dependent RNA polymerase (RdRp) controls viral RNA replication inside host machinery used for the proliferation of highly mutagenic and diverse virions [12]. Following the first interaction with coronaviruses,

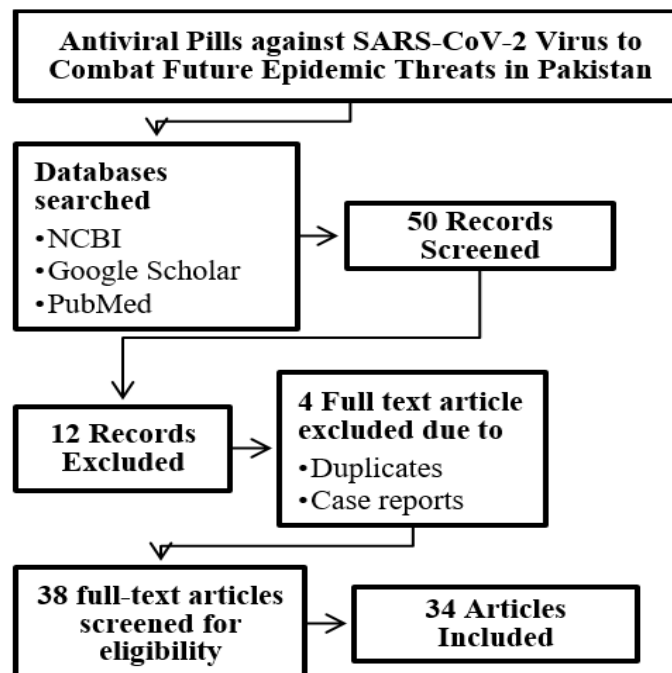


Fig. 1. The publication selection process summarized as a flow diagram.

Table 1. Different characteristics of Molnupiravir and Paxlovid

Characteristics	Molnupiravir	Paxlovid
Synonyms	Lagevrio; EIDD-2801; MK-4482; Molnupiravirum; Eidd 1931-isopropyl ester; WHO 11853	Nirmatrelvir; PF07321332; nirmatrelvir plus ritonavir; 7R9A5P7H32; WHO 12161
Class	Antivirals; esters; hydroxylamines; pyrimidinones; ribonucleosides; small molecules	Carboxamides; cyano compound; pyrrolidones; amines; small molecules; aza compounds; carbamate; fluorinated hydrocarbons; heterocyclic bicyclic compound; thiazoles
Mode of Action	SARS-CoV-2 RNA-dependent RNA polymerase inhibitor	Coronavirus-3C-like-proteinase inhibitor (nirmatrelvir); CYP3A-mediated metabolism of nirmatrelvir inhibitor (ritonavir)
Route of Administration	Oral	Oral
Pharmacodynamics	Molnupiravir hydrolyzes in cells to form N4-hydroxycytidine, it phosphorylates to Molnupiravir triphosphate and incorporates in viral RNA causing inactivating mutations, leading to new unstable virions.	Nirmatrelvir: attaches to the active site of SARS-CoV-2 main protease and blocks it, preventing it from processing polyproteins and halting viral multiplication. Ritonavir: prevents CYP3A-mediated nirmatrelvir metabolism, raising levels of nirmatrelvir in plasma; does not have activity towards SARS-CoV-2 main protease.
Adverse Effects	Diarrhoea, dizziness, headache, redness of the skin, vomiting, nausea.	Diarrhea, parageusia, high blood pressure, muscle ache
WHO ATC codes	J05 (Antivirals for Systemic Use)	J05 (Antivirals for Systemic Use)
EphMRA ATC code	J5B9 (Antivirals, others)	J5 (Antivirals for Systemic Use)
Molecular Formula	$C_{13}H_{19}N_3O_7$	$C_{23}H_{32}F_3N_5O_4$
Chemical formula	[(2R,3S,4R,5R)-3,4-dihydroxy-5-[4-(hydroxyamino)-2-oxopyrimidin-1-yl] oxolan-2-yl] methyl 2-methylpropanoate	(1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-[(2S)-3,3-dimethyl-2-[(2,2,2-trifluoroacetyl)amino]butanoyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide/1,3-thiazol-5-ylmethyl N-[(2S,3S,5S)-3-hydroxy-5-[[[(2S)-3-methyl-2-[[methyl-[(2-propan-2-yl-1,3-thiazol-4-yl)methyl]carbamoyl]amino]butanoyl]amino]-1,6-diphenylhexan-2-yl]carbamate

interferons, immunoglobulins, and natural killer cells trigger an immune response. T lymphocytes, macrophages, and polymorphonuclear leukocytes, that have infiltrated the alveoli during the severe phases of SARS-CoV-2 infection produce cytokines like cachectin and interleukins IL-1, IL-6. Acute respiratory distress syndrome (ARDS)

and multi-organ malfunction are caused by high levels of cytokines [11]. Because tissue factor is overexpressed in secondary hemostasis, hyperinflammation is often linked to thrombophilia.

Following five days of incubation, clinical symptoms of SARS-CoV-2 begin to develop.

Pyrexia, coughing, along with exhaustion are the more common signs, but there are many others including respiratory phlegm, headaches, coughing up blood, diarrhea, lymphocytopenia, and dyspnoea. Upper and lower respiratory signs notably sternutation, pharyngitis, and runny nose, are indicative of SARS-CoV-2's distinct clinical symptoms. Contrary to MERS-CoV and SARS-CoV patients, who exclusively have diarrhea, people infected with SARS-CoV-2 generally exhibit diarrhea as well as other stomach problems [13]. SARS-CoV-2 spreads from individual to individual via aerosol particles and drops. When a virus enters the body it binds to the cell receptors of the host, and enters by either fusing with cell membrane or endocytic activity [14]. Transmission of the SARS-CoV-2 virus causes the activation of antigen-presenting cells such as accessory cells and phagocytes by pro-inflammatory substances. Major histocompatibility complexes I and II (MHC I and II) activate cellular and humoral response mediated by B and T lymphocytes against the SARS-CoV-2 antigens. As a result, antibodies and cytokines are produced. Increased virus multiplication in later phases of the disease compromises the stability of the epithelium and endothelium. Cell death and depletion of surface-active agents are brought on by the virus's invasion of type II pneumocytes in the lower respiratory system. Alveolar interstitial thickness increased vascular porosity, and edema is all results of ongoing inflammatory reactions. Hyaline membranes may develop in the alveolar cavities as a result of pulmonary edema.

Alveolar deterioration and failure are the outcomes of all these biochemical abnormalities, which in turn limits the exchange of gases [15].

4. MODE OF ACTION OF ORAL ANTIVIRALS AGAINST SARS-COV-2

Both Molnupiravir and Paxlovid target the SARS-CoV-2 Virus in different ways meaning that both drugs have different mechanisms of action that target the virus and halt its replication.

4.1 Molnupiravir

The medicine Molnupiravir, formerly identified as EIDD-2801, is an isopropyl ester class of drug produced using the ribonucleoside analogue Beta-

D-N4-hydroxycytidine (NHC). It is subsequently transformed within cells into an activated state known as Molnupiravirtriphosphate (MTP). It works by inhibiting RNA-dependent RNA polymerase (RdRp), a key enzymatic protein involved in the SARS-CoV-2 RNA replication and translation process. This makes RdRp a prospective target protein for SARS-CoV-2 treatment [16, 17]. Molnupiravir can be orally administered due to higher bioavailability, unlike other monoclonal antibody therapy and ribonucleoside analogues that require in-patient intravenous dosing [18-20].

Molnupiravir works by preventing the enzymatic protein RdRp from functioning. This enzyme is among the Sixteen non-structural proteins (nsp), and it has an important role in catalyzing the viral RNA replicating machinery from existing templates. The activated state of Molnupiravir, Molnupiravirtriphosphate (MTP), is produced in the body and utilized as a substrate for RdRp. The host mitochondrial RNA polymerase could potentially integrate MTP as either cytosine or uracil analogue. When nucleoside triphosphate (NTP) and Molnupiravirtriphosphate (MTP) are present, SARS-CoV-2 RdRp incorporates MTP into the sub-genomic RNA or negative-stranded genome during positive-stranded genome transcription rather than cytosine or uracil nucleotide bases. In order to create a mutant positive-stranded genome and sub-genomic mitochondrial RNA, the acquired negative-stranded RNA containing MTP could be subsequently utilized as templates. Because of the existence of MTP in the negative-stranded genome, it results in mutations in the positive-stranded RNA, which therefore inhibits the development of functioning viral RNA and stops the virus from proliferating. Such a process is often renowned as an "error catastrophe" Molnupiravir has also been linked to genome alterations in humans by mammalian cell culturing studies [19, 21]. Figure 2 illustrates Molnupiravir's mode of action.

4.2 Paxlovid

The novel antiviral medication Paxlovid, formerly known as nirmatrelvir, was created by Pfizer [11]. The antiviral candidate Paxlovid is a modified version of lufotrelvir [22]. Lufotrelvir is a phosphate warhead-containing antiviral protease inhibitor [23]. On the contrary, Paxlovid was created for oral

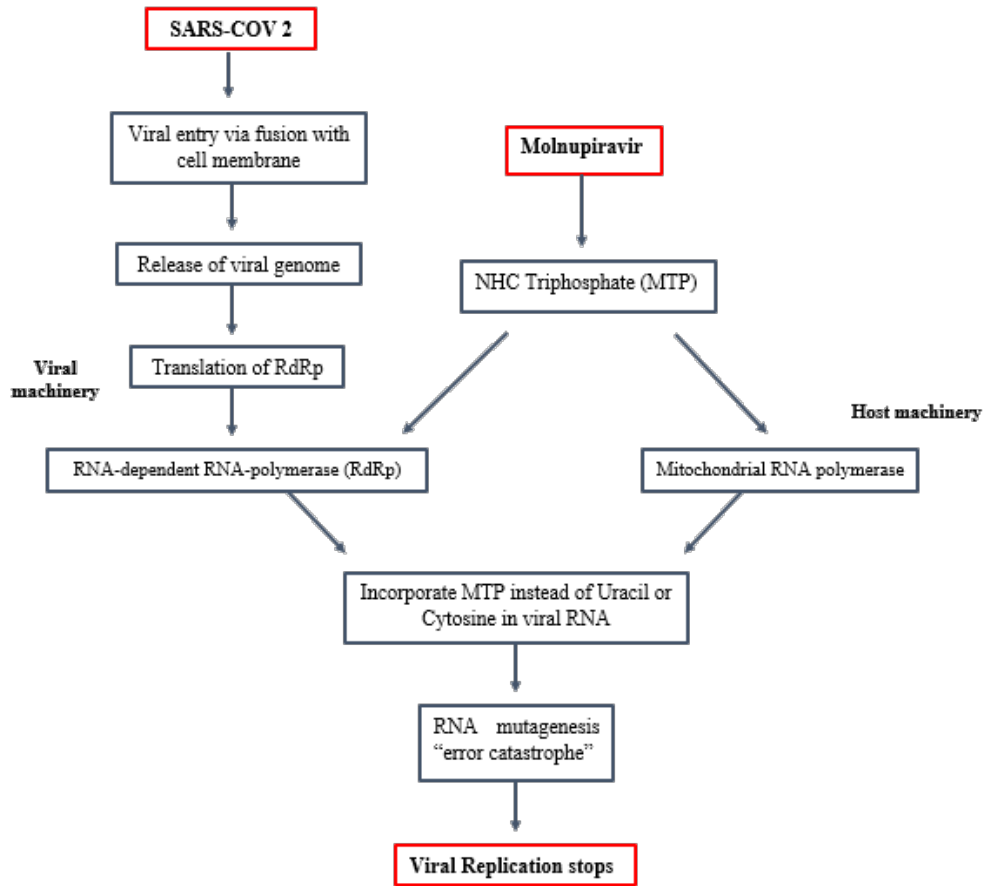


Fig. 2. Flow chart illustration of Molnupiravir mode of action

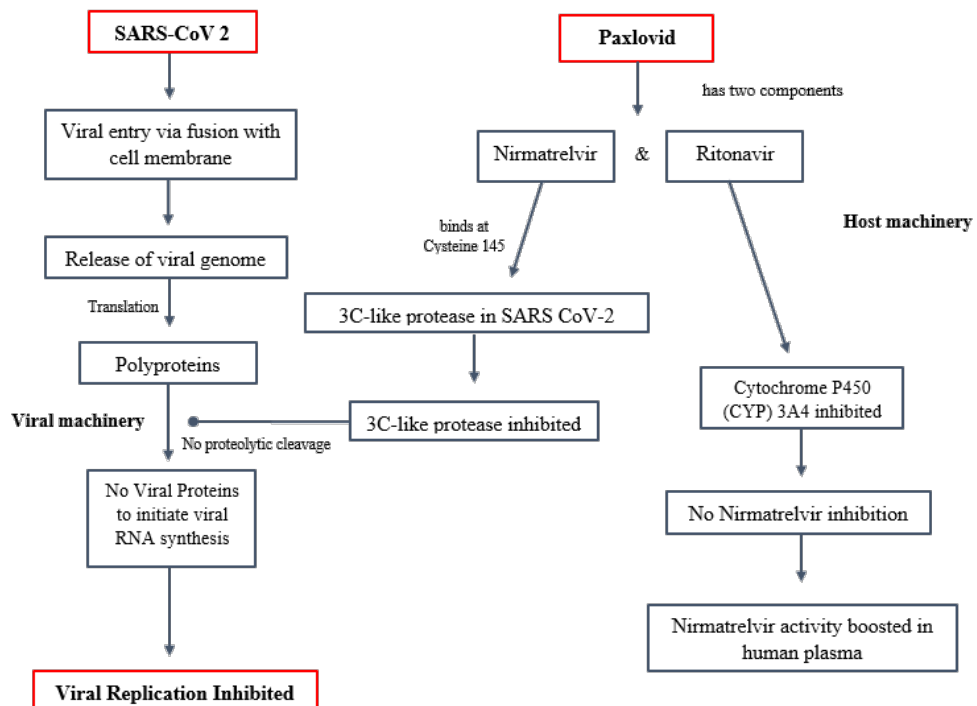


Fig. 3. Flow chart illustration of the mode of action of Paxlovid.

delivery by altering a tripeptide protein mimicking lufotrelvir [11].

Nirmatrelvir binds directly to the 3C-like protease (also referred to as SARS-CoV-2 Mpro active site) reversibly and exclusively hinders 3C-like protease activity by direct attachment to Cys145 [24]. Such type of protein inhibition prevents virus proliferation because the enzyme fails to digest polyproteins [16, 25]. When nirmatrelvir and ritonavir are given jointly, ritonavir pharmacokinetically enhances nirmatrelvir's activity and increases its half-life in the body.

Although ritonavir inhibits the protease activity of HIV, it cannot inhibit SARS-CoV-2 3C-like protease, which is why it is only used as an enhancer. It is reported to increase nirmatrelvir plasma concentration levels through the inhibition of cytochrome P450 (CYP) 3A4 inhibitor-mediated metabolism of nirmatrelvir [16, 25]. The increased absorption of Paxlovid appeared to become lower than the dose-proportional to steady state followed by two orally administered doses every day of Paxlovid (75 milligrams + 100 milligrams, 250 milligrams + 100 milligrams, and 500 milligrams + 100 milligrams) [10, 16]. By the second day, steady-state had reached (accumulation \approx 2-fold). The median periods to maximum concentration levels of ritonavir were 3.98 h and nirmatrelvir were 3.00 h in normal and fit participants following one dosage of nirmatrelvir 300 milligrams with ritonavir 100 milligrams. Paxlovid could be taken with or without meals, however consuming it with fatty meals slightly enhanced nirmatrelvir absorption compared to fasting conditions [10, 16]. The mechanism of action of Paxlovid is given (Figure 3).

5. THERAPEUTIC TRIALS

5.1 Molnupiravir

From the four trials using Molnupiravir, the first phase of the research had been conducted on 130 competent participants to determine the drug's tolerability as well as the effective dosage range. The drug was proven to be non-toxic and generally tolerable. The uptake had not been affected in the fed state and the studied dosages were between 50 to 800 milligrams (maximum standard dosage

1600 milligrams/ day). administered twice for 5.5 days. When contrasted to the Molnupiravir cohort, the frequency of side effects had been greater compared to placebo; it was 43.8 % versus 35.4 % for one dosage and 50 % versus 42.9 % for several ascending dosages, correspondingly. In a single ascending dosage trial, headaches were most frequently observed, whereas diarrhea was more frequently observed in multiple ascending dose research [4].

The AGILE trial had been a Phase Ib/IIa dosage increment investigation that included 18 SARS-CoV-2 infected individuals. Individuals who had been infected with SARS-CoV-2 within 120 hours after the development of symptoms were grouped and arbitrarily assigned three dosage cohort groups (300, 600, and 800 milligrams) containing six individuals, respectively. According to the findings, minor side effects in individuals who got 800 milligrams (25 percent) and individuals who got normal treatment (83 percent). Molnupiravir 800 milligrams two times per day had been deemed to be nontoxic and tolerable, as plasma concentrations were in between the range [20].

For the Phase IIa research, 202 non-immunized individuals affected with SARS-CoV-2 disease were included. The individuals were given Molnupiravir doses of 200, 400, and 800 milligrams. In contrast to the placebo group (18 %), the initial antibody level was greater (35 %). The timeframe for viral inactivation was considerably shortened (14 to 15 days) with 800 milligrams doses of Molnupiravir in comparison to the placebo, but not using Molnupiravir 200 milligrams and 400 milligrams. In individuals who tested negative for antibodies, the viral inactivation was shortened (14 to 27 days). On day 28, the viral inactivation with 800 milligrams of Molnupiravir was at 92.5 %, 400 milligrams at 91.3 %, 200 milligrams at 78.7 %, and placebo at 80.3 %. In the Molnupiravir cohort, viral isolation from nasopharynx samples was much lower than in the placebo; on day 3 it was 1.9 % vs. 16.7 % and on day 5, it was 0 % vs. 11.1 %. A substantial change in both Molnupiravir dosages of 800 milligrams and 400 milligrams were observed [27].

The median duration for resolving SARS-CoV-2 disease was 8 days (6.0 to 12.0) for the

Molnupiravir 800 milligrams group versus 8 and a half days (7.0 to 11.0) for the placebo at a confidence interval of 95 percent. Individuals who were not admitted to the hospital and had low to intermediate symptoms, as well as a single determinant at minimum for the development of acute disease, participated in the MOVE-OUT experiment, a phase III research investigation. The overall probability of inpatient treatment for any reason or having passed away by day 29 had been found to be reduced with Molnupiravir (7.3 % [28 of 385 individuals]) in comparison to placebo (14.1 % [53 of 377 participants]) within the ITT cohort. The observed change was -6.8 percent at a confidence interval of 95 (-11.3 to -2.4; $p = 0.001$). Elevated viral titers (greater than 106 viral copies per milliliters) at the start were associated with relative risk differences of -5.4 (-9.9, -1.0) at CI 95 % [17].

The Molnupiravir cohort experienced only 6.3 % vs. 9.2% of SARS-CoV-2 related inpatient treatments or fatalities as contrasted with the placebo (difference, 2.8 percentage points; 95 percent confidence interval, 5.7 to 0.0), according to a previously defined supporting assessment. On day 29, one fatality was recorded in the Molnupiravir cohort whereas nine deaths were observed in the placebo. In 216 of 710 individuals present in the Molnupiravir cohort and 231 out of 701 in the placebo experienced negative side effects. In 77.6 % of nasopharynx swabs, measurable viral genome had been identified in the beginning. The nasopharynx SARS-CoV-2 levels changed on average by -0.33 at a 95 % confidence interval (0.50, 0.16) across a period [25].

5.2 Paxlovid

In the randomized, double-blind, placebo-controlled, phase II/III EPIC-HR study (NCT04960202), Paxlovid was efficient in lowering the likelihood of acute SARS-CoV-2 infection in high-risk adults having SARS-CoV-2 symptoms [12]. Individuals needed a single determinant at minimum for acquiring acute SARS-CoV-2 infection, a COVID-positive test, and SARS-CoV-2 symptoms starting within five days after randomization to participate in the EPIC-HR study. Blood sugar, cardiac disease, autoimmune disease, high blood pressure, malignant tumors, obesity, severe respiratory, renal

illness, being older than 60 years, etcetera were constituted as risk factors. Individuals who received a vaccine or were previously infected with SARS-CoV-2 were not eligible for this trial.

EPIC-HR's cumulative effectiveness findings were similar to the findings of the planned interim assessment [12]. The modified intention-to-treat population was 697 in Paxlovid and 682 in placebo cohorts. Kaplan-Meier approximated the number of incidences of SARS-CoV-2 inpatient treatments or fatality on the 28th day to be 0.72 % with Paxlovid as compared to placebo which was at 6.53 % with a 95 % confidence interval, suggesting a reduced risk of hospitalization to 88.9 %. Paxlovid decreased the need for SARS-CoV-2 inpatient treatment or fatality due to any reason through day 28 by 87.8 percent compared to the placebo in individuals who were administered Paxlovid within five days of the onset of disease and had not received SARS-CoV-2 monoclonal antibodies. Modified intention-to-treat group had a population of 1039 while the placebo and Paxlovid groups had a population of 1046 in the Paxlovid and placebo cohort. The approximate incident rates were 0.78 % compared to 6.40 %. These rates have been comparable to those in the modified intention-to-treat groups when findings among all individuals given the drug within five days of the symptoms started (also those who got or were anticipated to get monoclonal antibodies) were evaluated. The effectiveness of Paxlovid had been the same in the modified intention-to-treat cohort 1 regardless of the categories grouped according to age (less and greater than 65 years), gender, diabetes, body mass index (underweight, normal weight, overweight, obese), time for the appearance of symptoms at the start of medication (less and greater than 3 days), and standard serological tests for the detection of SARS-CoV-2. Paxlovid was linked to approximately 0.9 log₁₀ viral copies per milliliters decline in SARS-CoV-2 genome titers on the fifth day in assessable modified intention-to-treat patients versus placebo ($p 0.001$), and a comparable outcome had been observed in assessable modified intention-to-treat cohort 1 patient [12].

In an intermediate assessment out of the phase II/III Evaluation of Protease Inhibition for COVID-19 in Standard-Risk Patients study (NCT05011513) in outpatient, normal risk group having lab serological

tests confirming SARS-CoV-2, Paxlovid had no substantially reduced SARS-CoV-2 symptoms in comparison to the placebo group [11]. Those without vaccinations who were at a minimal probability of inpatient treatment or dying were also part of this study, along with individuals over 18 who were immunized but had a single determinant at minimum for COVID-19 progression. Paxlovid or a placebo was given to individuals randomly after twelve hours for five days. Enrollment was only at 45 % of what was anticipated at the point of intermediate assessment. Paxlovid failed to achieve the main objective of prolonged, self-reported relief from SARS-CoV-2 disease manifestations all for 4 days consecutively compared to placebo. Nevertheless, compared to the placebo, Paxlovid resulted in a 70 percent decrease in inpatient treatment as well as a drop in SARS-CoV-2 titers up to almost 10 times. After randomization, 2 out of 333 individuals in the Paxlovid cohort were admitted to the hospital, but there had been no cause-related fatalities. Only 329 patients in the placebo cohort 8 had been hospitalized but there were no fatalities. The remaining participants (80 %) verified the initial assessment's findings. On the other hand, 3 out of 428 patients were admitted for inpatient treatment after randomization, while 10 out of 426 placebo group patients were admitted to the hospital with no sustained fatality [11]. In comparison to other innovative medications, Paxlovid pills deliver the most optimistic clinical result reducing inpatient treatment and fatality by up to 89 % [26, 28]. It is one of the most anticipated methods to overcome epidemic threats [29–31].

6. ANTIVIRAL PILLS AGAINST EPIDEMIC THREATS IN PAKISTAN

Pakistan is always at an increased risk of transmission of vector-borne diseases, infectious diseases, or epidemics due to economic instability and climate change. COVID-19 is one of the outbreaks which resulted in serious threats. Pakistan's present situation is unsatisfactory because it has a large population and lesser healthcare amenities. Pakistan is a third-world country with lower economic resources to deal with the SARS-CoV-2 epidemic in comparison to the United States, China, Russia, and the United Kingdom. The needed numbers of healthcare facilities are unfortunately not being met, which

is why controlling the spread of diseases and providing inpatient care is a challenge for Pakistan's government [32].

When it comes to vaccine hesitancy, Pakistan is not much different from the rest of the world. It is one of the two countries in the world, which could not eradicate poliovirus due to vaccine hesitancy prevalent in its population. Unfortunately, the COVID-19 vaccine has also come in the crosshairs of conspiracy theories and misperceptions in Pakistan and the saner voices have fallen prone to an astigmatic mentality [33].

The desire for better solutions, vaccine hesitancy, and better patient convenience from a less intrusive treatment led to the search for chemical molecules that could be administered as oral pills. Recently, Molnupiravir (EIDD-2801) and Paxlovid (PF-07321332), two potent oral antiviral pills were developed by Merck and Pfizer respectively [34].

7. CONCLUSION

As with several other respiratory illnesses, it is necessary to recall that immunization itself might not provide guaranteed protection, necessitating novel antiviral pills against SARS-CoV-2. In certain outpatient clinics, orally administered antiviral pills could be utilized effectively in the early phases of COVID-19 disease. Two highly effective orally administered antiviral pills for SARS-CoV-2 at the moment appear to be Paxlovid and Molnupiravir [35]. Approved medications for SARS-CoV-2 dramatically minimize mortality rate and inpatient care for individuals with light to moderate symptoms, according to initial investigations [36]. Both antiviral drugs can bridge the gap in the preparedness for viral outbreaks in low-income countries like Pakistan where vaccine hesitancy is one of the leading factors in combating disease. Lastly, possible impacts on cartilage and bones, observation of negative effects, as well as potential mutagenicity should be taken into consideration in the long run in prospective clinical studies of Paxlovid and Molnupiravir [35].

8. CONFLICT OF INTEREST

The authors declared that there is no conflict of interest and all authors contributed to the review and are liable

for the contents of the article.

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