Chapter

Treatments for the Infection by SARS-CoV-2

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Abstract

In late 2019, pneumonia cases from unknown origin were detected in Wuhan, China. The cause was a new coronavirus. The World Health Organization (WHO) named the virus SARS-CoV-2 and COVID-19 the associated disease. In the first months of 2020, this disease became a pandemic with a high lethality reported. Since then, the search for treatments began. We started by searching among treatments previously approved for human use that were not designed for COVID-19 and were considered to treat this condition. We continued searching on the therapeutics guidelines published by the WHO for the management of infection by SARS-CoV-2. Based on these results, we searched for the literature in PubMed to obtain further evidence on the drugs against SARS-CoV-2. The treatments presented in this chapter are Ivermectin, Hydroxychloroquine, Nitazoxanide, Azithromycin, Molnupiravir, Casirivimab-Imdevimab, Ritonavir-Nirmatrelvir, Ritonavir-Lopinavir, Remdesivir, and Favipiravir. Two years ahead of the start of the COVID-19 pandemic, a plenty of options for treatment have been investigated. Only a few of them have been shown to be efficient and safe. According to the WHO, Ritonavir-Nirmatrelvir outperforms other proposed therapeutics.

Keywords: COVID-19, SARS-CoV-2, therapeutics, molnuparivir, nirmatrelvir

1. Introduction

In late 2019, cases of pneumonia from unknown origin were detected in Wuhan, China. It was concluded that the cause was a new coronavirus [1, 2]. The World Health Organization (WHO) named the virus SARS-CoV-2 and COVID-19 the associated disease [1, 2]. In the first months of 2020, this disease became a pandemic with a reported high lethality. Since then, the search for treatments has begun.

SARS-CoV-2 is a coronavirus of the beta family and is related to the previously known SARS-CoV [3]. It is transmissible from human to human. The primary transmission is via respiratory droplets. Even so, transmission by other fluids has been reported. The protein that mediates the entry to the host cells is the so-called spike protein. It uses the angiotensin-converting enzyme 2 (ACE2) as a cellular receptor. It primarily

affects the lungs and the respiratory system with flu-like symptoms presentation [3]. Nevertheless, it also causes a wide spectrum of conditions from diarrhea to loss of smell and taste. The chief complication due to COVID-19 that can lead to death is pneumonia.

Once the SARS-CoV-2 enters the host cell, the viral RNA is attached to the host ribosome, translating into two large coterminal polyproteins. These proteins are then digested into components by proteolysis for packaging new virions. The papain-like protease (PLpro) and the coronavirus main protease (Mpro) are two proteases involved in this process. SARS-CoV-2 employs RNA-dependent RNA polymerase (RdRp) to replicate the genome of RNA. The four proteins: spike, Mpro, PLpro, and RdRp, are essential to virus assembly and pathogenesis. Mpro and RdRp are the targets for drugs against SARS-CoV-2 [4].

This pandemic has disrupted the global society. Besides global health, it has affected the economy and way of living since most of the interventions to stop the dissemination were non-pharmaceutical. Governments around the world exhorted people to stay at home and social distancing [5].

As a result of the global concern posed by this disease, some experiential recommendations emerged for its treatment. Social networks played a crucial role in the diffusion of these recommendations [6]. A couple of cases are hydroxychloroquine and ivermectin [7]. Much of the supposed evidence was absent or anecdotic. It generated false expectations and misinformation.

There were no previously approved therapeutics for COVID-19 since it was an emerging disease. Later in the pandemic, the WHO authorize the emergency use of some antivirals [8, 9]. The recommendations by other institutions of treatments for use outside of clinical trials were scarce. Such is the case for ivermectin [10].

This chapter aims to review the literature on therapeutics approved by the WHO for emergency use. It will also cover some of the treatments recommended and considered based on empirical results.

2. Material and methods

2.1 Search criteria

It was searched on the therapeutics guidelines published by the WHO [11] and the USA Federal Drug Administration (FDA) [12] for the management of infection by SARS-CoV-2. Based on these results, we searched for more literature in PubMed to obtain evidence from the drugs against SARS-CoV-2.

Besides searching for articles in Pubmed, we used the Google Scholar database to search about treatments against SARS-CoV-2 infection, including the words: Treatment, SARS-CoV-2, COVID-19, Therapeutics, WHO approved COVID-19 drugs, and FDA approved COVID-19 drugs.

The chief inclusion criteria were articles on treatments approved by WHO [11] and FDA [12]. The search also included treatments previously approved for human use but not for COVID-19 and, even so, were used.

3. Treatments suggested empirically

There are reports on drugs used empirically for the treatment of COVID-19, and the WHO has made statements on these treatments.

Drug	Indication
Ivermectin	Antiparasitic
Hydroxychloroquine	Antimalarial
Nitazoxanide	Antiparasitic
Azithromycin	Antibiotic

Table 1.
Some drugs used empirically without approval for emergency use.

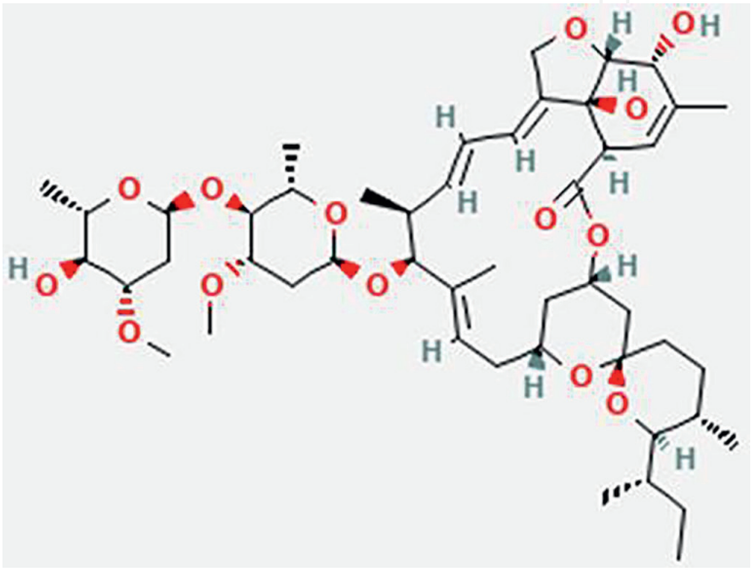

Figure 1.
Chemical structure of ivermectin. Source. Modified from: PubChem. National Library of Medicine [13].

Table 1 shows the drugs of empirical use without approval by the WHO and FDA, for their use against COVID-19 in humans, except in clinical trial settings.

3.1 Ivermectin

Ivermectin is a mixture of 22, 23-dihydroavermectin B1a, and 22, 23-dihydroavermectin B1b. It is macrocyclic lactose with a wide antiparasitic spectrum [10]. Its chemical structure [13], is shown in **Figure 1**.

It is considered that its action mechanism is by inhibiting the nuclear transport mediated by the heterodimer importin α/β1-responsible for the viral protein's translocation (HIV-1, SV40)-, necessary for its replication [14–16]. It has been reported that ivermectin inhibits the SARS-CoV-2 in vitro without stating clearly how it happens [16]. Since then, it was considered a potential treatment.

Even as studies suggest a reduction in mortality, most have methodological deficiencies [17–19]. Hence, further and rigorous evidence on the use of ivermectin against COVID-19 is necessary. Currently, the use of ivermectin is just recommended in clinical trial settings. Also, the Food and Drug Administration does not recommend the ivermectin use against COVID-19 due to the lack of evidence [20]. The same conclusion is supported by the Sanitary Technologies Assess Department from the Clinical and Sanitary Efficacy Institute [21].

The Pan American Health Organization states that there is no certainty about the risks and benefits from the use of ivermectin [22].

3.2 Hydroxychloroquine

Hydroxychloroquine is a 4-aminoquinoline drug aimed to treat malaria and rheumatologic conditions [22]. In **Figure 2**, its chemical structure is shown.

Due to the inhibition of SARS-CoV-2 in vitro, it was considered a potential treatment for COVID-19 [24]. Hydroxychloroquine received much public attention even at high political levels. It caused such a phenomenon that most random trials studying it were unable to finish properly, and those that were completed did not show any benefit [25].

Currently, the WHO makes a strong recommendation against its use in its latest therapeutics guidelines [11, 26].

3.3 Nitazoxanide

Nitazoxanide and its metabolite Tizoxanide could inhibit the in vitro growth of the canine coronavirus S-378 [26]. Wang M et al. [25] have reported that Nitazoxanide could also inhibit the SARS-CoV-2 growth (**Figure 3**).

Early studies suggested a beneficial effect of Nitazoxanide by reducing the disease severity of COVID-19 [28, 29]. Rocco et al [30], reported that Nitazoxanide did not show a difference in preventing admission to the intensive care unit for COVID-19 patients with pneumonia. In this study, it was showed a difference in secondary outcomes such as hospital discharge.

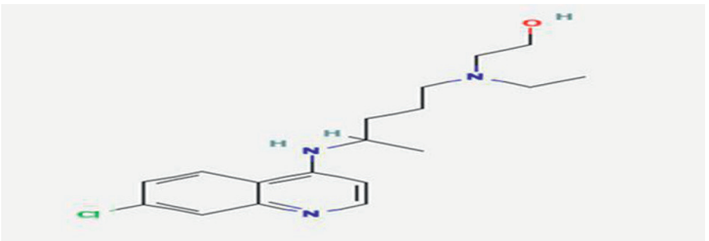

Figure 2.
Chemical structure of hydroxychloroquine. Source: Modified from PubChem. National Library of Medicine [23].

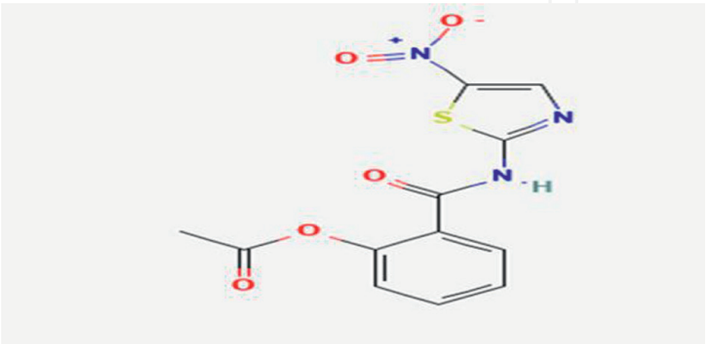

Figure 3.
Chemical structure of Nitazoxanide. Source: Modified from PubChem. National Library of Medicine [27].

There are few studies analyzing Nitazoxanide. So far, there is no evidence of a significant benefit for the COVID-19 treatment. The evidence on the use of nitazoxanide is scarce. The WHO does not include this drug in its living guideline for therapeutics and COVID-19 [11].

3.4 Azithromycin

Azithromycin is an antibiotic mainly prescribed for bacterial diseases and belongs to the family of macrolide [31]. This drug has been considered for COVID-19 treatment due to in vitro results. Its chemical structure is shown in **Figure 4**.

Oldenburg et al. [31], reported the results of a clinical trial involving azithromycin as a candidate. The primary outcome was the resolution of symptoms. It was not found a statistically significant effect between the experimental and the control group. From 23 secondary outcomes, only 5 showed statistically significant differences [33].

Azithromycin was chiefly used with other drugs. As it was used in combination with hydroxychloroquine, its effect and possible harms could not be clearly distinguished [34]. Nevertheless, so far, it is not recommended for COVID-19 treatment. The WHO only includes this drug tangentially in its therapeutics and COVID-19 living guideline while mentioning its use accompanied by hydroxychloroquine [11].

4. Treatments against COVID-19 considered for emergency use

In the following sections, we review some of the therapeutics and their recommendation status by the WHO [11] and FDA [12]. **Table 2** shows the drugs and treatments against COVID-19 treated in this section.

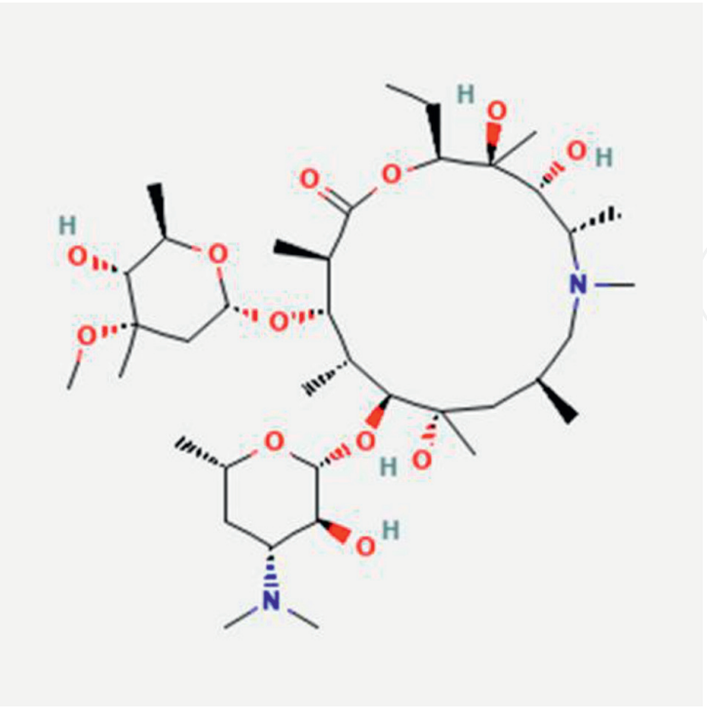

Figure 4.
Chemical structure of azithromycin. Source: Modified from PubChem. National Library of Medicine [32].

Drug	Indication	Dose	Observations
Molnupiravir	For patients with mild COVID-19 with hospitalization risk.	800 mg (four pills) twice a day for 5 days	Do not administer in children or pregnant women. There are no data about its safety.
Casirivimab-Imdevimab	Do not recommend for variants.	Intravenous. Ranging from 1200–2400 mg the total dose	The hospitalization risk decreases by 85%.
Ritonavir-Nirmatrelvir	Recommended as early as possible within the first 5 days since the onset of symptoms.	300 mg (two 150 mg tablets) of nirmatrelvir and 100 mg of ritonavir every 12 hours daily for 5 days	
Remdesivir	Recommended as early as possible within the first 7 days since the onset of symptoms.	Intravenous administration for 3 consecutive days with the following scheme: Day one: 200 mg Day two and three: 100 mg	Conditional recommendation since the existence of potentially most beneficial treatments.
Favipiravir		Not standardized yet	In animal models, it has potentiated the effect of molnupiravir.

Table 2.
Drugs for the emergency use against COVID-19.

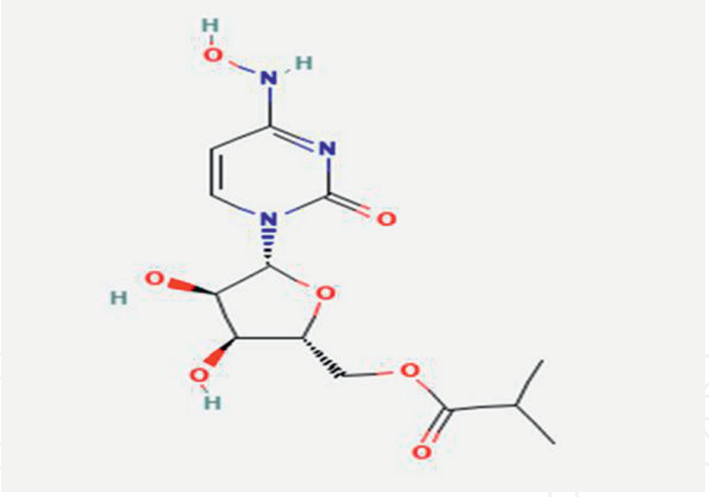

Figure 5.
Chemical structure of Molnupiravir. Source: Modified from PubChem. National Library of Medicine [36].

4.1 Molnupiravir

Molnupiravir is a drug originally designed to treat viruses such as influenza. In recent months, it has been proposed for use against COVID-19 [35]. The chemical structure is shown in **Figure 5**.

In the study by Jayk Bernal et al. [37], the molnupiravir group had better outcomes than the placebo one. The chief outcome was hospitalization or death.

Even as the sex was imbalanced, further analysis showed that the effect remained. There were no statistically significant differences regarding adverse events among the groups.

Singh et al. [35] conclude that the current evidence suggests that molnupiravir is effective for the prevention of hospitalization and deaths in mild COVID-19 patients. Nevertheless, further evidence is needed for the case of moderate and severe COVID-19 patients. Even far, Extance [38], mentions that the existence of only one pivotal study indicates that the evidence is very limited.

The WHO recommends the use of this drug conditionally due to the absence of data about long-term harms that may cause its use [11].

4.2 Casirivimab-Imdevimab

Casirivimab and imdevimab are monoclonal antibodies that target sites in the receptor binding domain of the SARS-CoV-2 spike glycoprotein [39]. The administration via has been one of the chief difficulties for their extensive use—its administration is intravenous.

The RECOVERY Collaboration Group included this treatment in their analysis [39]. They noted that casirivimab-imdevimab reduced the mortality significatively among seronegative patients (those without previously mounted humoral response).

The WHO recommends it conditionally. The reasons are that other drugs have proven to be more effective and safer. Also, these drugs are easiest to administer [11].

4.3 Ritonavir-Nirmatrelvir

Nirmatrelvir is a drug designed to treat covid-19 by targeting its main protease [40]. It has been administered with ritonavir. **Figure 6** shows the chemical structure of nirmatrelvir and ritonavir.

Hammond et al. [40] report that the incidence of hospitalization or death was lower by approximately 6% points in the treatment group than in the control group—observed in the interim and final analysis. The difference among adverse events was not statistically significant.

Its first approval for conditional use was issued in the United Kingdom on December 31, 2021. Since then, other countries have approved this drug in different modalities, such as for emergency use [43].

It is one of the few drugs strongly recommended by the WHO [11].

4.4 Ritonavir–Lopinavir

It is a combination of drugs that aim to inhibit the protease of SARS-CoV-2 and its use was motivated by previous experiences against SARS [44]. **Figure 7** shows the chemical structure of lopinavir.

Cao et al. [44] did not find any statistically significant difference between the control and experimental group in their trial. The primary outcome they took was the decrease of two points on a severe scale or discharge. They recommend further studies to prove or discard benefits from ritonavir–lopinavir.

The WHO makes a recommendation against the use of this combination [11].

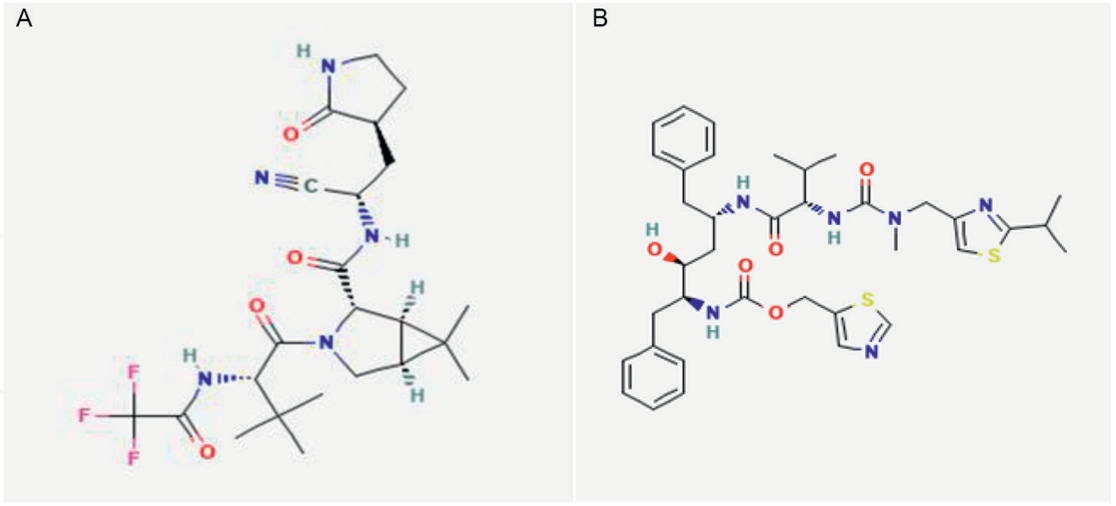

Figure 6.
Chemical structure of: (A) nirmatrelvir; and (B) ritornavir. Source: modified from PubChem. National Library of Medicine [41, 42].

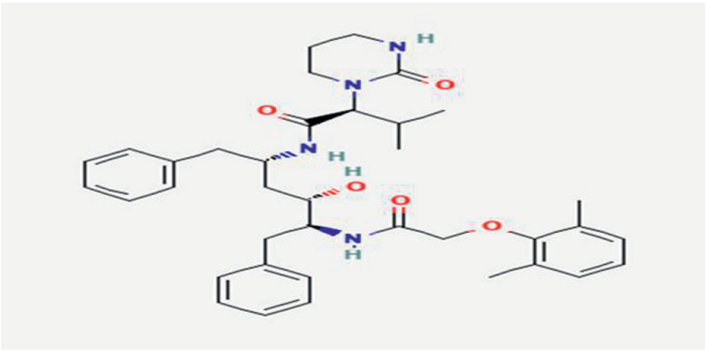

Figure 7.
Chemical structure of Lopinavir. Source: Modified from Pubchem. National Library of Medicine [45].

4.5 Remdesivir

Remdesivir is another drug that inhibits SARS-CoV-2 and was considered for its use due to previous research on its effect on SARS and MERS [46]. The chemical structure is shown in **Figure 8**.

According to Beigel et al. [46], remdesivir outperformed placebo in their clinical trial, which consisted of 1062 patients. They took discharge or hospitalization for monitoring as primary outcome. The patients in the remdesivir group reached the primary outcome approximately 5 days before the patients in the placebo group. In their trial, they administered remdesivir intravenously for three consecutive days with the following regime:

1. Day one: 200 mg

2. Day two and three: 100 mg (each day)

Wang Y et al. [48] did not find a statistically significant benefit from the use of remdesivir. Nevertheless, the samples consisted of 237 participants, and

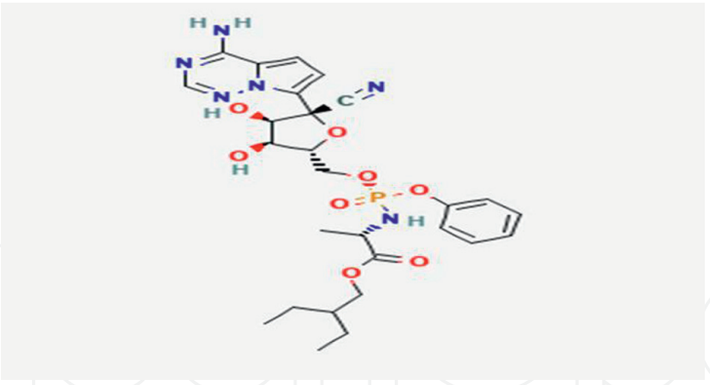

Figure 8.
Chemical structure of remdesivir. Source: Modified from Pubchem. National Library of Medicine [47].

a numerical difference among the groups was observed—supporting the use of remdesivir.

Spinner et al. [49], conducted a clinical trial comparing 5- and10-day treatment versus standard care for patients with moderate COVID-19. The differences in the primary outcome (degree on a seven-point scale) were statistically significant between the 5-day group and the standard care group. It was not observed for the differences between the 10-day group and the standard care group. Even though some results were statistically significant different, the authors are uncertain of the clinical importance.

The WHO conditionally recommends remdesivir. They suggest using it in the first 7 days after the onset of symptoms [11].

4.6 Favipiravir

Favipiravir is a drug with an active agent that halts viral replication of SARS-CoV-2 [50, 51]; its chemical structure is shown in **Figure 9**.

Manabe et al. [51] conducted a systematic review and meta-analysis on the use of favipiravir against SARS-CoV-2. They found evidence supporting the use of favipiravir to clear the virus. It was observed in various studies a viral clearance around the seventh day after the start of treatment. However, they suggest further analysis and controlled clinical trials since the evidence was heterogeneous and not straightforwardly comparable. Also, they conclude it is necessary for further research on the dose regime to have definitive conclusions.

The WHO only mentions favipiravir tangentially as a drug that might improve the outcomes by combining it with molnupiravir, observed in animal models [11].

5. On the current challenges on COVID-19 treatments

After the approval and research on treatments, there are two chief questions to address. The first question is how to distribute the drugs with equity. The other point is how they perform in the face of new SARS-CoV-2 variants.

Regarding the distribution of the treatments, the ones administered orally present clear advantages over the ones administered intravenously. Nevertheless, as pointed out by Bajaj and Stanford [53], there are important challenges to address. So far, the inequities detected are the manufacturing and pricing obstacles, and some countries buying most of the current stock [53].

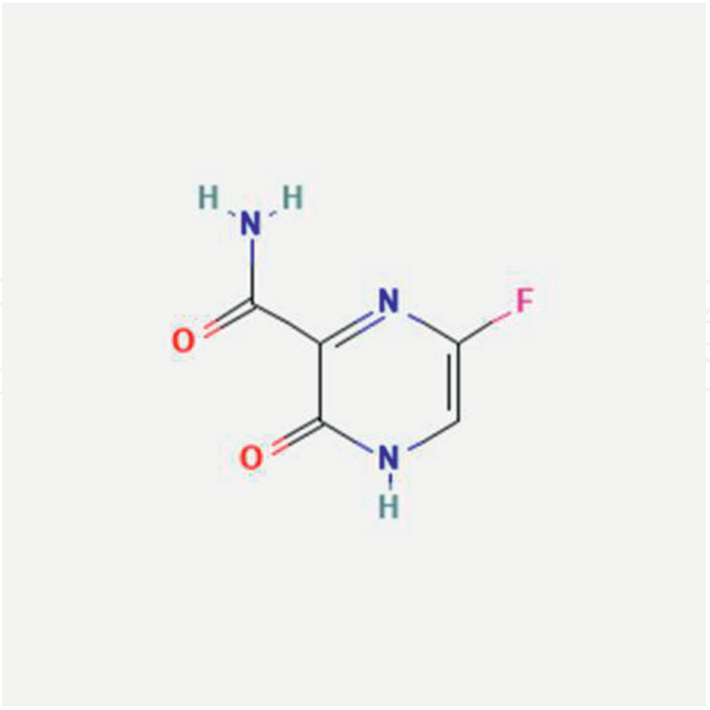

Figure 9.
Chemical structure of favipiravir. Source: Modified from Pubchem. National Library of Medicine [52].

In the face of new SARS-CoV-2, some studies have addressed the question on which therapeutics remain effective for COVID-19. According to the review made by Fernandes et al. [54], the currently approved antivirals, such as molnupiravir, ritonavir-nirmatrelvir, and remdesivir remain as effective for variants of concern as for the early versions of SARS-CoV-2. Mainly due to their mechanisms of action.

6. Conclusions

Two years ahead of the COVID-19 pandemic start, plenty of treatment options have been investigated. Only a few of them have resulted in effective and safe alternatives. The WHO [11] and the FDA [12] keep updated on the sources and status of the scientific evidence of each proposal. According to the WHO, ritonavir-nirmatrelvir outperforms other proposed therapeutics.

As SARS-CoV-2 continues mutating, an open question is whether these treatments will remain effective for these new versions. The evidence shows that they are for spike-mutated versions of the virus.

Finally, even though some drugs have been approved, availability is not even in the countries. The factors behind this include the distribution systems and logistics besides costs.

Conflict of interest

The authors declare no conflict of interest.

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