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Review

A review on the interaction of nucleoside analogues with SARS-CoV-2 RNA dependent RNA polymerase

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ABSTRACT

The outbreaks of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) in 2019, have highlighted the concerns about the lack of potential vaccines or antivirals approved for inhibition of CoVs infection. SARS-CoV-2 RNA dependent RNA polymerase (RdRp) which is almost preserved across different viral species can be a potential target for development of antiviral drugs, including nucleoside analogues (NA). However, ExoN proofreading activity of CoVs leads to their protection from several NAs. Therefore, potential platforms based on the development of efficient NAs with broad-spectrum efficacy against human CoVs should be explored. This study was then aimed to present an overview on the development of NAs-based drug repurposing for targeting SARS-CoV-2 RdRp by computational analysis. Afterwards, the clinical development of some NAs including Favipiravir, Sofosbuvir, Ribavirin, Tenofovir, and Remdesivir as potential inhibitors of RdRp, were surveyed. Overall, exploring broad-spectrum NAs as promising inhibitors of RdRp may provide useful information about the identification of potential antiviral repurposed drugs against SARS-CoV-2.

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1. Introduction

Recent novel severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), are continuously killing people worldwide [1,2]. The incubation period for CoV disease-2019 (COVID-19) is between 2 and 14 days and transmission of the disease from one person to another is

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caused by the respiratory drops of cough and sneezing of people with this disease [3–5].

The most common symptoms of this disease are fever, cough and muscle weakness, and fatigue [5–7]. Uncommon symptoms include headache, runny nose, sore throat, hemoptysis, diarrhea, loss of taste or smell, and acute respiratory failure [8,9]. Some therapeutic approaches such as oxygen therapy, respiratory support, mechanical ventilation, proper nutrition, and prevention of pulmonary embolism can be used as supportive medical treatments for COVID-19 patients [10,11]. In cases of severe infections, supportive therapies such as antiviral drugs and inflammatory cytokines as well as immune system modulator drugs can be used for patients [12,13]. For example, the United States National Institutes of Health list several antiviral drugs which may be used to treat COVID-19 including Remdesivir, Lopinavir/Ritonavir and Ivermectin.

The World Health Organization (WHO) has not yet approved the specific antiviral treatment for COVID-19, but according to past experience, the use of antiviral drugs has attracted a great deal of attention in development of promising therapeutic platforms against this disease [14–16]. For example, the US Food and Drug Administration has approved the antiviral drug Veklury (Remdesivir) for treating COVID-19 patients. The introduction of antiviral drugs can dramatically increase the lifespan of people living with SARS-CoV-2 and reduce its associated mortality [17,18]. However, the treatment process may be failed due to the adverse effects of treatment regimens, and the longevity of the SARS-CoV-2 treatment process [19–23]. SARS-CoV-2 replication cycle consists of several stages, many of which have been successfully used as targets for the development of antiviral drugs [17]. Currently, the focus of the world is on finding a therapeutic approach for treatment of COVID-19.

As the first country to host the virus, China began researching the SARS-CoV-2 from the beginning [24,25]. On the other hand, the most powerful independent computer system in the world (SUMMIT) has been able to identify elements or compounds that can prevent the SARS-CoV-2 outbreak [26]. Researchers have also run thousands of programs on a computer to determine which compounds can effectively prevent the body's cells from becoming infected with the SARS-CoV-2 [27]. In the course of this analysis, SUMMIT evaluated what compounds could interact with the main biological macromolecules of SARS-CoV-2 and thus preventing its interaction with cells [27].

What is certain is that efforts are underway to ensure different strategies to treat and mitigate the damage of COVID-19 including vaccination and antiviral therapy. Advances in development of antiviral drugs will dramatically change the fate of COVID-19 infection from a risky disease to a controllable chronic infection [14,16,28]. In the near future, developed antiviral drugs will show higher potential and greater tolerability than conventional drugs. Some detailed knowledge about the potential of medications and diets, toxicity, drug interactions, and drug resistance will help physicians choose the most appropriate treatment regimen for particular patients with different underlying medical conditions [29–33].

2. Different classes of inhibitors against SARS-CoV-2

Different classes of inhibitors can be developed for the treatment of SARS-CoV-2 infection. These classes include enzyme inhibitors (including protease, polymerase, methyltransferase (MTase) and exonuclease inhibitors), receptor inhibitors and viral fusion inhibitors [34–36]. The physio-pathological roles of these inhibitors are tabulated in Table 1.

3. RNA-dependent RNA polymerase (RdRp)

The activity of RdRp is vital for +RNA viral replications. After CoV entry into the host cell, the viral RNA, which consists of 14 open reading frames (ORFs), is released into the cytoplasm for viral replication (Fig. 1A) [43]. The ORFs 1a and 1b segments assemble two replication polyproteins which are further hydrolyzed in different non-structural proteins (nsps). The RdRp (nsp12) is involved in CoV genomes and protein synthesis [44]. RdRp is known to play a crucial role in the replication of RNA viruses [33]. The deep groove domain as the core segment of RdRp interconnected by fingers [two catalytic domains (F and G)], palm [five catalytic motifs (A–E)], and thumb parts covering the active site of enzyme (Fig. 1B) [45].

Table 1
The physio-pathological roles of different inhibitors used against SARS-CoV-2.

Inhibitors	Physio-pathological role	Ref.
Protease	Inhibit the cleavages of the long polyprotein chains to provide necessary proteins for replication of the virus	[37]
Polymerase	Inhibit viral replication	[38]
MTase	Inhibit the prevention of recognition by the host innate immune system	[39]
Exonuclease	Inhibit resistance to many of the available antivirals	[40]
Receptor	Inhibit the binding of virus to the host cells	[41]
Viral fusion	Inhibit the SARS-CoV-2 S protein-mediated cell-cell fusion	[42]

4. Nucleoside analogue (NA) inhibitors

In this review we aimed to present an overview on the application of NAs as potential enzyme inhibitors used to be repurposed as promising candidates in inhibiting SARS-CoV-2 polymerase.

In general NAs induce potential preventive effects on viral replication by three well-studied mechanisms (Fig. 1C) [46]. As for different CoVs, amino acid sequence similarity for viral RdRp ranges from 70 to 100%, it is suggested that NAs could promisingly act as wide-ranging inhibitors of CoV infection [47]. However, nsp14-ExoN proofreading activity of CoVs results in their protection from several NAs [48,49]. To potentially inhibit CoVs, well-developed NAs should be designed to either less recognized by ExoN or interact with polymerase at a rate exceeding ExoN excision velocity.

Some NAs are prodrugs, requiring intracellular phosphorylation to induce their antiviral effects [50,51]. In some cases, intracellular phosphorylation is performed by several host enzymes that convert the prodrug into monophosphate, diphosphate, and finally the active trisphosphate forms of these drugs [52].

Ju et al. [53] showed the ability of SARS CoV RdRp, which is almost similar to that of SARS-CoV-2, to incorporate 2′-F, Me-UTP, the active compound of Sofosbuvir prodrug, where it acts as potential agent to terminate the viral RNA replication.

Different NAs have been assessed to explore their efficiency in interacting with the active site of SARS-CoV-2 RdRp. *In vitro* studies and *in silico* analysis have revealed that some of the broad-spectrum antiviral drugs can be potential therapeutic platforms against the CoVs. NAs imitate the natural substrates of the SARS-CoV-2 RdRp and result in fast or slow chain termination based on their geometry and binding affinity. It has been shown that Cidofovir triphosphates serves as a potential candidate in a delayed terminator for SARS-CoV-2 RdRp, however Abacavir, Ganciclovir, and Stavudine triphosphates inhibit SARS-CoV-2 RdRp, and 2′-*O*-methylated UTP significantly terminates the SARS-CoV-2 RdRp reaction [54]. Further studies have been reported that Sofosbuvir, Alovudine, Tenofovir alafenamide, AZT, Abacavir, Lamivudine, and Emtricitabine can serve as potential inhibitor of the SARS-CoV-2 RdRp [55] determined by mass spectrometry (MS) Fig. 1D. Also, it has been revealed that rapid interaction of Favipiravir by viral RdRp leads to SARS-CoV-2 lethal mutagenesis [56]. Didanosine is one of the NAs whose administered dose in adults is based on body weight [57]. Repurposing Didanosine as a promising treatment for COVID-19 has been reported based on single-cell RNA sequencing outcomes [57].

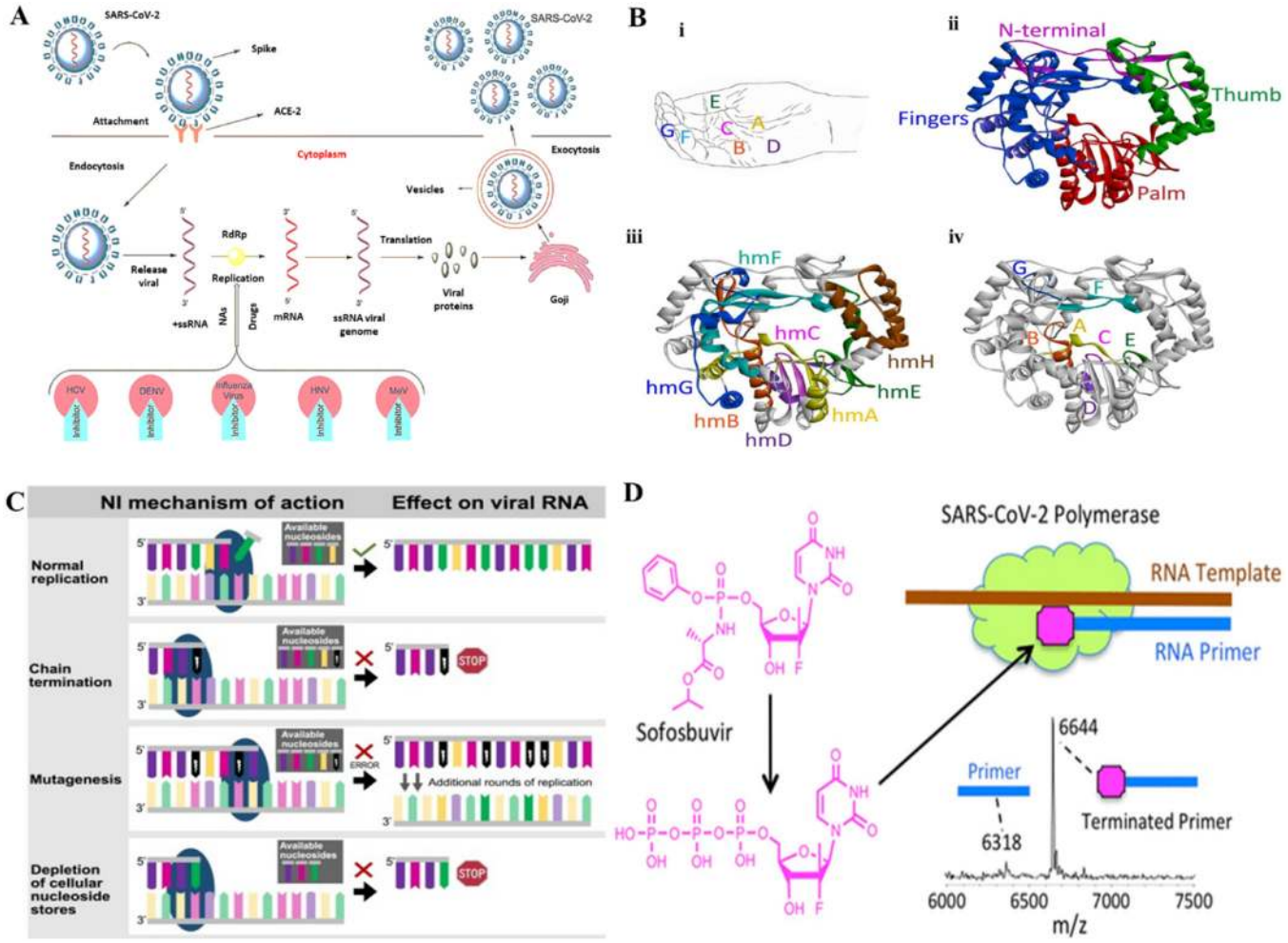

Fig. 1. (A) The life cycle of different RNA viruses *via* the RdRp (1). (B) Structure of RdRp (PDB ID: 1KHW), (i) motifs, (ii) ribbon structure, (iii) conserved homomorphs, (iv) functional motifs (3). (C) Different inhibition mechanisms by NA (4). (D) Prodrug activation Sofosbuvir and the inhibition of RdRp.
Reprinted with permission form Refs [43, 45, 46, 55].

5. Prediction of potential commercially NAs against SARS-CoV-2

Hu et al. [58] reported that in the computational studies, Abacavir (sulfate) as a NA showed the high binding affinity with several crucial proteins of SARS-CoV-2 such as RdRp, 3C-like protease, papain-like protease, and helicase with different affinities of 3.03 nM, 28.42 nM, 22.90 nM, and 3.06 nM respectively. As depicted in Fig. 2A, the key domains for binding in protein sequences are screened by heat-map analysis. In the case of 3C-like protease [Fig. 2A(i)], the crucial residues for binding exist at three main parts. It was determined that different kinds of small molecules lead to varying weights of these three segments. For papain-like protease [Fig. 2A(ii)], the preferred binding domains present at the 100-120th residue part. RdRp [Fig. 2A(iii)], shows a key position at 500-584th residues to be a critical binding domain for different small molecules. The ribbon model was also presented to visualize binding domains in 3D structures (Fig. 2B). As displayed in Fig. 2B(i), for 3C-like protease the domain in the middle section (180-200th residues) is the main binding domain because of high weight in most molecular modelling studies. The papain-like protease of SARS-CoV-2 is highly similar to that of SARS. It was shown that the central part of papain-like protease is involved in the interaction with small molecules [Fig. 2B(ii)]. Also, the model predicted for RdRp, showed that two probable sites exist in the protein structure [Fig. 2B(iii)] [58].

Ribavirin was reported to show potential antiviral activity against SARS-CoV [59] and MERS-CoV [60]. It was also shown that Acyclovir fleximer as an antiviral agent can inhibit MERS-CoV and HCoV-NL63 infection with IC_{50} values of 23 μM and 8.3 μM, respectively [61]. Moreover, Remdesivir has been shown to significantly block the replication of human CoV through inhibition of viral polymerase. For example, it was shown that Remdesivir has potential antiviral effects against SARS-CoV, MERS-CoV, and SARS-CoV-2 [47,62,63]. Some other nucleoside analogues such as β-d-N4-hydroxycytidine [64,65] and Gemcitabine [66] show potential antiviral effects against human CoV. Elfiky [67] showed that as SARS-CoV-2 RdRp show 97% homology to SARS, the interaction of different antiviral agents such as Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir with RdRp was docked to explore their binding affinity with SARS-CoV-2 proteins [Fig. 2C(i)]. They found that Setrobuvir, YAK, and IDX-184 show the highest binding affinity to SARS-CoV-2 RdRp among other antiviral agents [Fig. 2C(ii)].

Development of advanced docking algorithms has helped in the molecular recognition of various nucleoside analogue drugs against key inhibitors of SARS-CoV-2, however the stability of the complex formed, viability of molecular interactions and mechanism has been further established by studying their dynamics. In their computational study performed by Zhang and Zhou [68] they have depicted the antiviral property of Remdesivir using molecular dynamics simulations [68]. It

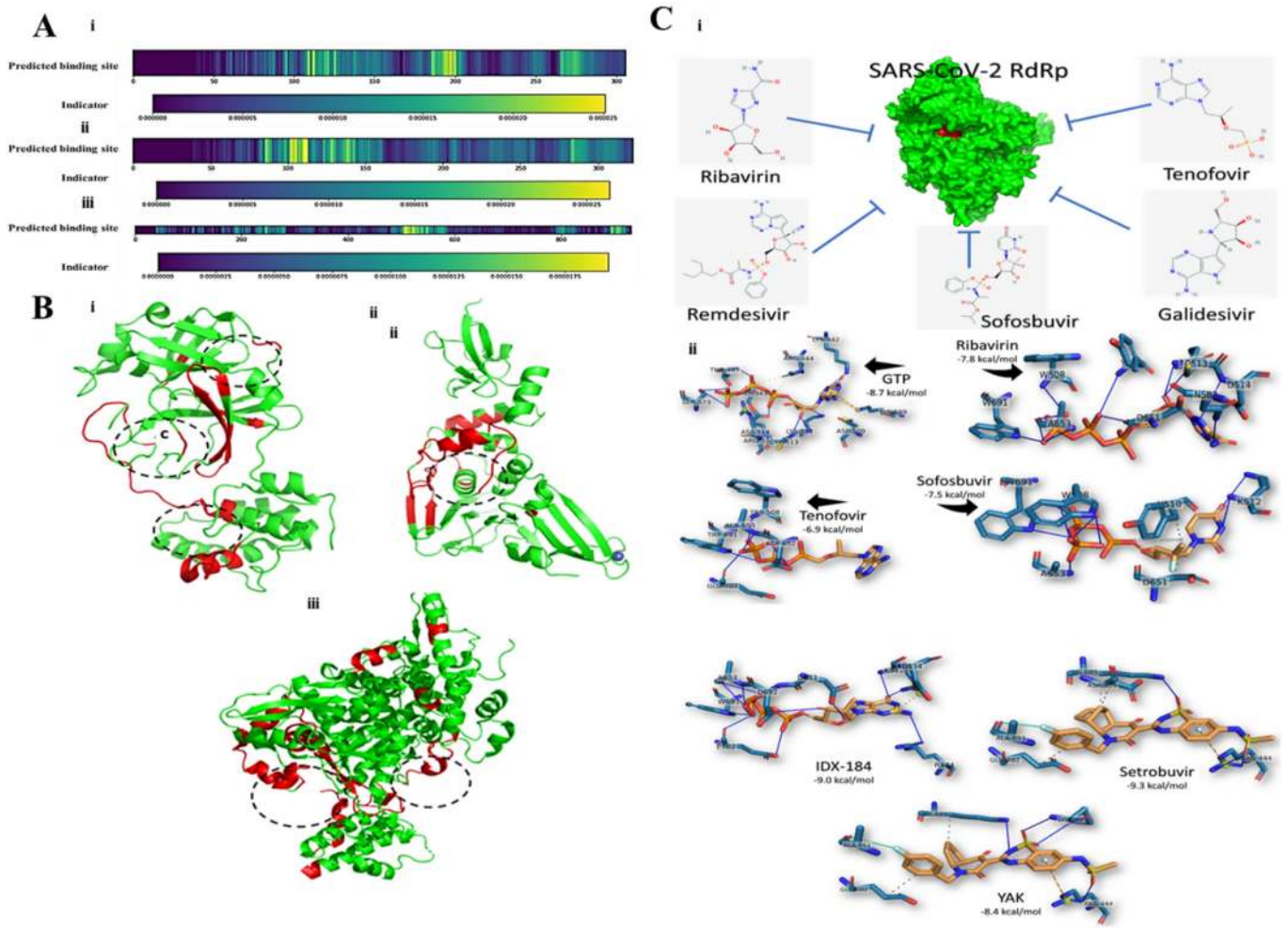

Fig. 2. (A) The binding domain of different protein sequences of SARS-CoV-2 predicted by heat-map analysis. (B) The visualization of 3D structure based on a ribbon model. (i) 3C-like protease, (ii) Papain-like protease, (iii) RdRp [58]. (C) Docking study of different nucleoside analogue and SARS-CoV-2 RdRp. (i) Schematic representation, (ii) binding energy calculation and contribution of residues [67].
Reprinted with permission form Refs [58, 67].

has been speculated that Remdesivir acts as a competitive inhibitor of RdRp against its natural inhibitor which is ATP. Free energy perturbation studies have shown that Remdesivir binds to RdRp with a 100-fold K_d when compared with ATP. The key residues involved for strong interactions were D618, S549 and R555. The resulting root mean square deviations (RMSD) and root mean square fluctuation (RMSF) values proved remarkable stability of the protein-drug complex during the course of time [69–72].

The study has been further confirmed under *in-vivo* conditions performed by Gordon et al. They elaborated the mechanism of Remdesivir antiviral activity and concluded that insertion of the triphosphate form of Remdesivir at a position (i) would terminate the synthesis of RNA at i + 3 position [72]. A second mechanism of inhibition has also been proposed by Tchesnokov et al. [38]. Increased concentrations of NTPs can adversely lower down the RdRp inhibition by Remdesivir. As a result, Remdesivir gets incorporated in the first transcription. It has been observed that upcoming UTP could not get incorporated opposite to Remdesivir residue. This is because of a significant steric clash with A558. This leads to a template dependent inhibition of SARS-CoV-2 RdRp [38].

Fig. 3 shows the two mechanisms of inhibition by Remdesivir. Although, other nucleoside analogues such as Gemcitabine and Sofosbuvir have shown quite strong interactions when molecular docking has been performed, molecular dynamics studies have revealed a higher RMSD and RMSF values when compared with Remdesivir. In their study, Zhang et al. [73] has shown that the Gemcitabine-RdRp and Sofosbuvir-RdRp complexes when simulated for a timescale of 100 ns have a greater RMSD and RMSF values when compared with Remdesivir [73]. Since molecular dynamics studies require a lot of computational cost therefore not much studies have been performed.

6. Clinical development of NAs

The recent advancement of NAs with antiviral efficiency can result in the development of anti-SARS-CoV-2 therapies [74]. The intracellular activation by active phosphorylation and associated metabolism should be considered during development of NAs as antiviral drugs. Several NAs as potential inhibitors of RdRp, such as Favipiravir, Sofosbuvir, Ribavirin, Tenofovir, and Remdesivir, were shown to be potential candidates for the possible treatment of SARS-CoV-2. Table 2 shows the practical considerations of antiviral therapies done against SARS-CoV-2.

7. Conclusion and remarks

In this paper, some potential NAs were introduced to be repurposed as promising therapeutic candidates for the treatment

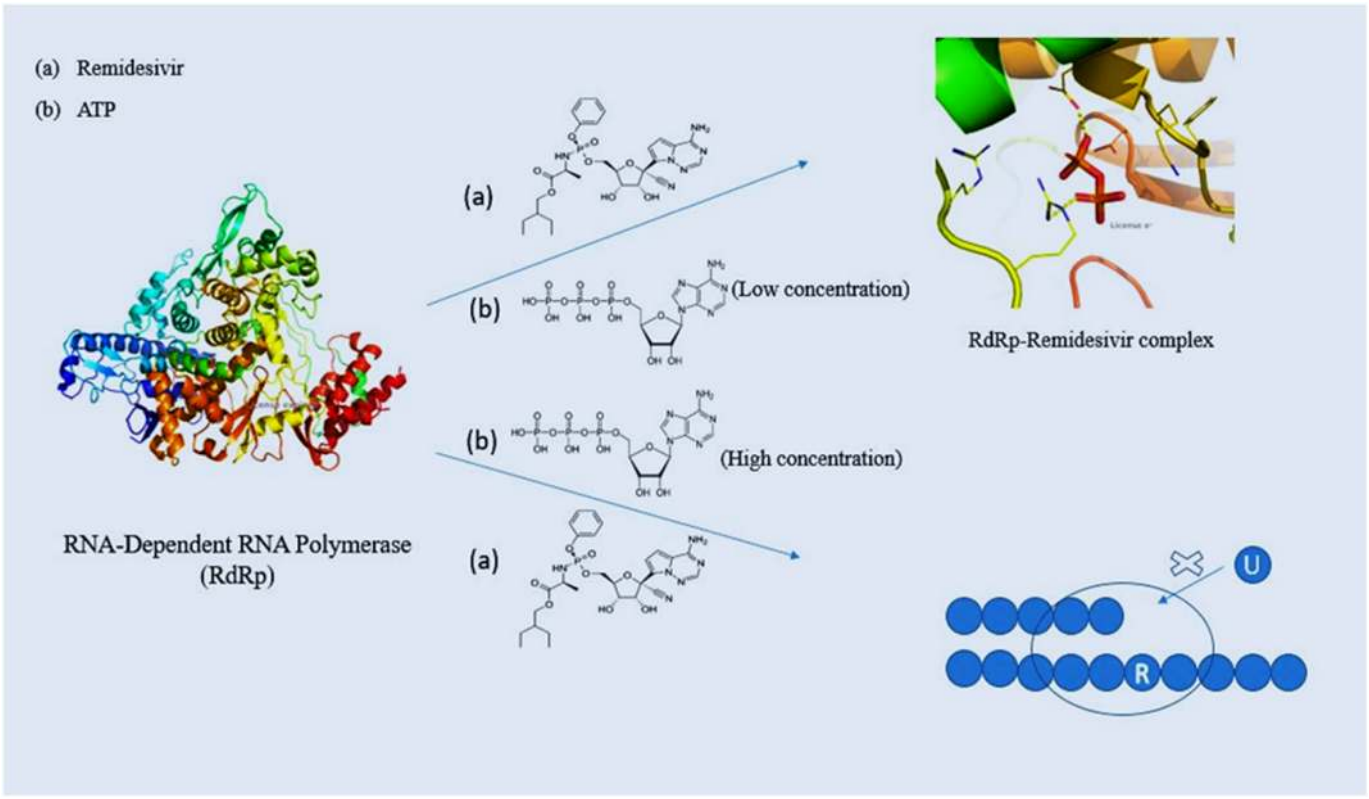

Fig. 3. Schematic representation of two different modes of action of Remdesivir. At low concentration of ATP, the RdRp-Remdesivir complex is formed which competitively inhibits the binding of ATP to RdRp. At high concentration, Remdesivir is incorporated in the first transcribe and compromises the uptake of UTP in the second transcribe resulting in chain termination.

of COVID-19 based on their interaction with RdRp. Currently, a number of NAs have been studied to inhibit human CoV *in vitro* and proceed into clinical trials against SARS-CoV-2. However more well-developed NAs are still demanded, considering factors such as therapeutic impacts, adverse effects, feasible synthesis, less labor, and cost effectiveness. It can be suggested that these candidates can be considered for the clinical treatment of COVID-19. Also, researchers should conduct more experiments on these drug candidates to provide guidelines for clinical trials and treatment of the SARS-CoV-2. Since, the rate of global infections is continuously increasing and the COVID-19 outbreak grows into a global concern, this review may pave the way for development of some promising therapeutic platforms.

Declaration of competing interest

The authors declare no conflict of interest.

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Table 2
Clinical outcomes of antiviral therapies reported against SARS-CoV-2.

Drug	Dosing	Outcome	Ref(s).
Favipiravir	1600 mg twice daily on day 1, 600 mg twice daily from day 2 to day 5	Patients had improvement and did not need mechanical ventilation over time, numerical decrease in time to defervescence	[75,76]
Sofosbuvir	A single daily oral tablet containing 400 mg for 14 days	Alone or in combination with other antivirals can decrease the median duration of hospital stay	[77–79]
Ribavirin	400 mg every 12 h for ribavirin	In combination with other antivirals shorter median time, improved recovery of 67%	[80,81]
Tenofovir	45 mg daily for 2 years for chronic hepatitis B	Possible clinical protective effect of Tenofovir	[82]
Remdesivir	IV over 30 min	Improvement of patients' survival, reduced rate of symptoms, proportion of ICU treatments	[83–86]

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