Beclabuvir can inhibit the RNA-dependent RNA polymerase of newly emerged novel coronavirus (SARS-CoV-2)

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Abstract

Recent emergence of novel coronavirus (SARS-CoV-2) in Wuhan, China has resulted more than 14,510 global deaths. To date well-established therapeutics modules for infected patients are unknown. In this present initiative, molecular interactions between well-known antiviral drugs against the Hepatitis-C virus (HCV) have been investigated theoretically against the RNA-dependent RNA polymerase (RdRp) of SARS-CoV-2. HCV and SARS-CoV-2 are both +ssRNA viruses. At 25°C beclabuvir, a non-nucleoside inhibitor of the RdRp of the HCV can efficiently bind to RdRp of the SARS-CoV-2 ($\Delta G_{AutoDock} = -9.95 \text{ kcal mol}^{-1}$) with an inhibition constant of only 51.03 nM. Both the $\Delta G_{London}$ and $\Delta G_{GBVI/WSA}$ values were - 9.06 and - 6.67 kcal mol$^{-1}$, respectively for SARS-CoV-2. In addition, beclabuvir also shows better binding free energy ($\Delta G_{vina} = 9.7 \text{ kcal mol}^{-1}$) than that of the Thumb 1 domain of RdRp of HCV ($\Delta G_{vina} = 7.7 \text{ kcal mol}^{-1}$). InterProScan has suggested the RNA-directed 5'-3' polymerase activity existed within 549 to 776 amino acid residues of RdRp. Moreover, major interacting amino acid residues were I591, Y621, C624, D625, A690, N693, L760, D762, D763 and E813-N817. Molecular interaction suggests occupancy of beclabuvir inside the active site environment of the RdRp which is essential for viral
RNA synthesis. In conclusion, results suggest beclabuvir has high therapeutic potential as an anti-SARS-CoV-2 drug.

Keywords

Novel coronavirus (SARS-CoV-2), RdRp, HCV, beclabuvir, *in silico*, molecular docking

Introduction

The newly emerged novel coronavirus (SARS-CoV-2) was first reported from patients with connection history at the Wuhan Seafood market in Hubei province of China in December 2019. Clinical symptoms of the infection caused by this newly arrived pneumonia virus were similar to the previously emerged severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) infections (Zou, Ruan et al. 2020). As of 23rd March, 2020, confirmed 3,32,930 positive cases have been registered with 14,510 global deaths out of which 3276 deaths occurred in China and 5476 deaths in Italy (WHO 2020). The super-spreader feature of SARS-CoV-2 is continuously increasing the confirmed positive cases and so far the estimated global death rate is 4.35 % (WHO 2020). Social distancing and travel restrictions have been implemented globally as non-pharmaceutical measures to control the fire of the outbreak (Wilder-Smith and Freedman 2020). In the beginning, governments of different nations evacuated their citizens from China and initiated quarantine protocols to save them. In certain serious areas of China and Italy citizens have been locked-down in their homes as they are at the fourth stage of the Pandemic (Fanelli and Piazza 2020). Due to the severity of
virus outbreak, the World Health Organisation (WHO) has declared this new novel coronavirus outbreak as a Pandemic (Gates 2020). Flowing China, Italy has now become the new epicenter of SARS-CoV-2 infection where 41035 positive cases and 3423 deaths of SARS-CoV-2 infection have been recorded with in a few weeks (Porcheddu, Serra et al. 2020).

In the South-East Asian region, India ranks as the third most-affected country after Indonesia and Thailand respectively (WHO 2020). India, has reported 295 confirmed positive cases and 10 deaths from SARS-CoV-2 infection as of 20th March 2020. Maharastra, the state of India, has become the most affected state, which indicates its vulnerability to infectious diseases. Patients with an international travel history and symptoms of viral-flu were suspected and tested with expensive SARS-CoV-2 test costing nearly 67 US$. The respiratory illness caused by this new SARS-CoV-2 collectively called, coronavirus disease 2019 (COVID-19) (WHO 2020). In the very beginning of 2020, and the new decade, COVID-19 has impacted on the global economy and resulted in a near shutdown of the global equity market, for example on 19th February 2020 Tesla, Inc. ended the day down by 17 %, which is the second-worst drop ever. The global airline industry has also been badly knocked-down by the COVID-19 global Pandemic.

Coronavirus is a member of a large virus family, the coronaviridae and subfamily orthocoronavirinae which usually causes respiratory illness to humans and animals (Van Der Hoek, Pyrc et al. 2004). Soon after the first report of the outbreak, a research group lead by Dr. Zhang at Fudan University, China has sequenced the complete genome which is nearly 30,000 nucleotides long and encodes 10 proteins (MN908947.3), (Wu, Zhao et al. 2020). Like SARS-CoV, the newly emerged novel coronavirus (SARS-CoV-2) is about 60 -140 nm in diameter and has trimeric spike

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glycoprotein (S), membrane capsid protein (M), small membrane protein, viral nucleoprotein (N) and an RNA dependent RNA polymerase (RdRp), which are essential for virus replication (Zhu, Zhang et al. 2020). Usually, entry of human coronavirus is mediated by interactions of spike glycoprotein with angiotensin converting enzyme 2 (ACE2), aminopeptidase N (AmoPep-N) and dipeptidyl peptidase 4 (DP-4), (Li, Moore et al. 2003; Raj, Mou et al. 2013). The new SARS-CoV-2 is phylogenetically closer to known coronavirus strains of bat-SL-CoVZC45 and bat-SL-CoVZXC21 than SARS-CoV (Lu, Zhao et al. 2020).

Research has suggested nonstructural proteins (NSPs) and structural proteins (SPs) of SARS-CoV-2 have linked a function. For example, NSP can block the host innate immune response and the viral envelope promotes viral assembly and release (Phan 2020). However, optimal therapeutic drug for treating the infected patients are still unknown. In the entire genome of SARS-CoV-2, 93 mutations were detected out of which 29 mis-sense mutations were found in the ORF1ab polyprotein that encodes the RdRp (Phan 2020). SARS-CoV-2 and HCV, are both +ssRNA viruses and have 22.22 % sequence similarities between their RdRps. In this study, an attempt has been made to identify the most efficient RdRp inhibitor of SARS-CoV-2 with the help of computational approaches by screening the inhibitory properties of commonly used RdRp inhibitors of the HCV.

Methods

Data sampling and analysis

The nucleotide sequences of SARS-CoV-2 were originally retrieved from NCBI-Virus, Accession Number: MN908947.3. Multiple sequence alignment was performed
using MEGA-v2016, (Dutta, Shityakov et al. 2018). The amino acid sequence of the viral RdRp was scanned for identification of known functional domains/motifs using InterPro Scanner (Hunter, Apweiler et al. 2009). Homology modeling of the RdRp was carried out using SwissModel and quality was checked using PROCHECK (Dutta, Nag et al. 2018). Rigid-body molecular docking between several established antiviral drugs and RdRp from SARS-CoV-2 was carried out using AutoDock (v4.2), (Dutta, Shityakov et al. 2018). Additionally, implicit solvation was performed using Molecular Operating Environment (v9.10) (Dutta, Shityakov et al. 2018). Molecular docking studies were visualized using PyMol (Dutta, Shityakov et al. 2018). Molecular interactions of different antiviral drugs i.e., beclabuvir, tegobuvir, dasabuvir, deleobuvir, setrobuvir, radalbuvir, lomibuvir, remdesivir, uprifosbuvir and favipiravir were investigated with the RdRp of SARS-CoV-2.

Results

The amino acid sequences of the viral RdRp were compared by multiple sequence alignment in order to understand the evolutionary difference among with previously reported coronavirus strains. Dissimilarities were prominent among coronavirus strains isolated from a different source of host organisms (Supplementary file, Figure 2). The RdRp (PDB:6NUR) of previously emerged SARS-CoV was used as a template in obtaining the homology model of the RdRp (Kirchdoerfer and Ward 2019). The homology model of RdRp showed 96.35 % sequence similarities with 6NUR. The GMQE and QMEAN were 0.83, and -0.71, respectively, where 98.1 % of the amino acid residues were within Ramachandran favored zone which combinedly suggest the high quality of the homology model. Molecular docking studies are
summarised in Table 1. Data presented in Table 1 suggest thermodynamically favoured binding properties of beclabuvir and other antiviral drugs with the RdRp of SARS-CoV-2. Among all the aniviral drugs studied beclabuvir showed the best $\Delta G_{\text{AutoDock}}$ of 9.95 kcal mol$^{-1}$ followed by tegobuvir (-9.68 kcal mol$^{-1}$) and dasabuvir (-9.38 kcal mol$^{-1}$). However, best $\Delta G_{\text{London}}$ was found for lomibuvir (-10.96 kcal mol$^{-1}$) followed by setrobuvir (-10.52 kcal mol$^{-1}$) and dasabuvir (-10.38 kcal mol$^{-1}$). Setrobuvir also displayed best $\Delta G_{\text{GBVI/WSA}}$ (-7.48 kcal mol$^{-1}$) followed by remdesivir (-7.36 kcal mol$^{-1}$), radalbuvir (-7.36 kcal mol$^{-1}$) and dasabuvir (-6.68 kcal mol$^{-1}$). Although, lowest inhibition constant is offered by remdesivir (18.12 nM) but, best $\Delta G_{\text{AutoDock}}$ (-9.95 kcal mol$^{-1}$) and inhibition constant (51.03 nM) is offered by beclabuvir with $\Delta G_{\text{London}}$ and $\Delta G_{\text{GBVI/WSA}}$ of -9.06 kcal mol$^{-1}$, -6.67 kcal mol$^{-1}$ respectively (Table 1). Currently, WHO is conducting a clinical trial program, called global "Solidary Trial", in which only remdesivir is included.

Discussion

Upon entry inside the host cell, viral RdRp enables multiplication of the +ssRNA virus (Fouad, Soliman et al. 2019) and eventually the consequences of the viral infection in the host (Kirchdoerfer and Ward 2019). Thus, RdRp has always been a favorite drug target in antiviral therapeutic research (Tchesnokov, Feng et al. 2019). Nowadays, different antiviral strategies such as, capping the virus particle which enables tethering it into the host epithelial cell membrane (O’Hanlon, Leyva-Grado et al. 2019), designing a DNA vaccine against the major glycoproteins displayed outside the viral capsid protein (Dutta 2020), targeted delivery of miRNA (Leon-Icaza, Zeng et al. 2019), combination antiviral drug therapy (Pruijssers and Denison 2019), etc are
commonly employed for therapeutic purposes. Results of the present study suggest that ATP binding domain and RNA-directed 5'-3' polymerase activity of the RdRp exist within 549-776 amino acid residues (GO:0003968) and this stretch of amino acids is crucial for RNA synthesis (Figure 3). Beclabuvir is a non-nucleoside polymerase inhibitor that potentially inhibit nonstructural protein 5B (NS5B) of HCV (Garimella, Tao et al. 2018). Upon intracellular uptake beclabuvir allosterically binds to the non-catalytic Thumb 1 site (Figure 4) of viral RdRp which slowdown the RNA synthesis process (Garimella, Tao et al. 2018). However, in the case of SARS-CoV-2 beclabuvir occupies the active site environment (ASE), (Figure 5) of the RdRp which is essential for the RNA-dependent polymerase activity (Fouad, Soliman et al. 2019). The major interacting residues were I591, Y621, C624, D625, A690, N693, L760, D762, D763 and E813-N817 (Figure 1). Moreover, beclabuvir also showed better binding free energy (ΔG\textsubscript{vina} = 8.0 kcal mol\textsuperscript{-1}) for the active site environment (ACE) of RdRp than that of HCV (ΔG\textsubscript{vina} = 7.7 kcal mol\textsuperscript{-1}). Hence the present study finds a high potential for beclabuvir to be effective as therapeutic agent against SARS-CoV-2 multiplication as well as infection. Properties of molecular interaction of beclabuvir and other FDA approved antiviral drugs against HCV infection are summarized in Table 1 which could also be effective to use against SARS-CoV-2 infection. This preliminary study may be contributory towards the anti-epidemic efforts against the newly emerged SARS-CoV-2 (Corman, Landt et al. 2020; Huang, Wang et al. 2020; Hui, I Azhar et al. 2020; Zhu, Zhang et al. 2020) and may help to shortlist antiviral drugs against SARS-CoV-2 for clinical trials.
Conclusion

Throughout history, the human race had been challenged by multiple global pandemics. However, with the advancement of medical science and at the age of Artificial Intelligence, global health disaster of this scale, probably would not be difficult to manage. However, the things that matter most are the time and the supply of resources. As reported by WHO, the original outbreak began in December-2019 and within three months, global death toll due to SARS-CoV-2 has reached the tragic milestone of 14,000. In conclusion, this rapid study suggests beclabuvir, and other commonly used antiviral drugs for HCV could be utilized as anti-SARS-CoV-2 drugs to control the devastation of the outbreak. However, more studies are required before the practical use of these antiviral drugs.

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Declaration of interests

The author declares no competing financial interests.
Figure Legends

**Figure 1.** Molecular interaction between beclabuvir and RNA dependent RNA polymerase of newly emerged novel coronavirus (RdRP_{SARS-CoV-2}). **A.** Major interacting amino acid residues which occupy the catalytic site of RdRP_{SARS-CoV-2}. **B.** Binding pose of beclabuvir with RdRP_{SARS-CoV-2}.

**Figure 2.** Phylogenetic position of the RdRP_{SARS-CoV-2}. Tree was constructed using multiple sequence alignment followed by neighbor-joining method with 1000 bootstraps replicates. The alpha-numeric values at right indicate Protein Data Bank accession ID. The numeric values at the top of the tree branch indicate bootstraps replicate values.

**Figure 3.** Protein domain/motif analysis of the RdRP_{SARS-CoV-2}. The yellow highlighted region indicates the catalytic site (RNA-directed RNA-polymerase activity) of the RdRP_{SARS-CoV-2}.

**Figure 4.** Molecular interaction between beclabuvir and NS5B_{HCV}. Beclabuvir binds at the thumb domain (blue) of NS5B_{HCV}.

**Figure 5.** Binding site of RdRP_{SARS-CoV-2} for commonly used antiviral drugs. **A.** Binding posture of beclabuvir at the catalytic site of RdRP_{SARS-CoV-2}. **B.** Overlapped binding sites of antiviral drugs with RdRP_{SARS-CoV-2} (Molecular surface mainly in blue-gray indicates the binding site).

**Table 1.** Summary of molecular docking properties among antiviral drugs and RdRP_{SARS-CoV-2}.
Table 1. Summary of molecular docking properties among antiviral drugs and RdRpsSARS-CoV-2.

| Rank | Drugs   | $\Delta G_{\text{AutoDock}}$ | $\Delta G_{\text{London}}$ | $\Delta G_{\text{GBVI/WSA}}$ | $\text{LE}$ | $\text{IC}$ | $\text{VdWE}$ | $\text{UE}$ | $\text{refRMS}$ |
|------|---------|-------------------------------|-----------------------------|-----------------------------|-----------|--------|---------|--------|--------|
| 1    | Beclabuvir | -9.95                         | -9.06                       | -6.67                       | -0.21     | 51.03  | -9.93   | -1.6   | 246.28 |
| 2    | Tegobuvir  | -9.68                         | -9.15                       | -6.5                        | -0.26     | 80.03  | -11.34  | -1.3   | 260.11 |
| 3    | Dasabuvir  | -9.38                         | -10.38                      | -6.68                       | -0.27     | 133.34 | -11.39  | -1.42  | 258.22 |
| 4    | Deleobuvir | -9.32                         | -8.59                       | -7.42                       | -0.21     | 147.52 | -10.03  | -2.55  | 257.38 |
| 5    | Setrobuvir | -8.71                         | -10.52                      | -7.48                       | -0.23     | 414.74 | -9.51   | -1.55  | 249.51 |
| 6    | Radalbuvir | -8.52                         | -9.2                        | -7.36                       | -0.22     | 568.39 | -11.8   | -2.81  | 254.26 |
| 7    | Lomibuvir  | -8.42                         | -10.96                      | -6.02                       | -0.27     | 667.5  | -11.11  | -1.88  | 256.5  |
| 8    | Remdesivir | -6.47                         | -9.2                        | -7.36                       | -0.15     | 18.12  | -11.43  | -3.49  | 269.88 |
| 9    | Uprifosbuvir| -6.17                         | -9.76                       | -6.41                       | -0.17     | 30.02  | -9.75   | -3.85  | 242.9  |
| 10   | Favipiravir | -5.66                         | -7.21                       | -4.19                       | -0.51     | 70.06  | -5.87   | 0.05   | 262.93 |

$^1$Gibbs’s free binding energy using Autodock, $^2$London binding free energy ($\Delta G_{\text{London}}$), $^3$Gibbs’s free binding energy generalised born volume intergral/weighted surface area (GBVI / WSA), $^4$ligand efficiency, $^5$inhibition Constant, $^6$Vdw hb desolv energy, $^7$unbound energy, cluster root mean square, reference root mean square, energy unit = kcal mol$^{-1}$. Inhibition constant unit = nM at 25º C temperature. *Ranking of the drugs are made based on $\Delta G_{\text{AutoDock}}$, $\Delta G_{\text{London}}$, $\Delta G_{\text{GBVI/WSA}}$ and inhibition constant.
FIGURE 1

A.

\[ \Delta G_{\text{Vina}} = -8.0 \text{ kcal mol}^{-1} \]
\[ \Delta G_{\text{AutoDock}} = -9.95 \text{ kcal mol}^{-1} \]
\[ \Delta G_{\text{London}} = -9.06 \text{ kcal mol}^{-1} \]
\[ \Delta G_{\text{GBVI / WSA}} = -6.67 \text{ kcal mol}^{-1} \]
FIGURE 1

B.
FIGURE 2

SARS coronavirus (2ACF)
  Severe acute respiratory syndrome-related coronavirus (2FAV)
    Middle East respiratory syndrome-related coronavirus (SDUS)
      Middle East respiratory syndrome-related coronavirus (SHIH)
        Severe acute respiratory syndrome-related coronavirus (1YSY)
        SARS coronavirus Frankfurt (5NFY)
          Severe acute respiratory syndrome-related coronavirus (2G9T)
            Severe acute respiratory syndrome-related coronavirus (2FYG)
              RNA-dependent RNA polymerase Wuhan seafood market pneumonia virus (YP 009725307.1)
                SARS-CoV (6NUR)
                  Severe acute respiratory syndrome-related coronavirus (2OP9)
                    Middle East respiratory syndrome-related coronavirus (4RSP)
                      Middle East respiratory syndrome-related coronavirus (5WKJ)
                        Middle East respiratory syndrome-related coronavirus (4YLU)
                          Middle East respiratory syndrome-related coronavirus (4WMD)
                            Human beta coronavirus (5WWW)
                              Severe acute respiratory syndrome-related coronavirus (2H8S)
                                Severe acute respiratory syndrome-related coronavirus (5TL6)
                                  Severe acute respiratory syndrome-related coronavirus (2F8E)
                                    Severe acute respiratory syndrome-related coronavirus (5E6J)
                                      Severe acute respiratory syndrome-related coronavirus (1QZ8)
                                        Human beta coronavirus (5W8T)
                                          Human beta coronavirus (4REZ)
                                            Human beta coronavirus (4P18)
                                              Human beta coronavirus (5BI8)
                                                Middle East respiratory syndrome-related coronavirus (5K03)
FIGURE 3

Entry matches to this protein

- Domain
  - RNA-dir_pol_C
    - InterPro domain
    - 549 - 776

GO terms

**Biological Process**
- transcription, RNA-templated (GO:0006351)
- viral RNA genome replication (GO:0036594)

**Molecular Function**
- RNA binding (GO:0003723)
- RNA-directed 3'-5' RNA polymerase activity (GO:0003966)
- ATP binding (GO:0005524)

**Cellular Component**
- None
FIGURE 4

\[ \Delta G_{\text{Vina}} = 7.1 \text{ kcal mol}^{-1} \]
FIGURE 5

A. 

B.
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