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Docking-based virtual screening and identification of potential COVID-19 main protease inhibitors from brown algae

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ABSTRACT

COVID-19 (SARS-CoV-2) is a viral disease that causes acute respiratory syndrome, which has increased the morbidity and mortality rate throughout the world. World Health Organization has declared this COVID-19 outbreak as pandemic and classified health emergency throughout the world. In the recent past, outbreaks of SARS and MERS have shown the interspecies transmission potential of coronaviruses and limitations of already prescribed drugs to overcome this global public health issue. Therefore, there is a dire need to identify a new regimen of targeted drugs from natural compounds having anti-COVID19 potential. This study aimed at screening 1018 brown algal natural compounds (many of them previously reported to have immune-modulatory effects) having probable anti-COVID19 potentials. The source compounds were extracted from MarinLit, a database dedicated to marine natural products and screened against COVID-19 main protease. The top seven compounds were further analysed, and their interactions with the active site were visualized. This study will further warrant screening the potent compounds against the virus in-vitro conditions.

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1. Introduction

Since the very recent outbreak of SARS-CoV-2 (novel COVID-19) that has emerged as a global pandemic and public health emergency of international concern (Chow et al., 2020), scientists worldwide have been working relentlessly to develop antivirals that can provide immunization against this deadly virus. Several studies have also been conducted to understand the virulence mechanisms of SARS-CoV-2. For instance, it has been suggested that SARS-CoV-2 can recognize human ACE2 more efficiently than the former SARS-CoV, thus increasing the capacity of the human-to-human transmission of SARS-CoV-2. Furthermore, the SARS-CoV-2 spike protein can be seen to have a strong binding affinity with human ACE2. Consequently, the spike protein directly binds with the host cell surface ACE2 receptor, facilitating the virus entry and replication (Wan et al., 2020; Zhang et al., 2020c). Hence, the ACE2 receptor can be regarded as an essential target against SARS-CoV-2.

Another desirable target for anti-corona virus drug design is the main protease which plays an essential role in viral gene expression and replication through the proteolytic processing of replicase poly-proteins translated from the viral RNA (Xue et al., 2008; Zhang et al., 2020b). Interestingly, the PDB 6LU7 protein structure, the main protease of SARS-CoV-2, has recently been determined (Liu et al., 2020). Thus, the screening of potential protease inhibitors blocking the replication of coronavirus is of great relevance for developing anti-corona viral therapeutics.

With the urging need to search for safe and efficient antivirals against SARS-CoV-2 (COVID-19), natural products and, in particular, plants have been of considerable interest among researchers (Islam et al., 2020; Mohammadi and Shaghaghi, 2020; Yang et al., 2020; Zhang et al., 2020a). Most recently, a study by Thuy et al. (2020) showed that the compounds of garlic essential oil possessed anticoronavirus properties, as they were found to have good inhibitory activities on ACE2 and PD6LU7 proteins.

In the last few decades, scientists have investigated a diverse class of natural products due to their pharmacologically active components. These natural products possess pharmacological properties having significant applications in the identification and isolation of bioactive compounds. Nearly 30% of biologically active formulations having signi

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Among these, marine-derived natural compounds possess a wide range of new substances with various pharmacological potentials (Arif et al., 2004). Since the last five decades, numerous investigations have demonstrated that marine algae (seaweeds), microorganisms, and marine invertebrates possess active compounds having therapeutic potentials against several diseases (Yasuhara-Bell et al., 2010). The marine environment is considered to provide chemical diversity in the development of novel pharmacologically active agents. Additionally, seaweeds possess certain novel bioactive constituents having pharmacological activities, which are not present in terrestrial organisms (Gustafson et al., 2004). These unique metabolites present in marine algae are phlorotannins, fucoids, fucoxanthin, oxylipins, meroditerpenoids, and diterpenes (Globmitza and Gersterberg, 1985; Duran et al., 1997; Reddy and Urban, 2009; Biris-Dorhoi et al., 2020). Various pharmacological application (antibacterial, antifungal, anti-inflammatory, neuroprotective, anti-tumor, etc.) of meroditerpenoids (Fallahydroquinone, Methoxybifurcarenone, & Sargaquinic acid), phlorotannins (7,2'-Bieckol, 7-Hydroxyeckol hepta-acetate), and diterpenes (Triacetoxy-18-hydroxy-2,7-dolabelladiene) isolated from different species of marine brown algae have been reported in the literature (Bennamara et al., 1999; Horie et al., 2008; Kim et al., 2016; Ioannou et al., 2011; Hamann et al., 2020).

Seaweeds are broadly classified into three classes, i.e. red seaweed (Rhodophyceae), green seaweed (Chlorophyceae), and brown seaweed (Phaeophyceae). These seaweeds are rich source of bioactive dietary components like proteins, polyunsaturated fatty acids, lipids, vitamins, terpenes (chroomeunicolide), dietary fibers, pigments (fucoxanthin, phycoerythrin, phycocyanin), colloids, minerals (Potassium, Iron, sulfur), aromatics, carbohydrates (fucoidan), acetonogens, polyphenols (phlorotannins), and antioxidants (de Souza Barros et al., 2013; Khalid et al., 2018). Earlier, seaweeds were used by food processing and pharmaceutical industries due to their gelling properties, but now scientists are investigating their therapeutic role as complementary and alternative medicine. Various studies have highlighted the use of seaweeds to manage different diseases like cancer, obesity, diabetes, hypertension, inflammation, neurological disorders, viral and bacterial infections (Khalid et al., 2018). Diverse class of primary and secondary natural compounds isolated from seaweed have shown promising effects against different viral, bacterial and fungal pathogens (Bedoux et al., 2017; Lima-Filho et al., 2002; Wang et al., 2012). Initially, screening these natural compounds with pharmacological properties is necessary to evaluate them as potential inhibitors for these viral proteins. Therefore, keeping in view the emerging use of seaweed natural products and their pharmacological role, this study was designed in which a database of 1018 natural compounds from Brown algae was scanned against the covid-19 virus. The top seven compounds were analysed, and their interactions with the active site were visualized, which are presented herein.

2. Materials and methods

2.1. Protein preparation

For the Covid-19 main protease, crystal structure from Protein Data Bank (PDB ID = 5R82) in complex with 6-(ethylenamino) pyridine-3-carbonitrile (RZS) was used as a template for the virtual screening (VS). The retrieved 3D crystal structure was prepared for the docking simulation by removing all the water molecules and any co-crystallized hetero molecules. For all atoms, the 3D-protonation was achieved in an implicit solvated environment (Temperature: 300 K; salt concentration: 0.1; pH: 7). 3D protonation was done for all atoms in an implicit solvated environment at pH 7, a temperature of 300 K, and a salt concentration of 0.1. The complete structure was energy minimized using Amber10:EHT force field until a root-mean-square (RMS) gradient of 0.1 kcal/mol/A was reached. The centroid of the native ligand determined the active sites of the proteins.

2.2. Dataset preparation

One thousand eighteen (1018) brown algal compounds were extracted from the MarinLit database and used to test against the main protease receptor. Ligand.mdmb database of compounds was built from SMILES format. By using the Amber10:EHT force field, the energy of compounds was minimized up to 0.001. The structure of the enzyme was opened in the Molecular Operating Environment (MOE) software.

2.3. Docking-based virtual screening

The targeted Covid-19 main protease was subjected to docking-based virtual screening using the MOE dock program. The docking procedure was validated by re-docking of the native ligands. Comprehensive re-docking protocols were carried out to validate the docking algorithm. Native co-crystallized ligands were extracted and prepared comparably as for others. Docking was carried out using the Triangle matcher algorithm (placement stage) and scored by the London dG scoring function. Subsequently, best-scored poses were submitted to rigid receptor protocol (refinement stage). The final score was calculated with GBVI/WAS dGsf scoring function. Next, we changed the placement parameter from triangle matcher to alpha triangle and none. While rescoring was carried out using other two scoring functions (ASE and affinity dG).

To validate whether our approach can distinguish between active and inactive compounds, we have chosen randomly 1500 drug-like decoys from our in-house database of decoys [25]. We docked the ‘validation set or decoy set’ into the binding site of Covid-19 main protease (PDB ID = 5R82) as a positive control.

3. Results and discussion

3.1. In silico docking results

Docking simulation is considered an essential tool in drug discovery and the first step in any drug design process. The binding energy and the explanation of the protein inhibitor interactions are valuable results for further experimental and theoretical studies. The scores ranked the compounds by GBVI/WAS binding free energy calculation (Kcal/mol). Compounds with binding energy values less than −8.500 kcal/mol were considered best for Covid-19 main protease inhibition. The top seven structurally diverse scaffolds were selected for further analysis (Table 1). All the selected compounds have shown the potential to inhibit the Covid-19 main protease. We also performed docking studies on lopinavir and Remdesivir as comparative standards. Moreover, we calculated the binding energy of phytochemical rutin found as the promising inhibitor of SARS-CoV-2 Mpro (Al-Zahrani 2020). The calculated binding energy values are enlisted in Table 2.

Surface diagrams of all the seven selected hits are shown in Figs. 1–3. Three-dimensional interaction plots of the selected compounds into the binding site of 5R82 are shown in Figs. 1–3. 7,2'-Bieckol with lowest binding energy (−10.7855) establishes hydrogen bond interactions with Thr24, Thr26, Gly143 and Glu189 (Fig. 1a). 7-Hydroxyeckol hepta-acetate forms hydrogen bond interactions with Thr26, Gly143, Cys145, Glu166, Glu189. Met165 forms a π-sulfur interaction with a methoxy group. While the π-σ type of interactions with Thr25 also stabilizes the ligand-enzyme complex (Fig. 1b). 5-Hydroxy-cystofuran-quinol forms three hydrogen bond interactions with Thr24, Thr26, Ser46. Met165 forms π-sulfur interactions with furan oxygen (Fig. 2a). Sargaquinic acid forms three hydrogen bond interactions with Pro168, Gly143, and Gln189. Met165 forms a π-sulfur interaction with the methoxy group (Fig. 2b). 3-D interaction plot of the triacetoxy-18-hydroxy-2,7-dolabelladiene shown four hydrogen bond interactions with Val42, Thr45, Ser46 and Gln189 (Fig. 3a).
Met165 forms a π-sulfur interaction. 3-D interaction plot of the Fallahydroquinone shown four hydrogen bond interactions with Thr24, Thr26, Glu166 and Gln189 (Fig. 3b). Methoxybifurcarenone has shown five hydrogen bond interactions with Thr24, Ser46, Met165, Glu166 and Arg188 (Fig. 3c).

Scientists via in-silico docking have studied the interaction among COVID-19 main protease and natural plant & marine products (Al-Zahrani, 2020; Gentile et al., 2020; Sampangi-Ramaiah et al., 2020). Chinese herbal medicines, plant phytochemicals (rutin), and some antiviral drugs (ritonavir) have been screened (in silico) to assess

Table 1

| Compound ID             | Structure | Binding energy (kcal/mol) |
|-------------------------|-----------|---------------------------|
| 7,2'-Bieckol            |           | -10.7855                  |
| 7-Hydroxyeckol-hepta-acetate |           | -9.9611                   |
| 5-hydroxy-cystofurano-quinol |           | -9.6373                   |
| Sargaquinonic acid      |           | -9.4775                   |
| Triacetoxy-18-hydroxy-2,7-dolabelladiene | | -8.8656                   |
| Fallahydroquinone       |           | -8.55697                  |
| Methoxybifurcarenone   |           | -8.5488                   |
their probable inhibitory effect on coronavirus-2019 (Narkhede et al., 2020; Zhang et al., 2020a). Nevertheless, no other investigation has analysed the interaction between natural compounds present in Brown algae and COVID-19 main protease to date. This study highlights the probable anti-COVID19 natural compounds present in brown algae. A total of 1018 natural compounds present in Brown algae were scanned against the COVID-19 virus. Out of these, the top seven compounds were further analysed, and their interactions with the active site were visualized. Docking revealed that all the compounds had significant binding in COVID-19 main protease (PDB ID = 5R82).

A plethora of research work has been performed to discover new drug candidates through drug repurposing and computational techniques since the worldwide spread of the COVID-19 pandemic. Several drug targets have also been explored. SARS-CoV-2 main protease (M<sup>pro</sup>) has been exploited as a validated target for drug discovery.

### Table 2

| Compound ID | Structure | Binding energy (kcal/mol) |
|-------------|-----------|--------------------------|
| Lopinavir   | ![Lopinavir Structure](image) | -9.2395 |
| Remdesivir  | ![Remdesivir Structure](image) | -9.0012 |
| Rutin       | ![Rutin Structure](image) | -8.5204 |

![Fig. 1. (a,b): (Left) Modelled mode of binding of compounds 7,2'-bieckol and 7-Hydroxyeckol hepta-acetate in Covid-19 main protease (PDB ID = 5R82) active site. (Right) Close-up view of 3-D interaction plot of compounds 7,2'-bieckol and 7-Hydroxyeckol generated by Discovery Studio Visualizer into the binding site of Covid-19 main protease (PDB ID = 5R82).](image)
Fig. 2. (a,b): (Left) Modelled mode of binding of compounds 5-hydroxy-cystofuranquinol and Sargaquinoc acid in Covid-19 main protease (PDB ID = 5R82) active site. (Right) Close-up view of 3-D interaction plot of compounds 5-hydroxy-cystofuranquinol and Sargaquinoc acid generated by Discovery Studio Visualizer into the binding site of Covid-19 main protease (PDB ID = 5R82).

Fig. 3. (a-c): (Left) Modelled mode of binding of compounds Triacetoxy-18-hydroxy-2,7-dolabelladiene, Fallahydroquinone and Methoxybifurcarenone in Covid-19 main protease (PDB ID = 5R82) active site. (Right) Close-up view of 3-D interaction plot of compounds Triacetoxy-18-hydroxy-2,7-dolabelladiene, Fallahydroquinone and Methoxybifurcarenone generated by Discovery Studio Visualizer into the binding site of Covid-19 main protease (PDB ID = 5R82).
efforts. Mostly, peptides and peptidomimetics having Michael Acceptors as warheads are discovered/identified as SARS-CoV-2 main protease inhibitors.

Natural products are considered a rich source of drug lead compounds due to their great structural diversity. Several classes of flavonoids, alkaloids and triterpenes have been found as inhibitors of SARS-CoV-2 main protease. In an in-silico study, Al-Zahrani found rutin as the promising inhibitor of SARS-CoV-2 $M_{\text{PBO}}$. A comprehensive review by Banerjee et al. (2020) and Vougogianipoulou et al. (2021) explored the recent developments in the search for small-molecule inhibitors, including natural products targeting the SARS-CoV-2 $M_{\text{PBO}}$. Alliin, oleic acid, kaempferol, quercetin, luteolin-7-glucoside, naringenin, and oleanoer are reported among natural products promising inhibitors of SARS-CoV-2 $M_{\text{PBO}}$.

Our current study performed docking-based virtual screening and identified potential COVID-19 main protease inhibitors from brown algae. We have performed docking simulations using Molecular Operating Environment (MOE 2016.0802) on crystal structure from PDB (ID = 5R82) in complex with non-peptide 6-(ethylamino) pyridine-3-carbonitrile (RZS).

The top seven structurally diverse scaffolds were selected for further analysis. Marine natural products (MNP) are reported to possess various pharmacological effects (Khalid et al., 2018; Gentile et al., 2020; Zaporozhets and Besednova 2020). Gentile et al. searched for new inhibitors of SARS-CoV-2 $M_{\text{PBO}}$ from a collection of fourteen thousand MNPs by using structure- and ligand-based screening. They identified few seaweed polyphenols (Phlorotannin) such as Heptafuhalol A, Phlorethopentafuhalol B, 8,8-Bieckol and Dieckol type of phytochemicals via in-silico screening. Moreover, some pseudopeptides / peptidomimetics such as Pseudotheonamide D, Aeruginosin 98B were also Pseudotheonamide C identified as potential inhibitors of $M_{\text{PBO}}$. Our current study focused on brown algae only. After a rigorous selection criterion (structural diversity skeleton type, RMSD values of docked compounds, and validation of docking protocol), we selected the top seven structurally diverse scaffolds. Several polyphenols with almost the same structural features have been reported by Gentile et al. However, we selected only two acetate derivatives of polyphenols. Moreover, studies have revealed that the inhibitors with non-peptide character help overcome various pharmacological problems associated with peptide protease inhibitors. Furthermore, they could be a helpful model in further functionalization to design novel compounds. Hence, our other selected compounds are also non-peptidomimetics and contain various structural features. The identified compounds establish hydrogen bond interactions with Thr24, Thr26, Thr45, Ser46, Gly143 (S1 subite), Cys145 (Catalytic dyad), Glu166 (S1 subite), Pro168, Glu189 (S4 subite). At the same time, Met165 (S2 subite) forms a $\pi$-sulfur interaction. 7,2'-Bieckol showed the lowest binding energy (high binding affinity, $-10.7855 \text{kcal/mol}$). Other compounds showed binding energy values in the range of $-9.9611$ to $-8.5488 \text{kcal/mol}$. Among seven identified compounds, four compounds showed better binding affinity (lowest binding energy) than lopinavir and Remdesivir used as comparative standards. Moreover, compounds also showed a better affinity with the enzyme than rutin.

4. Conclusions

The lack of specific COVID-19 drugs and/or vaccines and their rapid transmission rate has prompted scientists to investigate the new regimen of natural compounds having anti-COVID-19 potentials. Compounds from natural sources like seaweeds have shown their potential to combat various pathogenesis. Pathogenic SARS-CoV-2 has posed a significant threat to humankind in the last year or so, and therefore, the development of efficient therapeutics needs time. In the last decade, bioinformatics has played an essential role in rational drug discovery. In this study, a database of 1018 natural compounds from Brown algae was scanned against the COVID-19 virus. The top seven compounds were further analyzed, and their interactions with the active site were visualized. Molecular docking conducted in this study infers that all the compounds had significant binding in COVID-19 main protease ($\text{PDB ID} = 5R82$). Among all these examined compounds, 7,2'-Bieckol showed the lowest binding energy (high binding affinity, $-10.7855 \text{kcal/mol}$). Other compounds showed binding energy values in the range of $-9.9611$ to $-8.5488 \text{kcal/mol}$. Considering that no specific drug has been formulated for COVID-19 infection, ligands identified in this study may help provide baseline data in developing multi-targeted drug discovery against SARS-CoV-2. On the other hand, further in vitro and in vivo studies must be conducted to authenticate the anti-COVID-19 potential of these identified compounds.

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Declaration of Competing Interest

None.

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