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Short Communication

SARS-CoV-2 and its Focus on Antiviral Therapy

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DESCRIPTION

Despite the availability of vaccines that provide protection against severe illness from Coronavirus Disease (COVID-19), emerging variant strains of Severe Acute Respiratory Syndrome 2 Coronavirus 2 (SARS-CoV-2) are a source of concern. Investigation of antiviral therapeutics is a different research direction. In addition to structural proteins, SARS-CoV-2 non-structural proteins, such as the helicase, are of interest (nsp13). In this study, an initial screen of 300 ligands was performed to identify potential inhibitors of the SARS-CoV-2 nsp13, with the target region being the Nucleoside Triphosphatase site (NTPase activity). Polyphenols' antiviral activity has previously been reported in the literature, so phenolic compounds and fatty acids from the OliveNetTM library were used [1]. Antimicrobial and anti-inflammatory synthetic compounds were also chosen. SARS-CoV and MERS-CoV helicase structures were compared, as were the human RECQ-like DNA helicase, DHX9 helicase, PcrA helicase, hepatitis C NS3 helicase, and mouse Dna2 nuclease-helicase [2]. Sequence and structural homology between the various species was evident, as expected. A number of broad-spectrum and well-known inhibitors interacted with the NTPase active site, highlighting the need for more specific SARS-CoV-2 inhibitors. Potential lead compounds for the SARS-CoV-2 helicase were identified as acetylcysteine, clavulanic acid, and homovanillic acid.

Molecular dynamics simulations were carried out in triplicate with the leads bound to the SARS-CoV-2 helicase for 200 ns, with favourable binding free energies to the NTPase site. Given their accessibility, more research into their potential inhibitory activity could be considered. Emerging zoonotic RNA viruses have caused widespread public health concern in recent years. Novel Coronaviruses (CoVs) deserve special attention due to their high spread potential and transmissibility rate, which frequently leads to deadly epidemics across multiple countries, exacerbated by a lack of effective therapies. The majority of approved antiviral drugs are so-called Direct-acting Antiviral Agents (DAAs), compounds designed against viral proteins deemed essential for infection. For example, molnupiravir, a new oral antiviral highly effective in preventing severe disease based on the results of a recent Phase 2a trial, and remdesivir, whose efficacy against SARS-CoV-2 is highly controversial (Hsu, 2020), are nucleoside analogue prodrugs that act as competitive substrates for virally-encoded RNA-Dependent RNA Polymerase (RdRp) [1,3].

Host-Targeting Antivirals (HTAs) are a new class of antiviral agents that act on host-cell factors involved in viral replication. Most studies to date have concentrated on the analysis of viral proteins and the identification of potential DAAs. However, viruses encode a limited number of proteins, with only a subset of them suitable as drug targets. As a result, targeted disruption of the mechanisms devised by HCoVs to manipulate the host cellular environment during infection, such as those leading to immune evasion and host gene expression alterations, holds great promise for COVID-19 treatment. Computational methods have also enabled scientists to investigate various aspects of infectious diseases, and virtual screening tools have enabled the discovery of lead compounds from large ligand databases. According to Wu, the main strategies for combating the pandemic are testing broad-spectrum antivirals, screening existing databases for small molecules that may be effective against the virus and resulting disease, and developing novel drugs from scratch. We focused on the NTPase active site of the SARS-CoV-2 helicase in this study [2,4]. The active site domains of various species, including the microbial SARS-CoV, MERS-CoV, PcrA, and hepatitis C NS3 helicases, and the mammalian RECQ-like DNA, DHX9 (human) helicases, and Dna2 nuclease-helicase (mouse). For preliminary screening, a library of 300 compounds comprised of a curated database of natural and synthetic compounds was used.

CONCLUSION

Following additional modelling studies of interesting compounds, potential lead compounds for the SARS-CoV-2 helicase were identified, including acetylcysteine, clavulanic, and homovanillic acids. Drug repurposing has been an important part of the COVID-19 pandemic response, and there is a need to identify compounds that may have therapeutic potential or be used as prophylaxis. This procedure allows existing therapeutics to be re-evaluated and new applications to be discovered. Remdesivir, a potent RdRp inhibitor that can be used in

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patients requiring hospitalisation, was the first drug approved by the FDA as a treatment for COVID-19. Furthermore, compounds with anti-inflammatory properties and the ability to alleviate symptoms. This includes phytochemicals, and the antiviral properties of natural products have been studied.

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