Discovery of Multi-Target-Directed Ligands by Targeting Host-specific SARS-CoV-2's Structurally Conserved Main Protease

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April 28, 2020

Posted on Authorea 9 Apr 2020 — CC BY 4.0 — https://doi.org/10.22541/au.158645543.35598681 — This a preprint and has not been peer reviewed. Data may be preliminary.

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has resulted in the current COVID-19 pandemic. Worldwide this disease has infected around 1.5 million individuals with a mortality rate ranging from 5 to 10%. There are several efforts are going on in the drug discovery to control the SARS-CoV-2 viral infection. The main protease (MPro) plays a critical role in viral replication and maturation, thus can serve as the primary drug target. To understand the structural evolution of MPro, we have performed phylogenetic and SSN analysis, that depicted divergence of Coronaviridae MPro in five clusters specific to viral hosts. This clustering was also corroborated with the comparison of MPro structures. Furthermore, it has been observed that backbone and binding site conformations are conserved despite variation in some of the residues. This conservation can be exploited to repurpose available viral protease inhibitors against SARS-CoV-2 MPro. In agreement with this, we performed screening of ˜7100 molecules including active ingredients present in the Ayurvedic anti-tussive medicines, anti-viral phytochemicals and synthetic anti-virals against SARS-CoV-2 MPro as the primary target. We identified several natural molecules like ?-Viniferin, Myricitrin, Taiwanhomoflavone A, Lactucopicrin 15-oxalate, Nympholide A, Biorobin and Phyllaemblicin B that strongly binds to SARS-CoV-2 MPro among. Most of the predicted lead molecules are from Vitis vinifera, also reported for anti-tussive and/or antiviral activities. These molecules also showed strong binding with other main targets RdRp and hACE-2. We anticipate that our approach for identification of multi-target-directed ligand will provide new avenues for drug discovery against SARS-CoV-2 infection.

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