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Structural stability of SARS-CoV-2 3CLpro and identification of quercetin as an inhibitor by experimental screening

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Highlights

- SASR-CoV-2 3CLpro shows cooperative unfolding in which dimers or tetramers predominate depending on the pH.
- SARS-CoV-2 3CLpro shows a pH-dependent hydrolytic activity that correlates with its structural stability.
- SARS-CoV-2 3CLpro is an appropriate target for drug discovery given its high sequence identity among different coronaviruses.
- Quercetin has been identified as a SARS-CoV-2 3CLpro inhibitor by an activity-based experimental screening.
- Experimental and computational target engagement for quercetin was gathered by ITC, spectroscopy, TSA, and molecular docking.

Abstract

The global health emergency generated by coronavirus disease 2019 (COVID-19) has prompted the search for preventive and therapeutic treatments for its pathogen, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). There are many potential targets for drug discovery and development to tackle this disease. One of these targets is the main protease, Mpro or 3CLpro, which is highly conserved among coronaviruses. 3CLpro is an essential player in the viral replication cycle, processing the large viral polyproteins and rendering the individual proteins functional. We report a biophysical characterization of the structural stability and the catalytic activity of 3CLpro from SARS-CoV-2, from which a suitable experimental *in vitro* molecular screening procedure has been designed. By screening of a small chemical library consisting of about 150 compounds, the natural product quercetin was identified as reasonably potent inhibitor of SARS-CoV-2 3CLpro (K_i ~ 7 μM). Quercetin could be shown to interact with 3CLpro using biophysical techniques and bind to the active site in molecular simulations. Quercetin, with well-known pharmacokinetic and ADMET properties, can be considered as a good candidate for further optimization and development, or repositioned for COVID-19 therapeutic treatme

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