

## Apigenin, a Phytochemical Interacts with the SARS-CoV-2 Main Protease

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### Abstract

Severe acute respiratory syndrome Corona-virus 2 (SARS-CoV-2) emerged as a global risk and put the entire globe into unrest. Unavailability of specific drug against the virus is more imperative. This challenging situation requires development of bio-molecules for efficient treatment against severe acute SARS-CoV-2. The crystal structure of SARS-CoV-2 main protease ( $M^{pro}$ ) may be used for fast *in silico* docking. This may result into identification of active bio-molecules primarily phytochemical. *In silico* molecular docking revealed that the phytochemical, Apigenin effectively binds to the active pocket of the SARS-CoV-2 main protease.

**Keywords:** 2019-nCoV, SARS-CoV-2, SARS-CoV-2 main protease, Molecular docking, Phytochemicals, Apigenin.

### Introduction

Mankind has observed various pandemics throughout the history where some of them were more disastrous than the others to the humans. The emerging 2019 Novel coronavirus (2019-nCoV) threatens public health. 2019-nCoV is also referred to as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Initially observed in the Wuhan province of China [1, 2], now it's rapidly spreading around the world. SARS-CoV-2 belongs to the beta coronavirus genus, closely related to the previously identified severe acute respiratory syndrome corona-virus (SARS-CoV) [3, 4]. In November 2019, the first confirmed case of coronavirus was identified. Majority cases of COVID-19 show mild symptoms such as dry cough, fever, shortness of breath and fatigue whereas some progress to viral pneumonia and multi-organ failure. Public Health Emergency of International Concern (PHEIC) was declared by the World Health Organization (WHO) owing to its fast rate of transmission within the humans [1, 5, 6]. Crystal structure of the SARS-CoV-2 main protease ( $M^{pro}$ ) proves to be an exceptional ground for screening specific ligands [7]. SARS-CoV-2 main protease can be beleaguered for developing antibodies, diagnostics and vaccines. Reportedly,  $M^{pro}$  and other known viral proteins are defining features paving the path of virus from entry to infection in the host cell [8, 9, 10]. Moreover,  $M^{pro}$  can also be an effectual target to diminish the viral replications within the host cells since it facilitates the synthesis of functional viral proteins. The effectiveness of traditional medications on the restriction of COVID-19 growth does not have any scientific back up as of now, since the underlying molecular mechanisms are unclear. The phytochemicals are fundamentally bioactive compounds and has the potential to amend cellular physiology. Here, we report that apigenin, a phytochemical mostly enriched in some selected plants binds into the active site of the SARS-CoV-2 main protease as revealed by the *in silico* molecular docking and thus further studies may reveal the effectiveness of apigenin to be used as COVID-19 therapeutics.

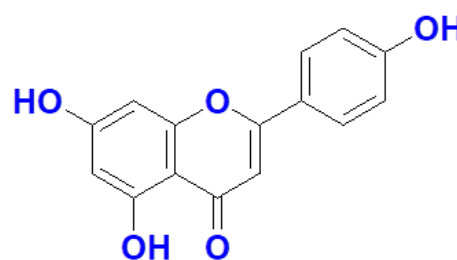
### Methods

#### Viral Protein Structure and Phytochemical dataset collection

The 3D structure of  $M^{pro}$  was accessed from Protein Data Bank accession 6M03 (Fig. 1). The SDF accession CHEBI:18388 corresponding to the apigenin (Fig. 2) was obtained and consequently both the protein and the ligands were used for *in silico* analysis.



**Fig 1:** 3-D Structure of the SARS-CoV-2  $M^{PRO}$  showing the active site of the protein.



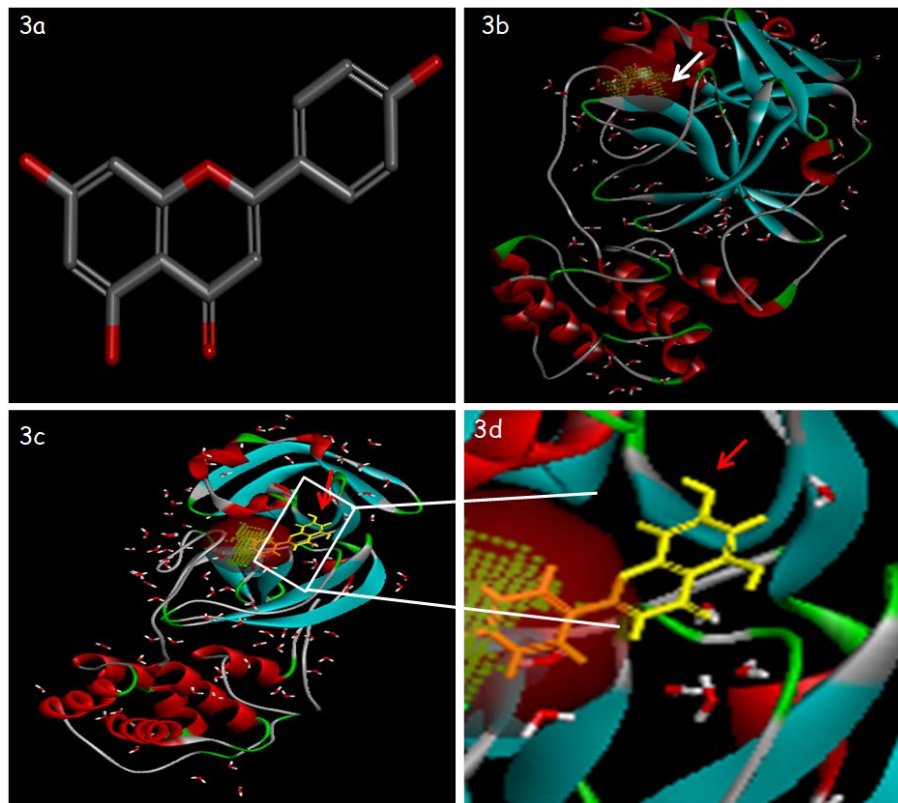
**Fig 2:** Chemical structure of Apigenin

**Molecular docking**

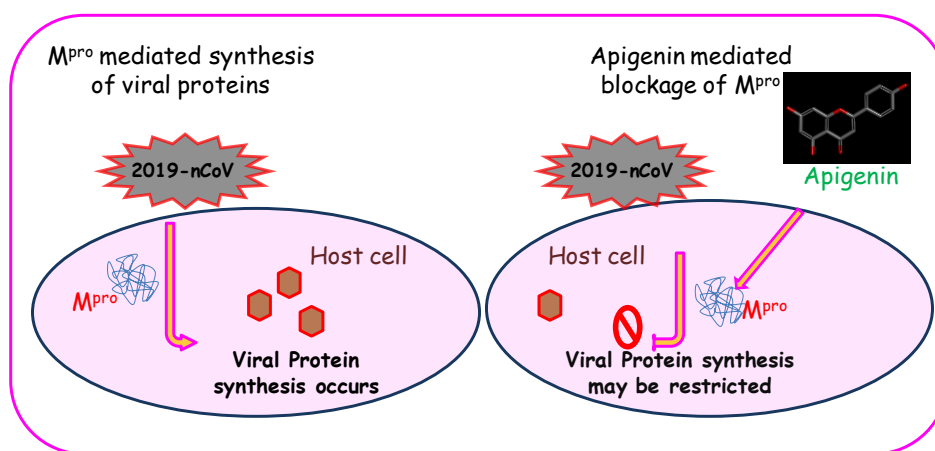
For the *in silico* molecular docking, BIOVIA’s Discovery Studio docking method was used [11]. The catalytic pocket of the M<sup>PRO</sup> protein was specified and targeted for binding of the ligand. CDOCKER Energy and CDOCKER Interaction Energy signify the affinity of the ligands with the protein receptors. Basically, high positive values of the CDOCKER Energy, CDOCKER Interaction Energy and a diminutive difference between the CDOCKER Energy and CDOCKER Interaction Energy are considered to be the most favourable [12].

**Results and Discussion**

It was found that apigenin; a common phytochemical specifically binds to the active pocket of the SARS-CoV-2 M<sup>PRO</sup> (Fig. 3), as apparent from higher CDOCKER energy and CDOCKER interaction energy (Table 1). Since, simple active bio molecule like apigenin effectively binds into the active pocket of the M<sup>PRO</sup> under *in silico* conditions it is quite possible to design pharmacophore molecules based on the structural and functional identity of apigenin and eventually can be used in the pharmaceutical sector. Chemical synthesis of apigenin can be cost effective as compared to the isolation process from specific plants.



**Fig. 3:** The active site of the SARS-CoV-2 main protease (M<sup>PRO</sup>) interacts with Apigenin. **3a:** Phytochemical, Apigenin. **3b:** Free form of M<sup>PRO</sup>. **3c:** M<sup>PRO</sup> associated with the ligand, Apigenin. **3d:** Magnified image showing the association of the Apigenin with the M<sup>PRO</sup>. (The white colored arrow and the red colored arrow indicate the active site of the M<sup>PRO</sup> and binding of Apigenin respectively).



**Fig. 4:** Apigenin, a phytochemical may inhibit COVID-19 M<sup>PRO</sup> and thus restrict the synthesis of viral proteins.

**Table 1:** CDocker energy and CDocker interaction energy values generated for the interaction of Apigenin with the active site of SARS-CoV-2 main protease (M<sup>pro</sup>).

Ligand		Receptor			Interaction status	
SDF Accession	Phytochemical	Protein	PDB Accession	Docking Result	CDocker Energy	CDocker Interaction Energy
CHEBI: 18388	Apigenin	Covid-19 Main protease	6M03	Positive	-17.94	-20.17

### Conclusion and Future perspectives

The current *in silico* molecular docking based study reveals that apigenin can target the reported SARS-CoV-2 M<sup>pro</sup> (Fig. 4). It would be extremely noteworthy being confirmed *in vivo*. It is crucial to develop diagnostic tools, potential therapeutics and antibodies selectively for the COVID-19 proteins. Phytochemicals like apigenin is commercially available and thus may be effectively prescribed to circumvent the current global scenario. Essentially, this study makes an attempt to reveal simple phytochemicals like apigenin which can be employed for designing novel therapeutics.

### Author contribution statement

GKP conceived the idea. AS, GKP, SJ, SKS, PKP performed the experiments. GKP analyzed the data. All authors have significant contribution in drafting the manuscript.

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### Conflict of interest

The authors declare that they have no conflict of interest.

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