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In silico Molecular Docking Reveals the Interaction of Coumarin with the Sars-Cov-2 Main Protease

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Abstract
2019 Novel corona-virus (2019-nCoV) has 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 2019-nCoV. The crystal structure of SARS-CoV-2 main protease (M^{pro}) is known and may be used for fast *in silico* molecular docking. This may result into identification of active biomolecules primarily phytochemical. *In silico* Molecular Docking revealed that the phytochemical, Coumarin effectively binds at the active pocket of the SARS-CoV-2 main protease.

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

Introduction
The pandemic situation caused due to the 2019-nCoV represents a severe public health calamity across the globe. The city of Wuhan was the epicentre where the outbreak of this human pathogen emerged, and resulted to human ailment, termed as COVID-19 [1, 2]. SARS-CoV-2 belongs to the beta corona-virus genus, closely related to the previously identified severe acute respiratory syndrome corona-virus (SARS-CoV) [3, 4]. 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 coumarin, 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 coumarin 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:28794 corresponding to the coumarin (Fig. 2) was obtained and consequently both the protein and the ligands were used for *in silico* analysis.

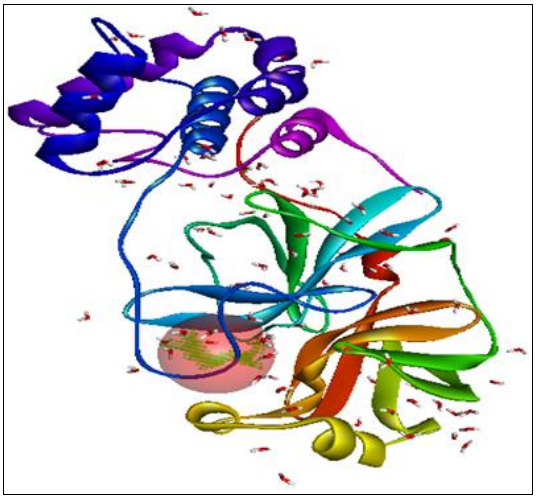

Fig 1: 3-D Structure of the SARS-CoV-2 M^{pro} showing the active site of the protein

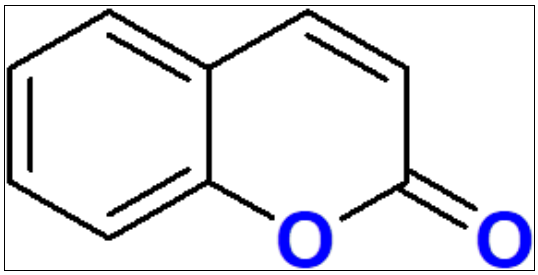

Fig 2: Chemical structure of Coumarin

Molecular docking
For the *in silico* molecular docking, BIOVIA's Discovery Studio docking method was used [11]. The catalytic pocket of the M^{pro} 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 coumarin binds to the active pocket of the SARS-CoV-2 M^{pro} (Fig. 3), as apparent from higher CDOCKER energy and CDOCKER interaction energy (Table 1). Since, simple active bio molecule like coumarin effectively binds into the active pocket of the M^{pro} under *in silico* conditions it is quite possible to design pharmacophore molecules based on the structural and functional identity of coumarin and eventually can be used in the pharmaceutical sector. Chemical synthesis of coumarin can be cost effective as compared to the isolation process from specific plants.

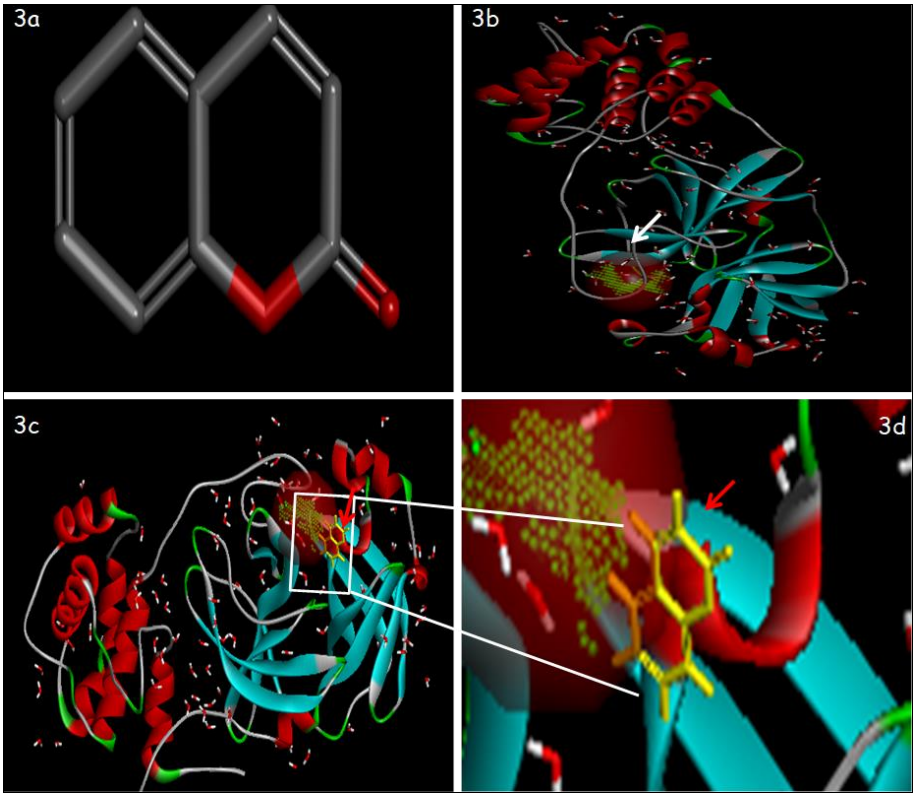

Fig. 3: The active site of the SARS-CoV-2 main protease (M^{pro}) interacts with Coumarin. **3a:** Phytochemical, Coumarin. **3b:** Free form of M^{pro}. **3c:** M^{pro} associated with the ligand, Coumarin. **3d:** Magnified image showing the association of the Coumarin with the M^{pro}. (The white colored arrow and the red colored arrow indicate the active site of the M^{pro} and binding of Coumarin respectively).

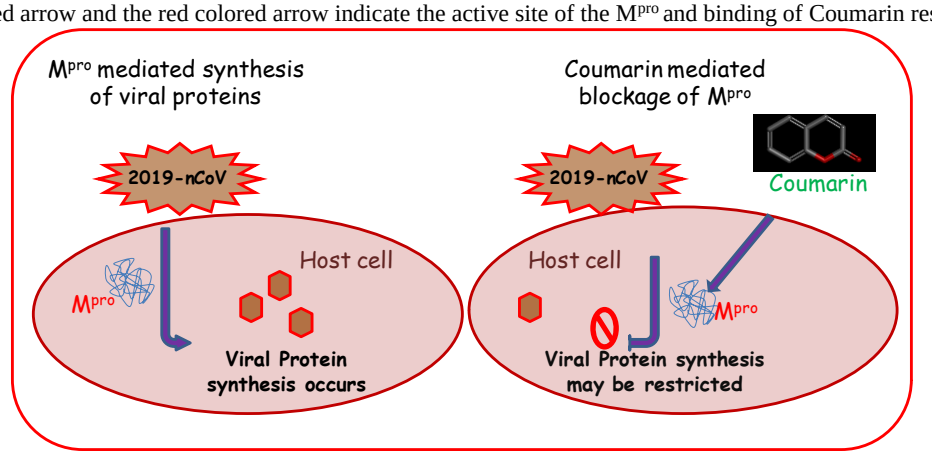

Fig. 4: Coumarin, a phytochemical may inhibit COVID-19 M^{pro} and thus restrict the synthesis of viral proteins.

Table 1: CDocker energy and CDocker interaction energy values generated for the interaction of Coumarin with the active site of SARS-CoV-2 Main Protease (M^{pro}).

ligand		**Receptor**			**Interaction status**	
SDF Accession	Phytochemical	Protein	PDB Accession	Docking Result	CDocker Energy	CDocker Interaction Energy
CHEBI: 28794	Coumarin	Covid-19 Main protease	6M03	Positive	-9.75	-12.48

Conclusion and Future perspectives

The current *in silico* molecular docking-based study reveals that coumarin can target the reported SARS-CoV-2 M^{pro} (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 coumarin 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 coumarin which can be employed for designing novel therapeutics.

Author contribution statement

GKP conceived the idea. AS, GKP, RN, 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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