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In Silico Molecular Docking-Based Screening Reveals Phytomolecules Against SARS-COV-2 Main Protease

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ABSTRACT

In past two decades, the globe has faced many infectious disease outbreaks. 2019 Novel Corona-virus (2019-nCoV) or the 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 demanding situation requires development of bio molecules for competent treatment against the SARS-CoV-2. The crystal structure of SARS-CoV-2 main protease (M^{pro}) may be used for fast *in silico* docking and novel pharmacophores can be discovered. This may result into identification of active bio-molecules largely phytochemicals. In silico Molecular Docking revealed that the phytochemical, Gallic acid effectively binds to the active pocket of the SARS-CoV-2 main protease.

KEY WORDS: 2019-NCOV, SARS-COV-2, SARS-COV-2 MAIN PROTEASE, DOCKING, PHYTOCHEMICALS.

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 (Chen et al., 2020, Huang et al., 2020). SARS-CoV-2 belongs to the Beta corona-virus genus, closely related to the previously identified severe acute respiratory syndrome corona-virus (SARS-CoV) (Lu et al., 2020, Wu et al., 2020). 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 (Chen et al., 2020, Chan et al., 2020, Li et al., 2020).

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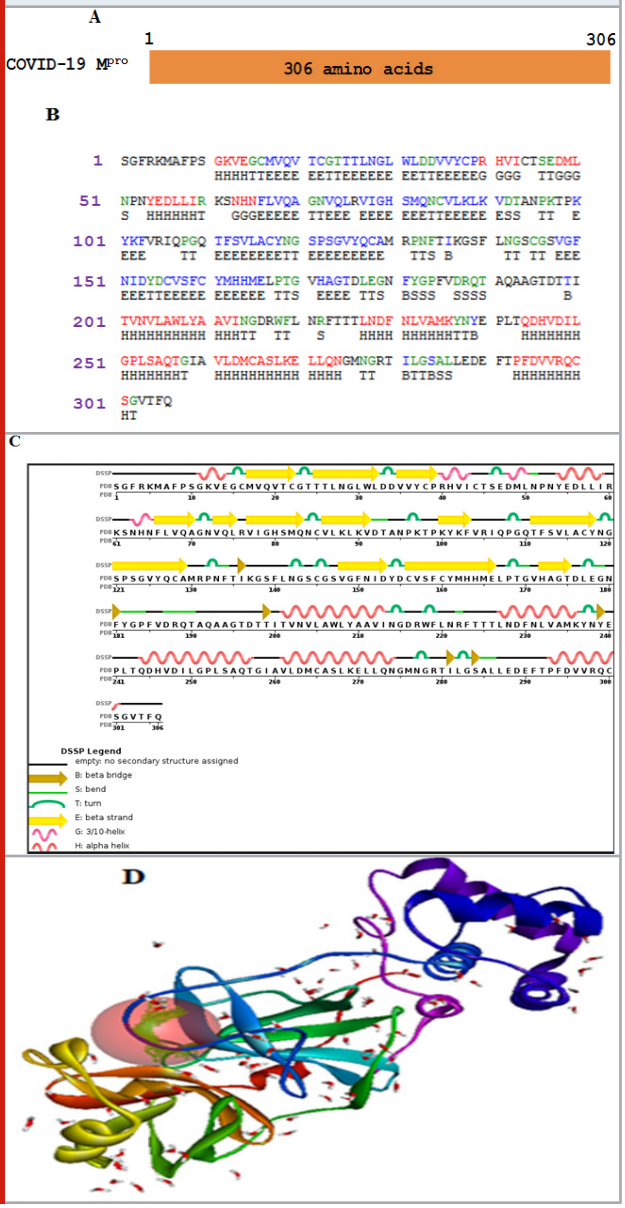
The virus is very contagious and infectious occurs through droplets from coughing and sneezing and touching infected surface. Its genome comprises of nearly 30,000 nucleotides and encoded by 4 structural proteins. Those are Nucleocapsid protein, Membrane protein, Envelope protein, and Spike protein. The virus possesses a positive single stranded RNA. It attacks human cells and converted them into factories of viruses. The capsid protein helps in its replication and transcription. Crystal structure of the SARS-CoV-2 main protease (M^{pro}) proves to be an exceptional ground for screening specific ligands (Liu et al., 2020). 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 (Wrapp et al., 2020, Lung et al., 2020, Sahoo et al., 2020a,b,c,d,e,f, Ton et al., 2020).

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. Plants are enriched with tremendous defense

response capabilities (Panda et al., 2016, Panigrahi et al., 2016, Panigrahi and Sahoo 2016, Panigrahi and Satapathy 2020a, Panigrahi et al., 2021). Elaborated defense mechanism(s) in plants need to be explored (Panigrahi and Satapathy 2020a,b,c). The phytochemicals are fundamentally bioactive compounds and has the potential to amend cellular physiology. Here, we report few phytochemicals which has the ability to bind to 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 phytochemicals to be used as COVID-19 therapeutics.

Figure 1: Amino acid sequence of COVID-19 M^{pro}. (A) Mpro contains 306 amino acids. (B) Sequence and Define Secondary Structure of Proteins (DSSP) image of COVID-19 M^{pro}. (C) Sequence chain image of COVID-19 Mpro. (D) 3-D Structure of the SARS-CoV-2 M^{pro} showing the active site of the protein. Images 1(B) and 1(C) were generated from the Protein Data Bank.



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 structure data files of the phytochemicals under study were retrieved from the EMBL-EBI database (Table 1). For instance, the accession CHEBI:30778 corresponds to the Gallic acid (Fig. 2). Consequently both the protein and the ligands were used for the *in silico* analysis.

Molecular docking: For the *in silico* molecular docking, BIOVIA's Discovery Studio docking method was used for molecular docking. 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 (Behera et al., 2020, Das et al., 2020, Jena et al., 2020, Ray et al., 2020).

Table 1. Cdocker Energy and Cdocker Interaction Energy values generated for the interaction of several phytochemicals with the active site of SARS-CoV-2 main protease (M^{pro}).

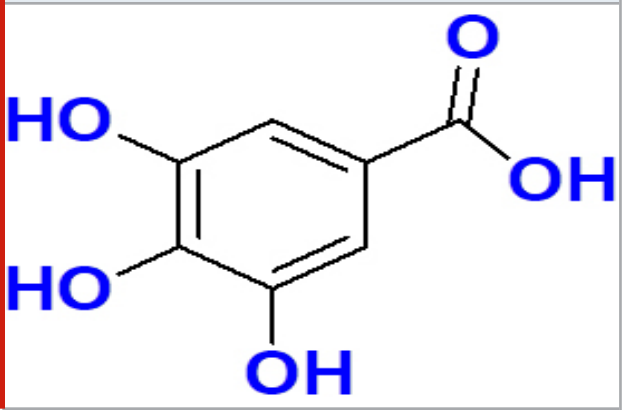
Sl. No.	Phytochemicals	C DOCKER ENERGY	C DOCKER INTERACTION ENERGY
1	Resveratrol	13.04	25.59
2	Phenyl isothiocyanate	13.76	16.31
3	Myricetin	23.39	24.93
4	Caffeine	10.2	18.61
5	Benzyl isothiocyanate	11.54	13.34
6	Kaempferol	20.69	26.33
7	Genistein	15.46	23.32
8	Daidzein	12.16	20.03
9	Theobromine	9.58	14.85
10	Quercetin	24.08	27
11	Pelletierine	10.51	18.36
12	Alliin	11.97	17.96
13	Gallic acid	23.43	20.24
14	Ellagic acid	14.56	24.23
15	Pelargonidin	9.62	29.89
16	Isorhamnetin	16.62	21.62
17	Epicatechin	19.37	27.87
18	Coumarin	11.6	14.69
19	Ferulic acid	17.07	20.79
20	Glutathione	38.56	28.77
21	Sulforaphane	18.51	16.9
22	Salicylic acid	14.28	16.4
23	Eugenol	8.19	18.38
24	Apigenin	19.26	24.2
25	Luteolin	22.63	25.96

RESULTS AND DISCUSSION

Through the process of molecular docking i.e.*in silico* molecular docking, some phytochemicals have shown their effectiveness against the particular disease. As the crystal structure of SARS-CoV-2 has been solved i.e. main protease (M^{pro}), it can be considered as the root way for the screening of inhibitory ligands to detect bioactive molecules. Through *in silico* molecular docking, Gallic acid has remarkably shown the effectiveness against

COVID-19 by binding to the active sites of SARS-CoV-2 main protease (M^{pro}). It was found that Gallic acid,a common phytochemical, specifically binds to the active pocket of the SARS-CoV-2 M^{pro} (Fig. 3), as apparent from higher -CDOCKER energy and -CDOCKER interaction energy. Since, simple active bio molecule like Gallic acid effectively binds into the active pocket of the Mpro under *in silico* conditions it is quite possible to design pharmacophore molecules based on the structural and functional identity of Gallic acid and eventually can be used in the pharmaceutical sectors. Chemical synthesis of Gallic acid can be cost effective as compared to the isolation process from specific plants.

Figure 2: Chemical structure of Gallic acid



CONCLUSION AND FUTURE PERSPECTIVES

As the coronavirus outbreak became the nightmare for the whole human society and the devastation caused by it is unpredictable and beyond imagination, the world has not left with enough time to discover a new drug or vaccine for it due to the requirement of sufficient time. Due to its highly contagious nature, it is considered as global pandemic within no time by taking many lives of people. But future studies on Gallic acid may become the building block for the medication and treatment against the SARS-CoV-2. The current *in silico* molecular docking based study reveals that Gallic acid can target the reported SARS-CoV-2 M^{pro}. 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 Gallic acidis 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 Gallic acid which can be employed for designing novel therapeutics (Fig. 4).

CRediT authorship contribution statement: Annapurna Sahoo: conceived the idea, performed the experiments, analyzed the results, wrote the manuscript, have read and approved the final manuscript before submission. Kunja Bihari Satapathy: conceived the idea, analyzed the results, have read and approved the final manuscript before submission.

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

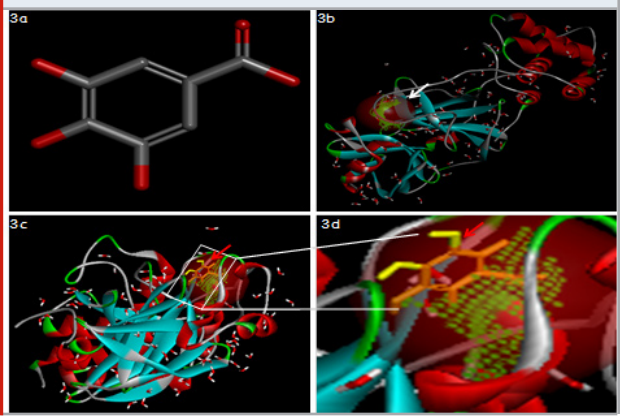
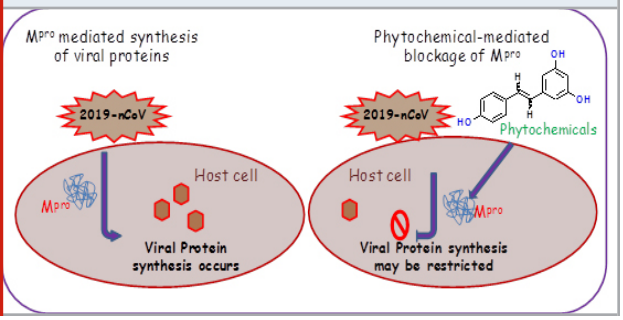


Figure 4: Phytochemicals inhibit the activity of COVID-19 M^{pro}.



Declaration of competing interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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