Biosc.Biotech.Res.Comm. Special Issue Vol 13 No 12 (2020) Pp-127-130

BBRC
Bioscience Biotechnology Research Communications

Potent Phytomolecules Against the RNA Dependent RNA Polymerase of the SARS-COV-2

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ABSTRACT

The 2019 Novel coronavirus (2019-nCoV) threatens public health. The 2019-nCoV is also referred to as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Specific drug against the virus is yet to be discovered. Development of pharmacophores for proficient treatment against severe acute SARS-CoV-2 is challenging. The solved cryo-EM structure of SARS-CoV-2 RNA dependent RNA polymerase (RdRp) can be used as one of the primary target molecule and possible inhibitory ligands may be screened using in silico molecular docking. Primarily phytochemicals can be screened to detect any potential bio active molecules. In silico molecular docking revealed that the phytochemical, Quercitin may effectively bind to the active site of the SARS-CoV-2 main protease.

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

INTRODUCTION

Coronavirus (COVID19) has become a critical public issue across the global since December 2019 which was suspected to be originated from a wet market in Wuhan, Hubei province, China (Chen et al., 2020, Huang et al., 2020). More than 6 million cases have been reported in 213 countries and territories.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). It was named as a coronavirus because corona represents crown-like spikes on the outer surface of the virus. Coronaviruses are minute in size (65-125 nm in diameter), enveloped viruses with a single-standard RNA genome. COVID19 ranges from 26 to 32 kilobases which makes it the largest RNA virus. There are four subgroups of coronaviruses family alpha (α), beta (β), gamma (γ) and delta (δ) coronavirus. Among these types, only alpha and beta CoV can infect humans.

The coronavirus disease 19 (COVID-19) is a highly transmittable and pathogenic viral infection caused by sever acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Genomic analysis revealed that SARS-CoV-2 is phylogenetically related to severe acute respiratory syndrome-like (SARS-like) batviruses; therefore bats could be the possible primary reservoir. 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). Spike protein (S) of SARS-CoV-2 interacts with human Angiotensin-converting enzyme 2 (ACE2). All coronaviruses contain specific genes in ORF1 downstream regions that encode proteins for viral replication, nucleocapsids and spikes formation. The glycoprotein spikes on the outer surface of coronaviruses are responsible for the attachment and entry of the virus to host cells.

ARTICLE INFORMATION

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Received 06th Oct 2020 Accepted after revision29th Dec 2020
Print ISSN: 0974-6455 Online ISSN: 2321-4007 CODEN: BBRCBA

Thomson Reuters ISI Web of Science Clarivate Analytics USA and Crossref Indexed Journal

NAAS Journal Score 2020 (4.31) SJIF: 2020 (7.728)

Online Contents Available at: http//www.bbrc.in/

The receptor binding domains (RBD) is loosely attached among virus; therefore, the virus may infect multiple hosts. Other coronaviruses mostly recognize aminopeptidases or carbohydrates as a key receptor for entry to human cells while SARS-CoV and MERS-CoV recognize exopeptidases. The entry mechanism of a coronavirus depends upon cellular proteases which include, human airway trypsin-like protease (HAT), cathepsins and transmembrane proteases serine 2 (TMPRSS2) that split the spike protein and establish further penetration changes. MERS-coronavirus employs dipeptidyl peptidase 4 (DPP4), while HCoV-NL63 and SARS-coronavirus require angiotensin-converting enzyme 2 (ACE2) as a key receptor. SARS-CoV-2 possesses the typical coronavirus structure with spike protein and also expressed other polyproteins, nucleoproteins, and membrane proteins, such as RNA polymerases, 3-chymotrypsin-like proteases, papain-like protease, helical, glycoproteins, and accessory proteins.

The spike protein of SARS-CoV-2 contains a 3-D structure in the RBD region to maintain the van der waals forces. The 394 glutamine residues in the RBD region of SARS-CoV-2 are recognized by the critical lysine 31 residue on the human ACE2 receptor. COVID19 causes respiratory diseases in human, from the common cold to more rare and serious diseases such as the severe Acute Respiratory Syndrome (SARS) and the Middle East respiratory Syndrome (MERS), both of which have high mortality rates and were detected for the first time in 2003 and 2012, respectively. According to the WHO, this contamination is spreading with human to human contact, droplets, and fomites. Crystal structure of the SARS-CoV-2 main protease (Mpro) 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, Mpro and other known viral proteins including RNA dependent RNA Polymerase (RdRp) 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, Mpro 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. Plants are enriched with tremendous defense response capabilities (Panda et al., 2016, Panigrahi et al., 2016, Panigrahi and Sahoo 2016, Panigrahi and Satapathy 2020, Panigrahi et al., 2021). Elaborated defense mechanism(s) in plants need to be explored (Panigrahi and Satapathy 2020a, 2020b, 2020c). Here, we report few phytochemicals which has the ability to bind to the active site of the SARS-CoV-2 RdRp 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.

METHODS

Viral Protein Structure and Phytochemical dataset collection: The 3D structure of RdRp was accessed from Protein Data Bank accession 6VYO (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:16243 corresponds to the Quercitin (Fig. 2) was obtained. Consequently both the protein and the ligands were used for *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 RdRp 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).

RESULTS AND DISCUSSION

Structure-based virtual screening refers to *in silico* identification of potential chemical molecules out of large number of compound libraries, which have high affinity to proteins of known structure, based on the binding of the small molecule with the protein binding pocket. It was found that quercitin binds to the active pocket of the SARS-CoV-2 RdRp (Fig. 3), as apparent from higher CDOCKER energy and CDOCKER interaction energy. Since, simple active bio molecule like quercitin effectively binds into the active pocket of the RdRp under *in silico* conditions it is quite possible to design pharmacophore molecules based on the structural and functional identity of quercitin and eventually can be used in the pharmaceutical sector. Chemical synthesis of quercitin can be cost effective as compared to the isolation process from specific plants.

Figure 1: 3-D Structure of the SARS-CoV-2RdRp showing the active site of the protein.

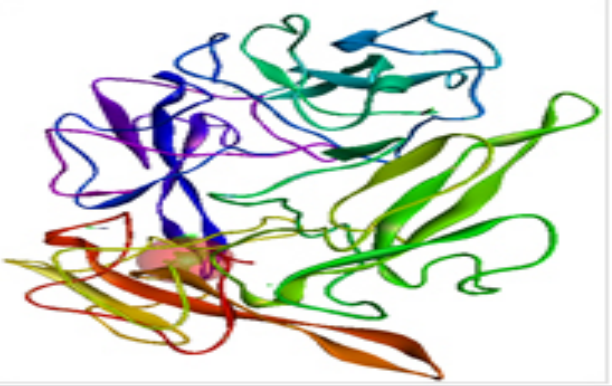
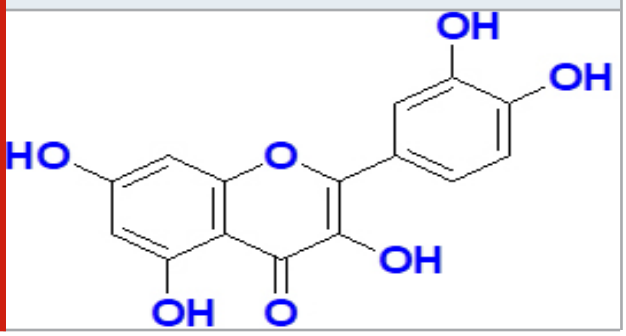


Table 1. Cdocker Energy And Cdocker Interaction Energy values generated for the interaction of several phytochemicals with the active site ofSARS-CoV-2 RNA dependent RNA polymerase (RdRp).

Sl. No.	Phytochemicals	C DOCKER ENERGY	C DOCKER INTERACTION ENERGY
1	Ferulic acid	9.16158	11.6305
2	Genistein	10.4129	19.1312
3	Quercetin	10.57	14.6
4	Glutathione	16.4	7.76
5	Luteolin	7.23	10.5
6	Caffeine	5.45	14.1

Figure 2: Chemical structure of Quercitin



CONCLUSION AND FUTURE PERSPECTIVES

Phytochemicals are produced by plants as secondary metabolites to protect them from predators. Some phytochemicals have been used as poisons and other as traditional medicine. This work is mainly focused on identification of the particular phytochemical responsible for inhibiting and controlling of COVID-19. The current *in silico* molecular docking based study reveals that quercitin can target the reported SARS-CoV-2RdRp. 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 quercitin 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 quercitin which can be employed for designing novel therapeutics (Fig. 4).

CRediT authorship contribution statement: Gagan Kumar Panigrahi: 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.

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.

Figure 3: The active site of the SARS-CoV-2 RdRp with Quercitin. 3a: Phytochemical, Quercitin. 3b: Free form of RdRp. 3c:RdRp associated with the ligand, Quercitin. 3d: Magnified image showing the association of the Quercitin with the RdRp. (The white colored arrow and the red colored arrow indicate the active site of the RdRp and binding of Quercitin respectively).

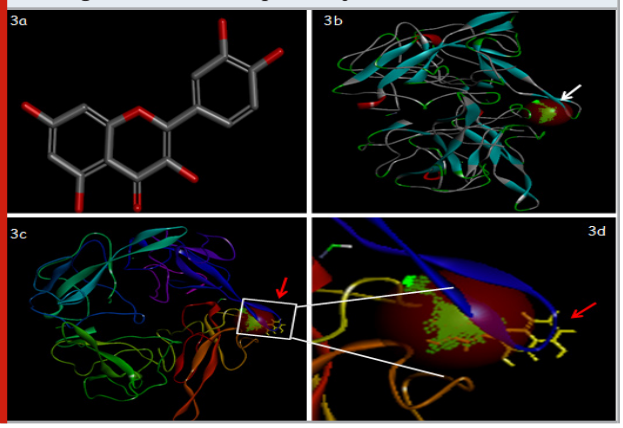
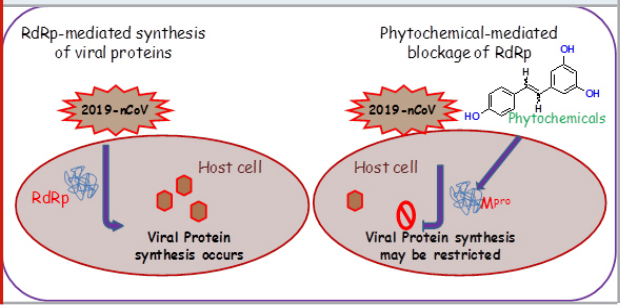


Figure 4: Phytochemicals inhibit the activity of COVID-19 RdRp.



ACKNOWLEDGEMENTS

Authors are thankful to the administration and management of Centurion University of Technology and Management, Odisha, India for providing necessary facilities to conduct the experiment.

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