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Computational prediction of *Carica papaya* extracts as potential drug agents against RNA polymerase and Spike proteins of SARS-nCoV2

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Abstract: The emergence of COVID-19 outbreak caused by SARS-nCoV2 (Severe Acute Respiratory Syndrome novel coronavirus 2), lead to the mass-scale mortalities around the world within a short span of time. The hour of the need is to develop the strategies and designing drugs/vaccines to control the spread of this contagion. In this paper, we predict the promising drug agents from the *Carica papaya* compounds by docking them with two major drug target proteins of SARS-nCoV2, spike (7BZ5) and RNA-dependent RNA polymerase (7BW4). For this purpose, we used Molecular Operating Environment Software (MOE) for ligand-protein interactions and docking scores. Furthermore, we used PubChem, PDB and SwissADME web portals to retrieve ligands structures, proteins structures and to check Lipinski's physiochemical parameters respectively. Cumulatively, this docking study has shown significant binding energies that (-4.2034 to -8.9013 Kcal/mol) indicates their potential against COVID-19 treatment. This study needs further evaluation on experimental basis.

Keywords: SARS-nCoV2; COVID-19; *Carica papaya*; spike protein; RdRP; RNA-dependent RNA polymerase; ligand-protein docking; computer-aided drug design; MOE; molecular operating environment; lipinski's rule; molecular docking; novel coronavirus

1 Introduction

COVID-19 has been spreading around the globe in a vigorous manner since December 2019. Due to increase in confirmed cases and mortality rate worldwide, World Health Organization (WHO) declared the pandemic of novel coronavirus (SARS-nCoV2) as a global health emergency (Ahmed et al., 2020, Cucinotta and Vanelli, 2020, Hall Jr and Ji, 2020, Khaerunnisa et al., 2020, Kronbichler et al., 2020). This causative agent lead to the disturbance in respiratory tract and show symptoms like pneumonia that can damage various body organs in severe conditions (Prasanna and Abilash, 2020, Wang et al., 2020).

At present, no explicit remedies for COVID-19 are available, also the handling of this pandemic is deficient (Khaerunnisa et al., 2020). The researchers have identified major target proteins for drug designing which may be considered are: main protease/3C-like protease (3CL^{pro}), papain-like protease (PL^{pro}), spike protein and polymerase protein RdRP (Bouchentouf and Missoum, 2020, Zhang et al., 2020, Mirza and Froeyen, 2020).

SARS-nCoV2 is an RNA virus having positive sense single strand of 27-32 kb approximately (Dhama et al., 2020, Khan et al., 2020). Due to its crown like appearance under electron microscope it is termed as CORONA (Pal et al., 2020). This virus is made up of different kind of structural proteins includes: Spike (S), envelope (E), membrane (M) and nucleocapsid (N) proteins, among them, S protein provides attachment site to host cell (Goswami et al., 2020, Li et al., 2003). ACE2; angiotensin-converting enzyme 2 is present on human cell membrane which work as receptor for SARS-nCoV2 (Wrobel et al., 2020). Spike protein significantly contributes the entry of virus into host cell which is concerned focus of therapeutic and vaccine design (Salvatori et al., 2020). The other target RNA-dependent RNA Polymerase is also considered to be the potent source for dealing with this disease. Coronaviruses assemble a multi RNA-synthesis complex of viral non-structural proteins (Nsps), which is accountable for transcription and replication of viral genome (Khan et al., 2020). Hence, the polymerase is a promising drug target (Peng et al., 2020). It infects the wide range of hosts including humans and other animals as well. Presumably, the transmission of this virus in humans is via droplets which come out of an infected person's mouth after sneezing or coughing along with direct contact (Khalid et al., 2020, Zou et al., 2020).

Different web-based or stationary based softwares were used for the computational analysis of drug designing. We used Molecular Operating Environment (MOE) software for molecular docking studies. It is a complete package which integrates ligand-protein docking, drug likeness attributes, molecular and binding interactions, modeling and simulations of structures and docking scores for interpreting the compatibility among the docked compounds (Santiago et al., 2008, Dar and Mir, 2017). Actively, our research is focused on the computational estimation of *Carica papaya* compounds having anti-inflammatory as well as immunomodulatory activities as a latent drug target, counter to SARS-nCoV2 RNA-Polymerase RdRP (7BW4) and Spike (7BZ5) protein. This study reassures scientists and pharmaceutical industries to have in-vitro and in-vivo investigations on those ligands for COVID-19 clinical trials.

Figure 1 Comprehensive work stream of docking study

2 Materials and method

2.1 Picking out the medicinal herb

A lot of research is carried out on *Carica papaya*, commonly known as Papaya which is renowned for its medicinal properties among different regions of the world. It has potential for treating various ailments such as asthma, ulcer, diabetes and cardiovascular diseases (Rivera-Pastrana et al., 2010). Papaya extracts have significant immunostimulatory, antioxidant and inflammation reducing activities (Pandey et al., 2016). For these significances, scientists may consider papaya's derived substances for immunotherapeutic purposes against COVID-19 viral pandemic in near future under clinical tests.

2.2 Preparation of ligands

Firstly, by searching *Carica papaya* compounds from literature, we used chemical database (e.g. PubChem) to retrieve structures, and then using Molecular Operating Environment (MOE) software for preparation of ligands (Pandey et al., 2016). Table 2 reports the major chemical derived compounds of *Carica Papaya* collected. Furthermore, we downloaded *Canonical Smiles* of all associated ligands and exported one by one in MOE *builder module* to construct fully prepared ligands for molecular docking.

2.3 Preparation of proteins (enzymes)

Secondly, for major drug targets we selected two proteins of SARS-nCoV2 coronavirus having different nature (Wu et al., 2020, Wrobel et al., 2020). 3D structures of Spike S1 protein (<https://www.rcsb.org/structure/7BZ5>) and RNA-dependent RNA Polymerase (RdRP) (<https://www.rcsb.org/structure/7BW4>) are downloaded from Protein Data Bank (RCSB-PDB) under PDB ID of 7BZ5 and 7BW4 respectively. Crystallographic properties of 7BZ5 and 7BW4 are shown in Table 1. The structures of proteins are presented in Figure 2. We used *open* command to visualize these structures in MOE window and created the pure form of protein to make them ready for docking with the desired ligands. This step was carried out in the following ways. At first, we removed all the water molecules from the surface of protein and already

attached inhibitors to avoid hinderance at interaction region while molecular docking for precise results. Secondly, we made *structure preparation* of selected proteins in MOE to resolve its chains error. After that, we found the active sites in *Site Finder* tab of MOE to create the space for attachment site for our ligands. As we were not familiar with the active site residues of an enzyme, we selected the longest chain from the list of possible catalytic sites, appeared on *Site Finder* window. In addition to, dummy sites were created by clicking on *Dummies* tab. Moreover, on completion of these steps our protein was fully prepared for docking.

Table 1 Crystallographic properties of proteins (enzymes)

<i>Enzyme</i>	<i>PDB Code</i>	<i>Classification</i>	<i>Organisms</i>	<i>Expression System</i>	<i>Resolution</i>	<i>Method</i>	<i>Total Structure Weight</i>	<i>Chain</i>
Spike (S1)	7BZ5	Viral protein	SARS-nCoV2	Homo sapiens	1.84 Å	X-RAY Diffraction	73.36 kDa	A
RdRP	7BW4	Replication	SARS-nCoV2	Escherichia Coli	3.70 Å	Electron Microscopy	159.03 kDa	A

2.4 Docking process

The interaction of our chosen ligands with the active sites of the 7BZ5 and 7BW4 was carried out by means of *dock* feature implanted in MOE, using its own built-in algorithms and tools. Additionally, the molecular interactions with the binding site of the receptors consumed some time to complete. The docking scores of the ligands displayed in a tabulated form in a new window after completion. Together with, ligands 2D and 3D interactions were also visible by choosing their options as well. These interactions showed that where the probable hydrogen bonds were formed with amino acids. Our main emphasis was on the binding energies or E-Score of this docking process to consider *Carica papaya* compounds as a potent drug agents (Krovat et al., 2005).

Figure 2 Proteins used for docking studies: (a) Spike; 7BZ5 and (b) RdRP; 7BW4

3 Results and discussions

Our docking results revealed that some compounds of *Carica papaya* extracts have the lowest energies with different nature of proteins 7BZ5 and 7BW4 respectively. Here we deliberated the ligands properties and their docking scores. Moreover, the medicinal significance, ligand-protein interactions and surface maps of major compounds (having best docking scores) were also described one by one in detail.

3.1 Ligands and their lipinski's physiochemical properties rule

Initially, we confer about the ligands, which we selected and prepared for our docking purposes. Chemical structures, their general names, PubChem ID's and molecular formulas of chemical compounds from *Carica papaya* are reported in Table 2. Additionally, Lipinski's rule key physiochemical parameters were also studied for each ligand (testified in Table 2) along with the violations of this rule by using SwissADME web tool to evaluate drug likeliness attributes (<http://www.swissadme.ch/index.php>). There are total 12 derived compounds of papaya, which were studied and observed. Out of which 4 compounds (Papain, β -Cryptoxanthin, Lycopene and Lutein) violate the Lipinski's rule with 2 violations each. Rest of the ligands have zero violations and fulfil the properties of this rule. So, all these ligands are acknowledged according to Lipinski's rule of 5 and could be considered as potential inhibitors (Benet et al., 2016). Many studies also suggested that Lipinski's physiochemical rules are not applicable on natural as well as on artificial drugs (Zhang and Wilkinson, 2007).

Table 2 Chemical structure of derived substances from *Carica papaya* with Lipinski's rule

Pub Chem ID / Molecular Formula	Structure and Name	Lipinski's Physiochemical Parameters Rule	
		Properties	Value
637542 C ₉ H ₈ O ₃	p-Coumaric Acid	MW (g/mol) H-donor H-acceptor LogP LogS TPSA (Å ²)	164.16 2 3 1.26 -2.02 57.53
		Violations	0
5280343 C ₁₅ H ₁₀ O ₇	Quercetin	MW (g/mol) H-donor H-acceptor LogP LogS TPSA (Å ²)	302.24 5 7 1.23 -3.16 131.36
		Violations	0
5280863 C ₁₅ H ₁₀ O ₆	Kaempferol	MW (g/mol) H-donor H-acceptor LogP LogS TPSA (Å ²)	286.24 4 6 1.58 -3.31 111.13
		Violations	0
445858		MW (g/mol) H-donor H-acceptor LogP	194.18 2 4 1.36

C ₁₀ H ₁₀ O ₄	Ferulic Acid	LogS TPSA (Å°)	-2.11 66.76
		Violations	0
3705436		MW (g/mol)	451.48
		H-donor	8
		H-acceptor	8
C ₁₉ H ₂₉ N ₇ O ₆		LogP	-2.09
		LogS	1.13
		TPSA (Å°)	235.25
		Violations	2
5281235		MW (g/mol)	552.87
		H-donor	1
		H-acceptor	1
C ₄₀ H ₅₆ O		LogP	10.20
		LogS	-10.33
		TPSA (Å°)	20.23
		Violations	2
446925		MW (g/mol)	536.87
		H-donor	0
		H-acceptor	0
C ₄₀ H ₅₆		LogP	11.90
		LogS	-11.92
		TPSA (Å°)	0.00
		Violations	2
5281243		MW (g/mol)	568.87
		H-donor	2
		H-acceptor	2
C ₄₀ H ₅₆ O ₂		LogP	9.21
		LogS	-9.64
		TPSA (Å°)	40.46
		Violations	2
5280489		MW (g/mol)	536.87
		H-donor	0
		H-acceptor	0
C ₄₀ H ₅₆		LogP	11.11
		LogS	-11.04
		TPSA (Å°)	0.00
		Violations	0
89594		MW (g/mol)	162.23
		H-donor	0
		H-acceptor	2
C ₁₀ H ₁₄ N ₂		LogP	1.50
		LogS	-1.89
		TPSA (Å°)	16.13
		Violations	0
2346		MW (g/mol)	149.21
		H-donor	0
		H-acceptor	1
C ₈ H ₇ NS		LogP	2.91
		LogS	-3.07
		TPSA (Å°)	44.45
		Violations	0
305		MW (g/mol)	104.17
		H-donor	1
		H-acceptor	1
C ₅ H ₁₄ NO ⁺		LogP	-1.38
		LogS	-0.10
		TPSA (Å°)	20.23

3.2 Docking scores

Table 3 reports E-score (Kcal/mol) or binding energies obtained from docking of *Carica papaya* compounds with 7BZ5 and 7BW4. Acquired results showed that Lutein gave the lowest binding energy i.e. -8.9013 Kcal/mol in complex with 7BZ5 (Spike protein), which is the best score in our research compared to other docked compounds. In addition, Lycopene gave the lowest energy i.e. -8.7148 Kcal/mol in complex with our second selected protein 7BW4 (RNA-Dependent RNA polymerase), which is another best score among all docked compounds. These scores are the reckoning-based analysis in search for scheming the drugs against COVID-19.

Table 3 Docking results of *Carica papaya* compounds with 7BZ5 and 7BW4

Ligands	Scores (Kcal/mol)	
	7BZ5	7BW4
p-Coumaric Acid	-4.8987	-4.3025
Quercetin	-6.3272	-5.5544
Kaempferol	-5.4416	-5.5174
Ferulic Acid	-5.0683	-5.0404
Papain	-8.6222	-7.9099
β -Cryptoxanthin	-8.6993	-8.5152
Lycopene	-8.3588	-8.7148
Lutein	-8.9013	-8.4875
β -Carotene	-8.7844	-8.1668
Nicotine	-4.9437	-5.0314
Benzyl Isothiocyanate	-4.6074	-4.4378
Choline	-4.2034	-4.2146

3.3 Medicinal significance of ligands

The major compounds which gave the best docking score and lower energies were meant to be the therapeutic drugs used against the causative agent (SARS-nCoV2). Their medicinal significance was studied and described as followed: the first major compound is Papain having properties like immunomodulatory, anti-oxidant and used for the treatment of inflammation (Mamboya, 2012). It has enzymatic activities which act as inhibitor as well. The second major compound having good docking score is β -Cryptoxanthin which belongs to carotenoids family. (<https://www.phytochemicals.info/phytochemicals/beta-cryptoxanthin.php>) The antioxidant property of this compound prevents cells and its machinery from making free radicals which otherwise can damage the cells and tissues (Burri et al., 2016). The third major compound which has maximum docking score with RdRP protein (7BW4) of -8.7148 Kcal/mol is Lycopene. It is a naturally occurring carotenoid which is a powerful antioxidant molecule that scavenges ROS; reactive oxygen species (Story et al., 2010). It has a potential health benefits in many biological activities in humans. It also uncovered a critical antiviral impact and anticytotoxic movement against HSV-1 contamination. The fourth major compound is Lutein which gave the maximum docking score with Spike protein (7BZ5) of -8.9013 Kcal/mol. It is rich in anti-oxidants, which

plays an anti-inflammatory role as per literature studies (Buscemi et al., 2018). It also protects cells against the harmful effects of free radicals. In the preceding, the fifth major compound is β -Carotene which is a strong antioxidant, human metabolite having chemopreventive activities. It stimulates immune system by the release of killer cells, lymphocytes and phagocytes (Lustgarten et al., 2011). All these ligands have scientifically impactful against the damage caused by the foreign agents of viral infection and acts as the immunomodulator in cellular events.

3.4 Interactions of ligands with 7BZ5 complex

By using MOE software, we got the results of all possible ligand-protein interactions after the completion of docking process. All the observable interactions of 7BZ5 complex with the major compounds of *Carica papaya* having the lower binding energies are discussed in table 4. Firstly, the ligand interactions with the active site of spike protein (7BZ5) can be easily observed. Secondly, the probable hydrogen interactions with the amino acids, type of bonding, their required energies (in Kcal/mol) and their distances in Angstrom ($\text{\AA}$) are mentioned. Thirdly, the surface maps are graphically represented with the attachment sites of ligands in Spike protein. Besides, there are some compounds which have the best docking scores with non-perceptible hydrogen interactions.

Table 4 2D and 3D interactions of the major compounds from *Carica papaya* with 7BZ5

2D-Interactions / Ligand Bonding	Possible Interactions and Name				3D-Interactions / Surface Maps
	Amino Acid	Type	Distance (Å)	Energy (Kcal/mol)
GLU-214	H-donor	2.78	-7.2
	TYR-130	H-acceptor	3.02	-1.1	
	GLY-213	H-acceptor	2.92	-1.5	
	LYS-216	π -H	3.99	-0.6	
	Quercetin
ASP-123	H-donor	3.10	-2.5
	GLY-213	H-acceptor	3.16	-1.0	
	GLU-214	H-acceptor	3.27	-1.9	
	ASP-123	H-acceptor	3.02	-4.4	
	LYS-216	H-acceptor	3.10	-8.0	
	SER-129	π -H	3.83	-0.6	
Papain
ASP-123	H-donor	2.72	-2.9
	β -Cryptoxanthin

There are non-observable interactions, only Van der Waals (electrostatics) interactions are evident.
Lycopene
ASP-123	H-donor	3.30	-1.0
	LYS-216	H-acceptor	3.08	-0.6	
Lutein
There are non-observable interactions, only Van der Waals (electrostatics) interactions are evident.
	β-Carotene				

3.5 Interactions of ligands with 7BW4 enzyme

After the completion of docking process, we got the results of all possible ligand-protein interactions of major compounds of *Carica papaya* (having the best docking scores) with 7BW4 as shown in table 5. Primarily, the 2D-interactions of ligands with the active sites of (7BW4) RNA-dependent RNA polymerase (RdRP) is displayed. Furthermore, the noticeable hydrogen interactions with the amino acids, type of bonding, their distances in Angstrom (Å), binding energies (Kcal/mol) and 3D-interactions are mentioned. Moreover, there are two compounds (Lycopene and β-Carotene) which have non-perceptible hydrogen interactions as well.

Table 5 2D and 3D interactions of the major compounds of *Carica papaya* with 7BW4

2D-Interactions / Ligand Connections	Possible Interactions and Name				3D-Interactions / Surface Maps
	Amino Acid	Type	Distance (Å)	Energy (Kcal/mol)
ASP-618	H-donor	2.78	-2.6
	ASP-618	H-donor	2.89	-1.4	
	ASP-618	H-donor	3.40	-0.8	
	ARG-553	π -cation	3.44	-0.6	
	Quercetin				
	ASP-623	H-donor	2.98	-0.9	
	ALA-554	H-donor	3.12	-1.1	
	CYS-622	H-acceptor	3.35	-2.6	
	ARG-	H-	2.95	-2.8

553	acceptor
	ARG-553	H-acceptor	2.91	-3.2	
	ARG-553	H-acceptor	2.92	-4.1	
	Papain
ASP-865	H-donor	2.72	-2.5
	ARG-858	H-acceptor	2.88	-1.7	
	β-Cryptoxanthin
There are non-observable interactions, only Van der Waals (electrostatics) interactions are evident.
	Lycopene
ASP-164	H-donor	2.90	-2.9
	ARG-858	H-acceptor	3.24	-1.7	
	Lutein
There are non-observable interactions, only Van der Waals (electrostatics) interactions are evident.
	β-Carotene				

4 Conclusion

By and large, the current study has provided insights into computational prophecy about the drug agents from *Carica papaya* compounds which may be beneficial against SARS-nCoV2. The two main targets of viral proteins (Spike, RdRP) are tested and predicted as evident agents because of their molecular binding and docking score with the selected ligands. Therefore, the major compounds from *Carica papaya* (includes: Papain, beta-Cryptoxanthin, Lycopene, Lutein and beta-Carotene) have more potential to inhibit COVID-19 as compared to other drugs used at present for the treatment of this disease. Moreover, these compounds have immunomodulatory significance and ability to fight against the inflammation caused by this virus. Consequently, these results encourage further in vivo and in vitro investigations to be used as drug against SARS-nCoV2 preveniently.

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Figures

Figure 1

Comprehensive work stream of docking study

(a)

(b)

Figure 2

Proteins used for docking studies: (a) Spike; 7BZ5 and (b) RdRP; 7BW4