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Research Article

In-Silico Study of the Inhibitory Effect of Some Flavonoids Compounds and their Derivatives on SARS-COV-2

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ABSTRACT
The pandemic of Coronavirus Disease 2019 forms a big threat to all people in the world around us. In Iraq, there is a direct increase in the incidence, with a slight decrease in the mortality rate, and that leads us to attempt to find any way to stop or lessen the virus's harmful symptoms. In the current study, we used molecular docking to detect the probable inhibitory effect of fifteen natural compounds of some Flavonoids and their derivatives and two antiviral drugs against two of very important SARS-COV-2 proteins the papain like protease (PLpro) and RNA dependent RNA polymerase (RdRp) that was performed using Molecular Operating Environment software(MOE).
All the chosen flavonoids and their derivatives, plus the two antiviral drugs docked in the active sites of the viral proteins (PLpro), some of the natural flavonoids like Glycitein 7-O-glucuronide and Theaflavin, gives energy complex scores about -6.96308947 and -6.99058199 Kcal/mol which is better than the energy score is given by Sofosbuvir and Darunavir -6.81020832 and -6.93942785 Kcal/mol respectively. And the docking of the compounds into the active sites of (RdRp) protein gives energy binding scores for Theaflavin monogallate -7.84163618 kcal/mol and that better than the complex's score given by docking of the Sofosbuvir and Darunavir into the same protein which gives -7.30999422 and -7.67598867 kcal/mol respectively. That's mean these flavonoids and their derivatives can be used as COVID-19 treatment. Otherwise, the infected people with COVID-19 can consume food rich with these Flavonoids to inhibit the virus or at least decrease its symptoms.
Also from docking of flavonoids into both viral proteins, we can notice that all-natural compounds reported energy binding scores, and the Flavonoid derivatives have a better energy binding score than flavonoid themselves.

Keywords: Flavonoids, Papain like protease, RdRp, Flavonoid derivatives, Theaflavin, 6WX4, 7BV2.

INTRODUCTION

Since December 2019 all the world around us suffering from a pandemic of Coronavirus Disease 2019 (COVID-19). It is the most recently discovered coronavirus that causes infectious zoonotic disease (which can infect a broad range of hosts including humans) named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1,2]. The virus belongs to the family Coronaviridae, which has four subgroups the alpha (α), beta (β), gamma (γ), and delta (δ) coronavirus and the 'common human coronaviruses' are 229E (α coronavirus), NL63 (α coronavirus), OC43 (β coronavirus) and HKU1 (β coronavirus) [3]. They usually cause a respiratory infection extending between the common cold and severe state diseases, virtually over the past two decades, coronaviruses (CoVs) have been associated with significant disease outbreaks in East Asia and the Middle East, severe acute respiratory syndrome (SARS) and the Middle East respiratory syndromes (MERS) began to emerge in 2002 and 2012, respectively [2]. At present-day, the novel coronavirus (SARS-CoV-2), causes a disease characterized by a respiratory syndrome with a variable degree of severity, ranging from a mild upper respiratory tract illness to severe interstitial pneumonia and acute respiratory distress syndrome [4].
COVID-19 is typically rapidly spread from one person to another via respiratory droplets produced during coughing and sneezing [3] and generally has a less severe clinical picture than MERS and SARS but it can spread in the community more easily and that made this virus a global health threat with its continuing pandemic in many countries and regions [2,4]. Today in Iraq the number of infected people reaches 168,290 with a mortality rate of about 3.9 % with a threat of the second wave in the next autumn and that is relatively high percent lead us to try to find any way to stop or lessen the harmful symptoms as well as the very rapid spread of this virus along with the community [5, 6].
The using of plants extracts regard as one of the most ancient and powerful means enabled human to survive and treat multiple of disease across years, Despite several advancements in the field of

synthetic drug chemistry and antibiotics, Today, the world is gradually turning to plant formulations which are known to be effective against a large list of diseases and illnesses [7]. The plant's secondary metabolites are a group of plant products which have low molecular weight compounds formed generally by specific plant`s organs, tissues, and cells[8]. They have high pharmaceutical properties effective for human health and widely used in the drug and pharmaceutical industry and are include many related metabolites like alkaloids, amines, steroids, insecticides, and flavonoids [7]. Flavonoids are a group of polyphenolic compounds that hold an aromatic ring bearing at least one hydroxyl group [9]. They are commonly found in fruits, vegetables, nuts, seeds, and honey, etc. They are known to have medicinal properties and play a major role in successful medical treatments from ancient times [7]. flavonoids have been reported on their effective antioxidants, anticancer, antibacterial, cardioprotective agents, anti-inflammation, immune system promoting, and interesting candidate for pharmaceutical and medical applications [9]. All these valuable properties directed us to make a study by molecular docking using Molecular Operating Environment (MOE software) about the inhibitory effect of some available and medically important flavonoids on two of the more important SARS-CO-V2 proteins the papain like protease enzyme (PLpro) [10], and RNA dependent RNA Polymerase (RdRp) which also known as NSP12, catalyzes the synthesis of viral RNA [11].

MATERIAL AND METHODS

Medicinal compounds choice

In this study, we tried to select a Multiple of medicinally reported important and more available flavonoids and a few of their derivatives to detect their inhibitory effect on COVID 19 (RdRp plus PLpro) proteins. The selected flavonoids and their derivatives are Kaempferol, Myricetin, Epicatechin, Chrysin, Taxifolin, Glycitein, Malvidin, Theaflavins, Pinocembrin, Naringenin, Theaflavin monogallate, Glycitein7-O-glucuronide, Myricetin3-O-rhamnoside, Epicatechin-o-gallate, and Pinocembrin7-O-rhamnoside.

Preparation of both enzymes and ligands

The download of COVID-19 PLpro and $RdRp^{pr}$ three dimensional structures was done from Protein Data Bank under PDB ID 6WX4 and 7BV2 respectively [12,13]. Crystallographic properties of 6WX4 and 7BV2 proteins are reported in table 1. The more suitable region of the receptor that forming interactions with ligands can be recognized by the protocol of active site prediction and isolation [14]. Then Hamiltonian PM3 (Parametric model 3) set in MOE was used and field strengths within the MMFF94x (Merck molecular force field) energy of the protein was minimized. Besides, the protein surface must be clear from water molecules because the latter may hide the interaction region during docking. The active sites of 6WX4 and 7BV2 were identified by using the model of site-finder set in MOE as shown in **Figure 1 and 2**.

Table 1: Crystallographic properties of covid-19 proteins.

Protein	Pdb code	Classification	Organism	Expression system	Resolution	METHOD	Total structure weight (da)	Chain
Papain like protease	6WX4	Hydrolase	SARS-CoV-2	*Escherichia coli* BL21(DE3)	1.66 Å	X-Ray Diffraction	37130	D
RNA dependent RNA Polymerase	7BV2	Viral Protein	SARS-CoV-2	Spodoptera Frugiperda	2.50 Å	Electron Microscopy	109070	A

And Table 2 reports the major chemical structure of the chosen flavonoids which collected from (Chequer et al. 2013) [15]. The 2-dimensional (2D) structures of flavonoids chemical compounds were downloaded in SDF format from PubChem [16]. Lipinski's physicochemical parameters rule [17, 18] were also studied for each flavonoid (ligand) and reported in table 3. Chemical structures of main drugs under clinical tests for the treatment of COVID-19 are reported in table 4 [19, 11]. Also, both natural ligands (Flavonoids compounds) and proposed drugs were submitted to energy minimizing under default conditions of pH = 7 and temperature = 300°K.

Table 2: The chemical structures of flavonoids

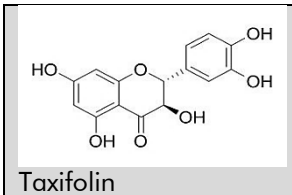
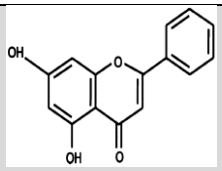
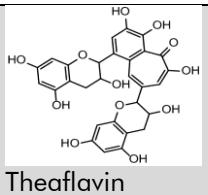
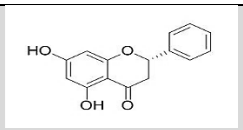
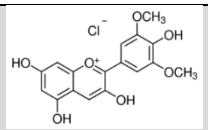
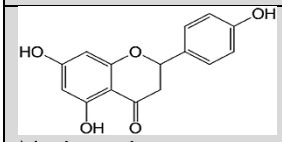
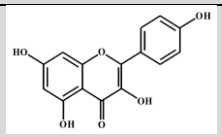
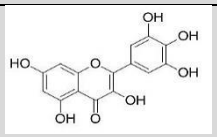
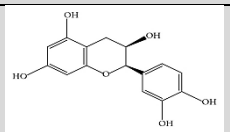
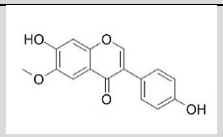
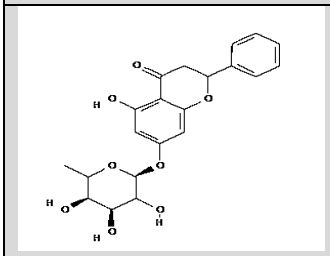
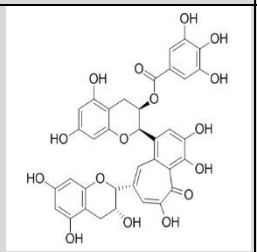
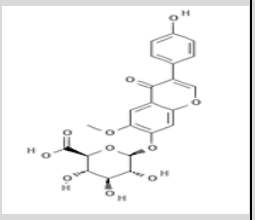
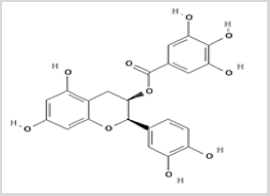
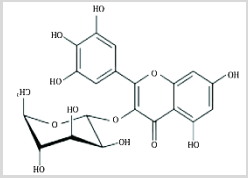
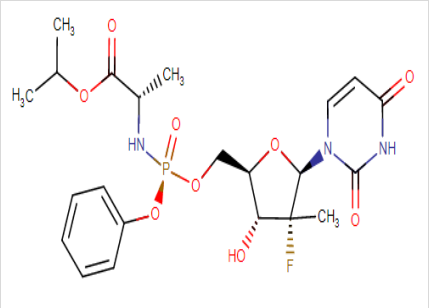
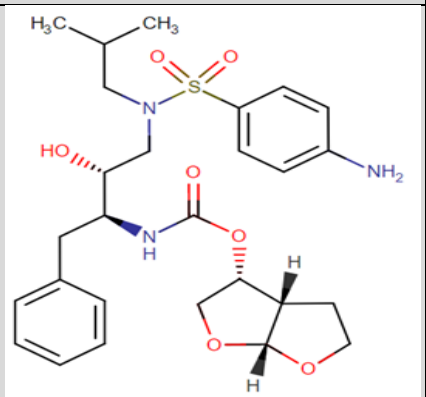
 Taxifolin	 Chrysin	 Theaflavin	 Pinocembrin	 Malvidin
 Naringenin	 Kaempferol	 Myricetin	 Epicatechin	 Glycitein
 Pinocembrin7-O-rhamnoside	 Theaflavin monogallate	 Glycitein7-O-glucuronide	 Epicatechin-3-O-gallate	 Myricetin 3-O-rhamnoside

Table 3: Physicochemical Lipinskis parameters for flavonoids compounds.

Ligands	MW (gm/mol)	toxicity	H-don	H-acc	TPSA (A⁰)	Rot B	Log p	Log s	Lip_Drug l.
1.Kaempferol	287.246	Non	3	5	86	1	1.48	-2.93	1.0
2.Myricetin	319.244	Non	6	7	130.61	0	2.34	-2.20	1.0
3.Naringenin	273.264	Non	2	5	66.76	1	1.56	-2.25	1.0
4.Chrysin	256.256	Non	3	3	69.92	0	2.56	-3.06	1.0
5.Epicatechin	288.255	Non	4	5	90.15	1	2.52	-1.89	1.0
6.Glyciten	284.266	Non	0	3	27.69	1	1.73	-3.95	1.0
7.Malvidin	332.307	Non	3	6	79.15	2	1.43	-2.78	1.0
8.Pinocembrin	258.272	Non	2	4	66.76	1	1.52	-2.71	1.0
9.Taxifolin	304.253	Non	5	7	127.45	1	1.44	-2.00	1.0
10.Theaflavin	562.482	Non	6	9	139.84	0	3.61	-4.66	0.0
11.Theaflavin monogallate	708.54	Non	11	12	254.9	3	5.26	-7.38	0.0
12.Glycitein 7-O-glucuronide	460.391	Non	6	10	172.21	5	-0.13	-3.558	1.0
13.Myricetin 3-O-rhamnoside	464.379	Non	8	11	206.6	3	0.53	-2.716	1.0
14.Epicatechin-o-gallate	441.368	Non	6	8	179.97	4	3.49	-3.289	1.0
15.Pinocembrin7-O-rhamnoside	402.399	Non	4	8	116.45	3	-0.54	-2.439	1.0

Table 4: The chemical structure of the examined antiCOVID-19 drugs.

drugs	Chemical structure	Drug bank Accession Number	Lipinski's rules	
			properties	value
Sofosbuvir		DB08934	MW(g/mol) H-donor H-acceptor Log P(o/w) Log S TPSA (A°) RotB	541.554 5 11 0.558 -1.275 144.57 11
Darunavir		DB01264 (EXPT00002)	MW(g/mol) H-donor H-acceptor Log P(o/w) Log S TPSA (A°) RotB	560.776978 1 7 1.595 -3.183 121.709 4

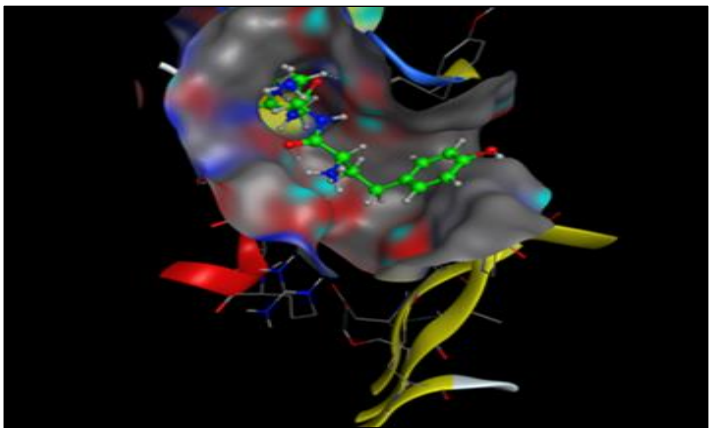


Fig.1: The active site of RNA dependent RNA polymerase (PDB 7BV2) in complex with Remdesivir.

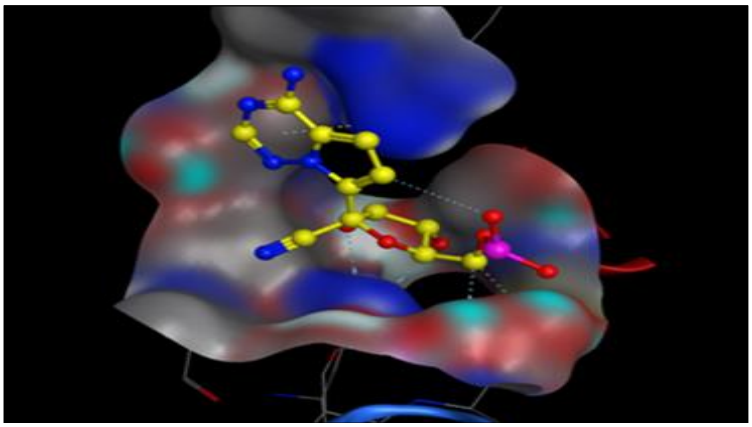


Fig.2: The active site of Papain like protease (PDB 6WX4) enzyme inhibited by peptide inhibitor VIR251.

Docking and Building Complexes

Docking using the Dock module in MOE software consists of positioning ligands into the active site of 6WX4 and 7BV2 with most of the default tools to expect how molecules interact with the binding site of the receptor [20]. The first docked molecules series were proposed drugs and respective reference inhibitors (PRD_002390 of 6WX4 and F86 for 7BV2) to compare obtained scores with scores from chosen ligands of flavonoids and a few of their derivatives.

RESULTS

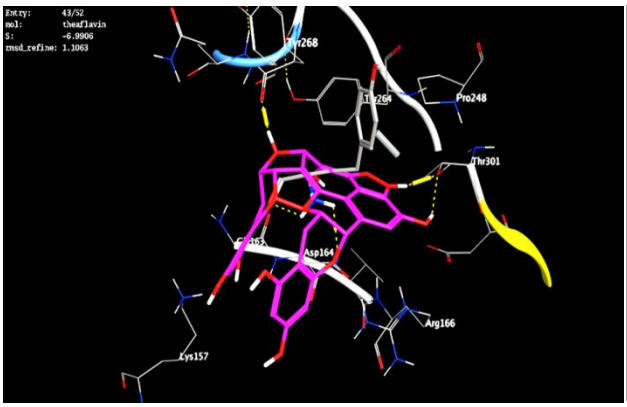
All the gained scores of docking of drugs and inhibitor ligands (PRD_002390 and F86). Under clinical test with the SARS COV2 proteins (PDB ID 6WX4 and 7BV2) were shown in table 5. As well as the docking scores of flavonoids compounds with the same viral proteins were shown in table 6 and Table 7(a-o) and Table 8(a-o). the natural flavonoids like Glycitein 7-O-glucuronide and Theaflavin, gives energy complex scores about -6.96308947 and -6.99058199 Kcal/mol when docked within the SARS COV2 PLpro, while the docking of the Theaflavin monogallate into the active sites of RdRp viral protein gives energy binding scores -7.84163618 kcal/mol as shown in Figure 3 and 4.

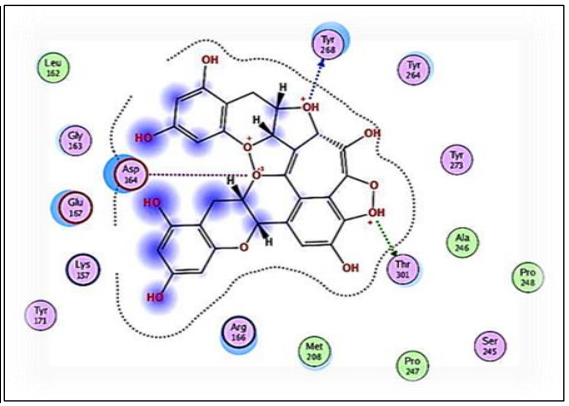
Table 5: Score of binding for docking of SARS COV2 proteins with some drugs and inhibitor.

Drugs and Inhibitors	The score of binding (Kcal/mol)	
	6WX4	7BV2
1. PRD_002390	-8.20934486	/
2. F86 (Remdesivir)	/	-6.22851563
3. Sofosbuvir	-6.81020832	-7.30999422
4. Darunavir	-6.93942785	-7.67598867

Table 6: Binding score for docking of SARS COV2 proteins with choosing flavonoids and a few of their derivatives.

Flavonoids and derivatives	The score of binding (Kcal/mol)	
	6WX4	7BV2
1.Kaempferol	-5.29018021	-6.12179089
2.Myricetin	-5.86744404	-5.85045195
3.Naringenin	-5.87787628	-5.97152519
4.Chrysin	-4.68946028	-5.42630672
5.Epicatechin	-5.05769491	-4.75056934
6.Glyciten	-5.25532818	-4.14114809
7.Malvidin	-5.46971416	-5.60388279
8.Pinocembrin	-5.2122879	-5.77658463
9.Taxifolin	-5.13097095	-5.547822
10.Theaflavin	-6.99058199	-6.61838436
11.Theaflavin monogallate	-6.26978922	-7.84163618
12.Glycitein 7-O-glucuronide	-6.96308947	-6.61669445
13.Myricetin 3-O-Rhamnoside	-6.19278622	-7.35158348
14.Epicatechin-O-gallate	-6.24127769	-6.42785978
15.Pinocembrin7-O-Rhamnoside	-5.98144579	-6.40977716





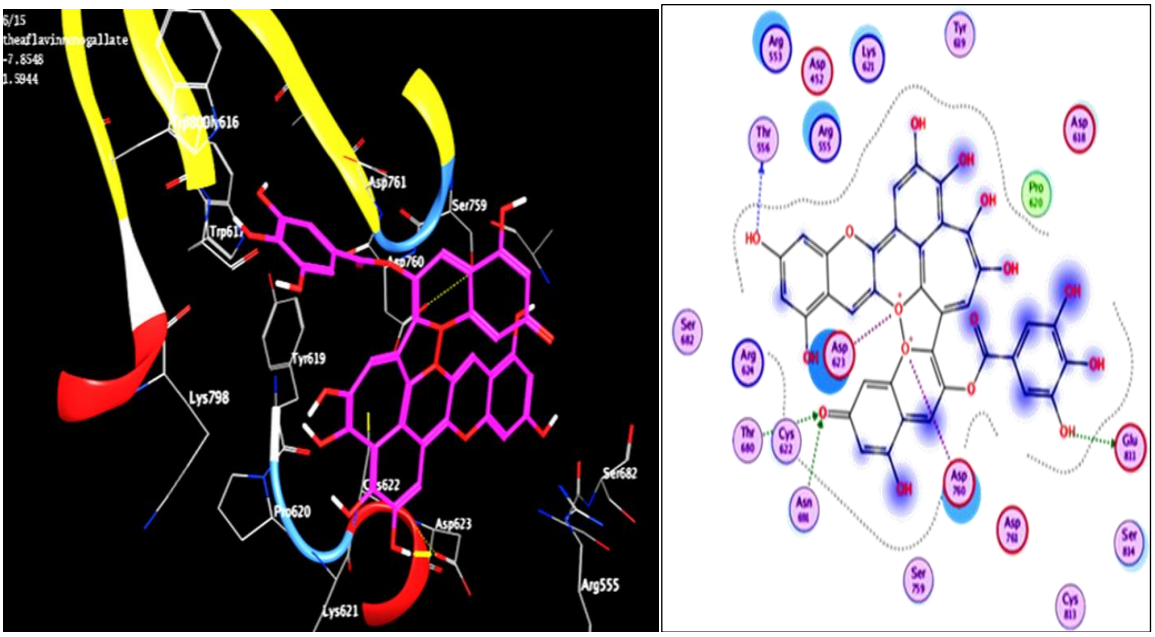


Fig.3: The2D and 3D possible interaction of Theaflavin and Glycitein-o-7glucorenoid with SARS COV2 PLpro respectively.

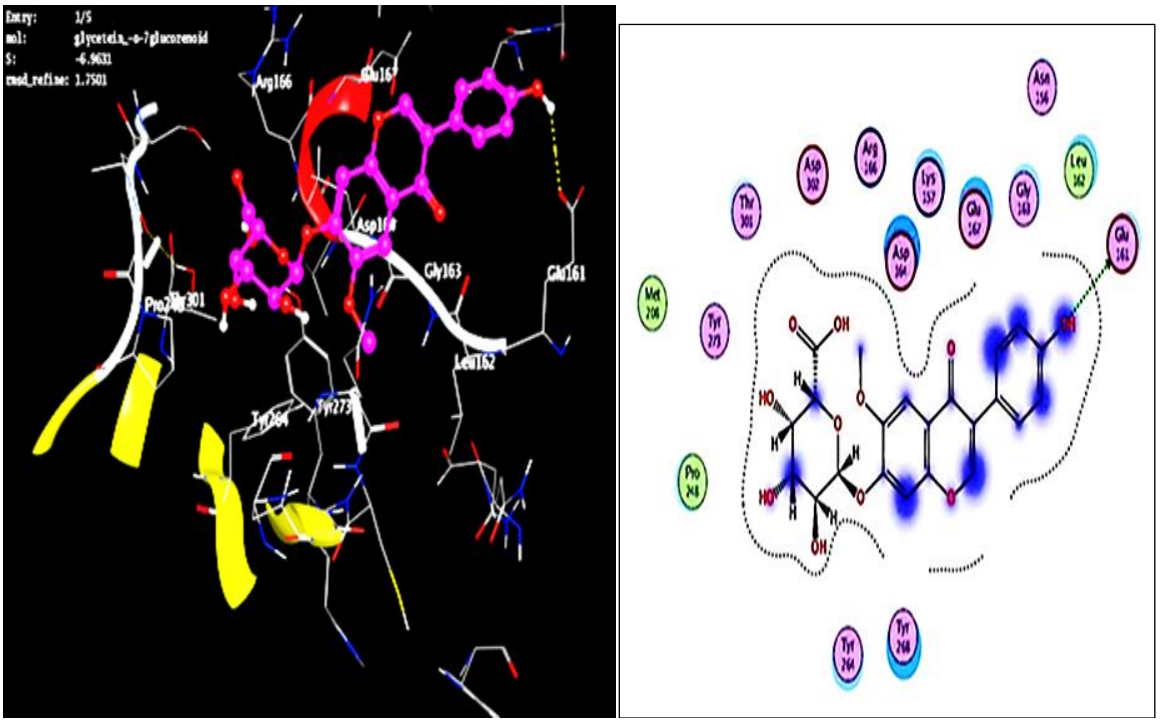
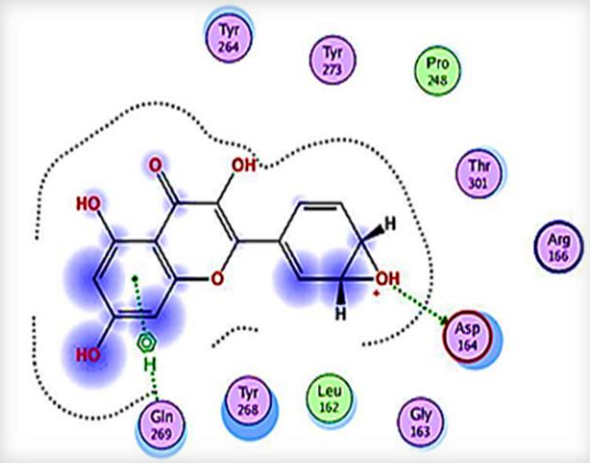
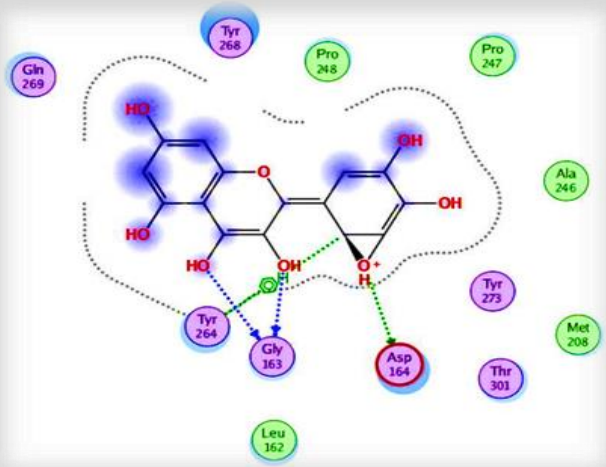
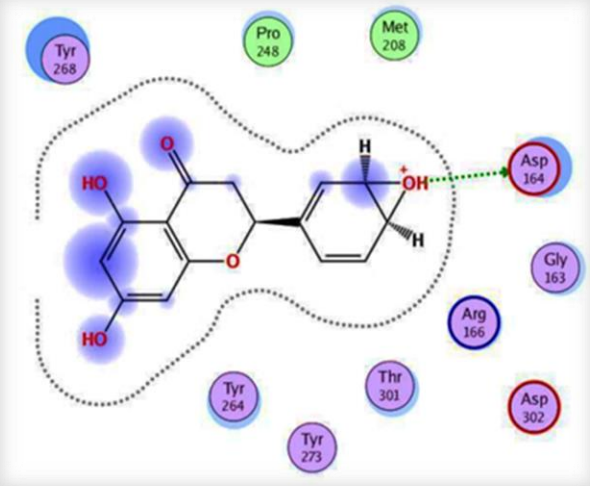
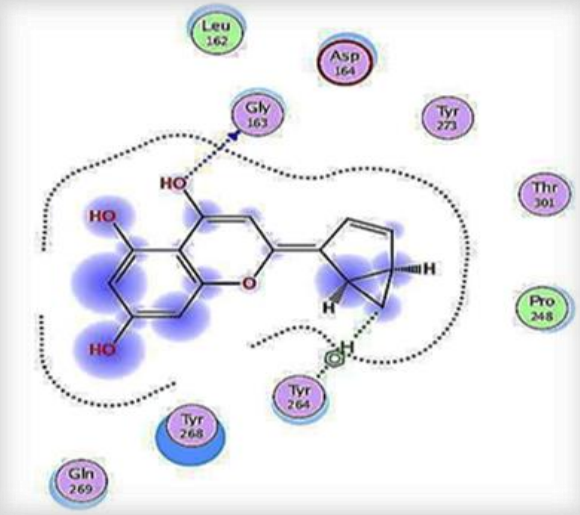
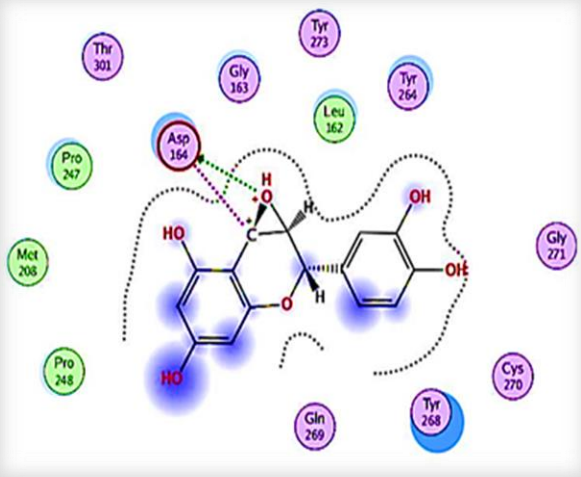
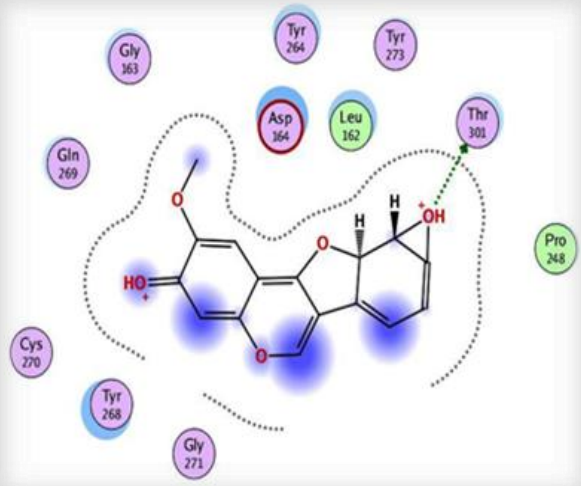
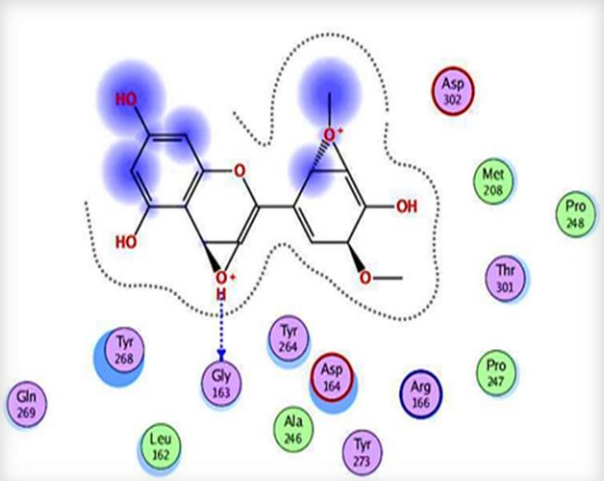
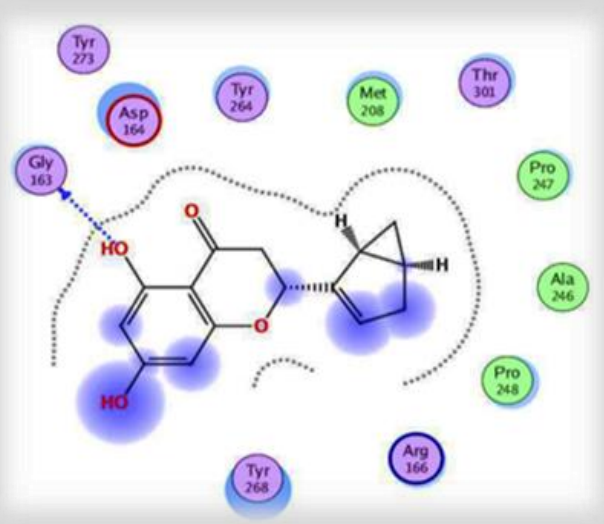
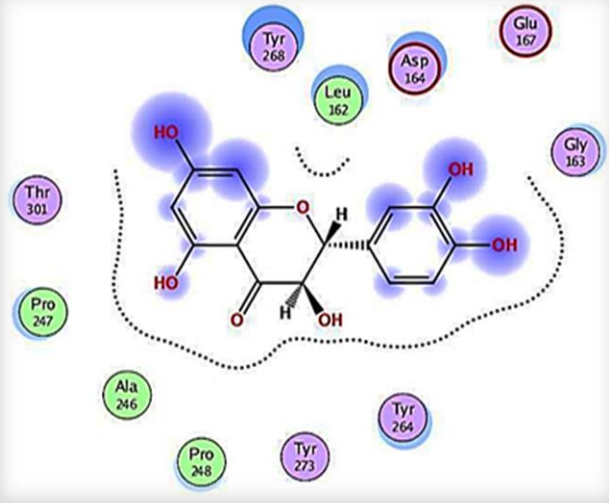


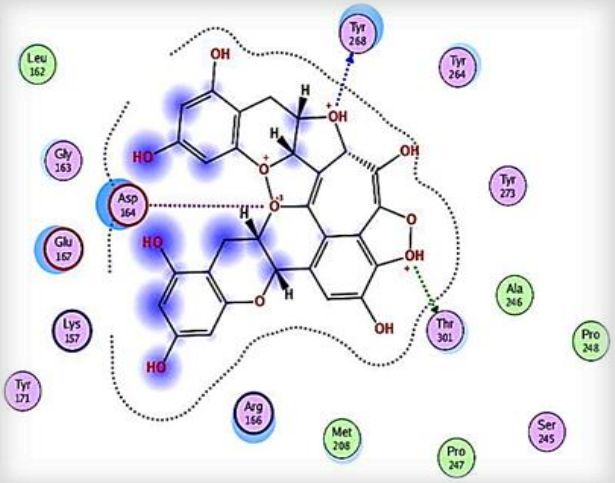
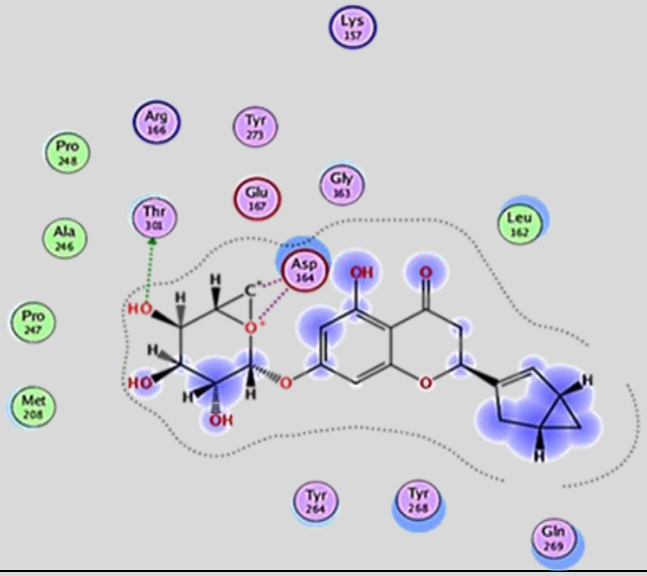
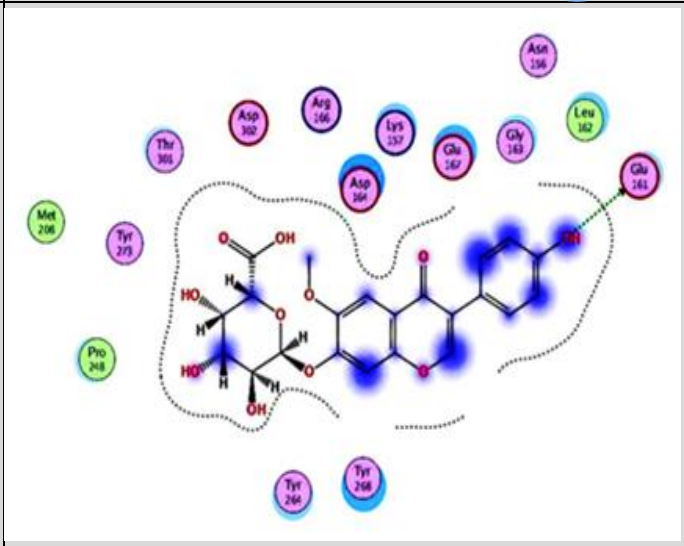
Fig.4: The 2D and 3D possible interaction of Theaflavin monogallate with SARS COV2 RdRp protein.

Table 7: The theoretical binding complex gained by docking of flavonoids and their derivatives with SARS COV2 Papain like protein ID 6WX4.

Selected compounds	2D possible interaction of compounds	Types of binds
a. Kaempferol		The amino acid ASP 164 (H-donor) with 2.66 A° distance and energy of -14.9 kcal/mol. The amino acid GLN 269 form (π-H) bond with 4.31 A° distance and -0.7 kcal/mol.
b. Myricetin		The (H-donor) hydrogen bonds formed by amino acids GLY136, ASP164, and GLY136 with 3.04 A°, 2.62 A°and 2.86 A° distances and energy of -2.1,-28.0, and -1.6 kcal/mol respectively. The amino acid ASP164 (ionic) with 2.62 A° distance and -28.0 kcal/mol. And The TYR 264 (π-H) with 4.55 A° distance and energy of -1.0 kcal/mol.
c. Naringenin		The amino acid ASP164 form (H-donor) with 2.6 A° and energy of –20.2 kcal/mol.

d. Chrysin		The GLY163 form (H-donor) bond with 2.94 A° distance and -1.5 kcal/mol. And The amino acid TYR 264 form (π-H) bond with 4.5 A° distance and energy of -0.6 kcal/mol.
e. Epicatechin		The amino acid ASP164 forming (H-donor) bond with 2.59 A° distance and energy of -8.8 kcal/mol. The amino acid ASP164 forming (Ionic) bond with 3.34A° distance and -7.9 kcal/mol.
f. Glycitein		The amino acid THR 301 (H-donor) bond with 2.58 A° distance and energy of -0.9 kcal/mol.

g. Malvidin		The amino acid GLY163 form(H-donor) bond with 2.96 Aº distance and energy of -1.6 kcal/mol.
h. Pinocembrin		The amino acid GLY163 forming (H-donor) bond with 2.78Aº distance and energy of -2.6 kcal/mol.
i. Taxifolin		Non-perceptible interactions, only electrostatics (Van der Waals) interactions are perceptible.

j. Theaflavin		Both amino acids TYR 268 and THR 301 forming (H-donor) bonds with a distance of 2.79 A° and 2.69 A° and energy -4.5 and -12.8 kcal/mol respectively. The amino acid ASP164 forming (Ionic) bond with a distance of 3.77 A° and energy of -1.0 kcal/mol.
k.Pinocembrin-o-rhaminosid		The amino acid ASP164 forms two Ionic bonds with 3.27A° and 2.65A° distance and energy of -2.9 and -7.3 kcal/mol respectively. The amino acid THR 301 forming (H-donor) bond with 2.97A° distance and energy of -0.7 kcal/mol.
l.Glycitein-o-7glucorenoid		One (H-donor) hydrogen bond by the amino acid GLU161 with 3.37 A° distance and energy of -0.6 kcal/mol.

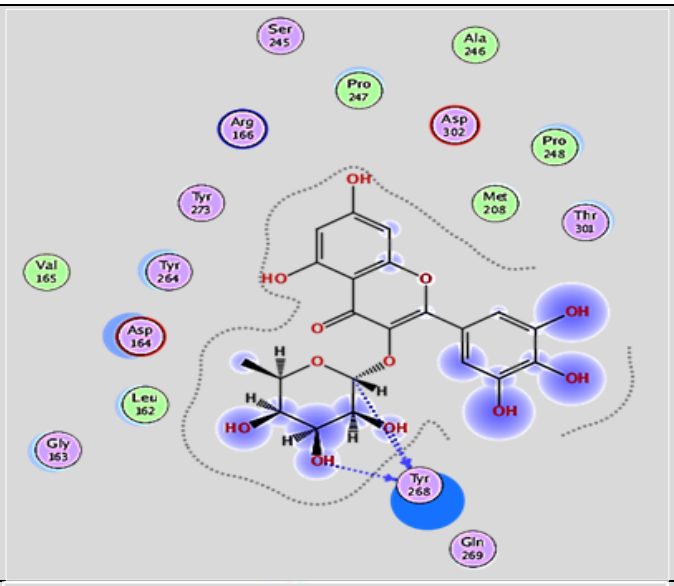
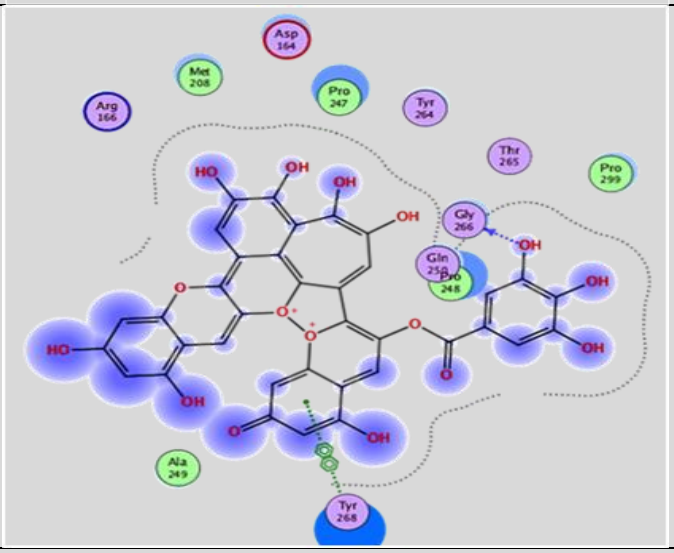
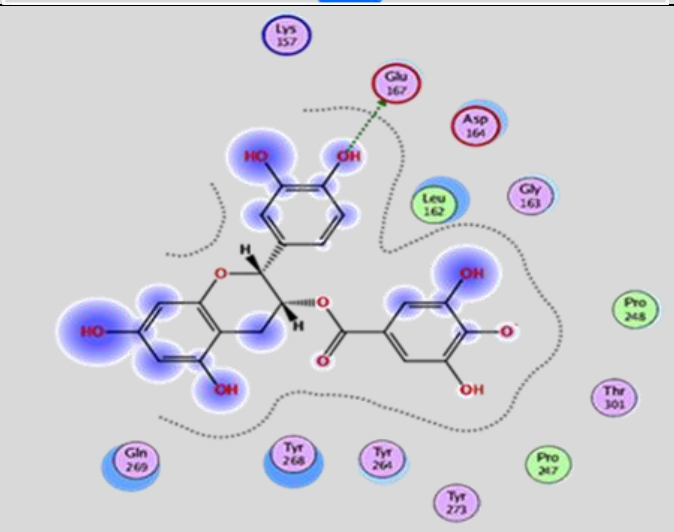
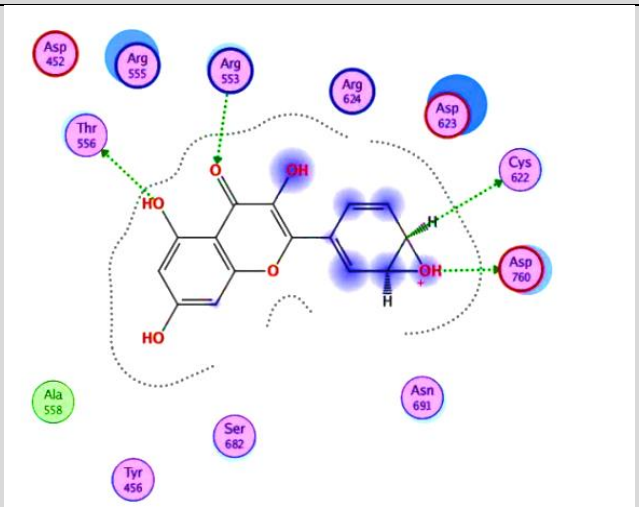
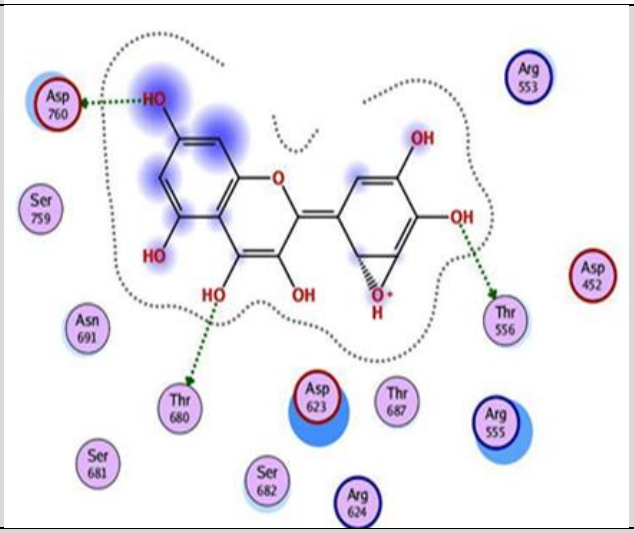
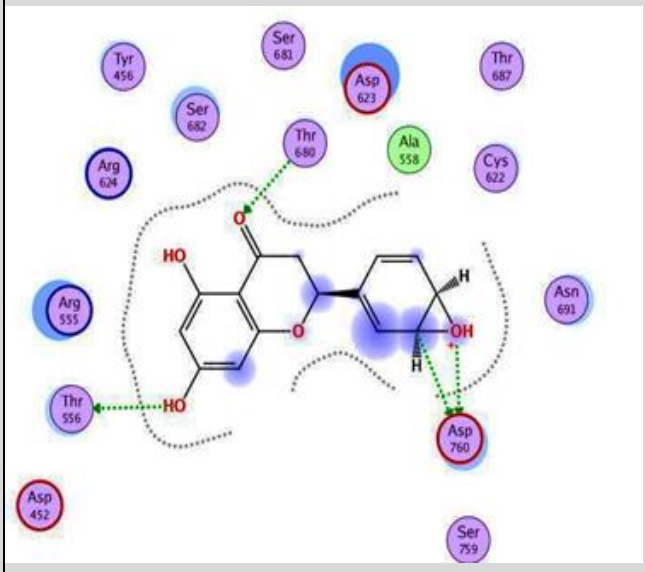
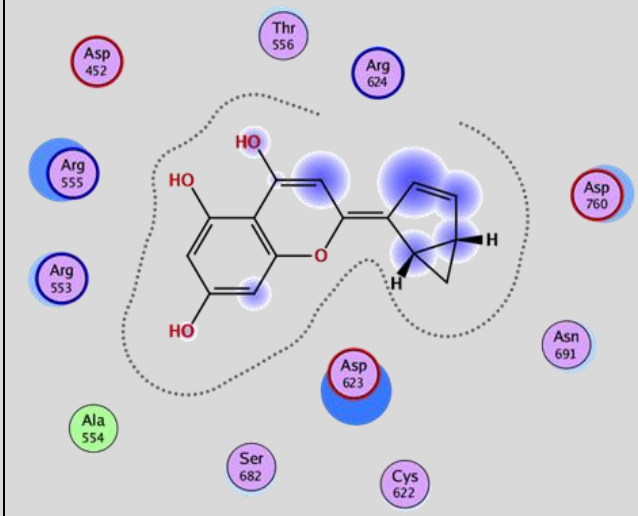
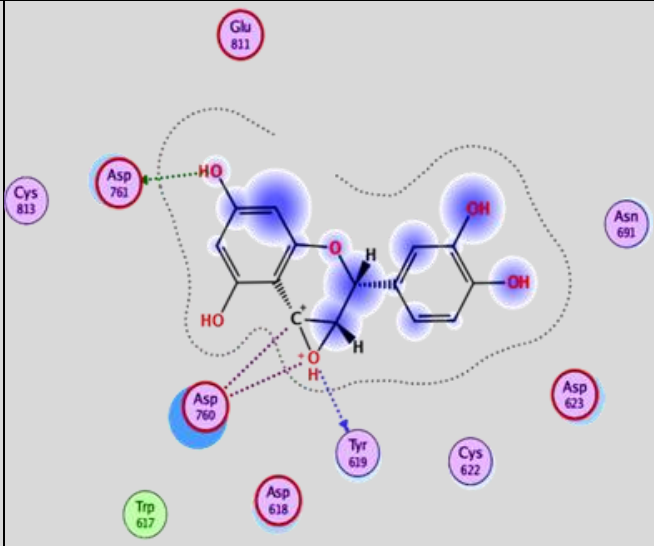
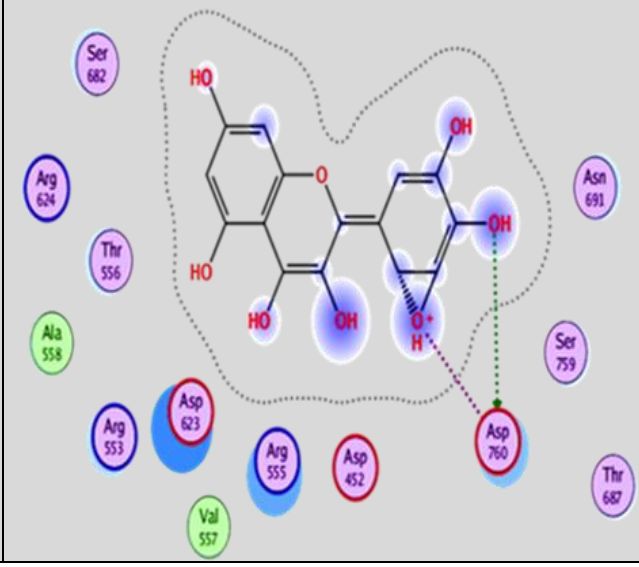
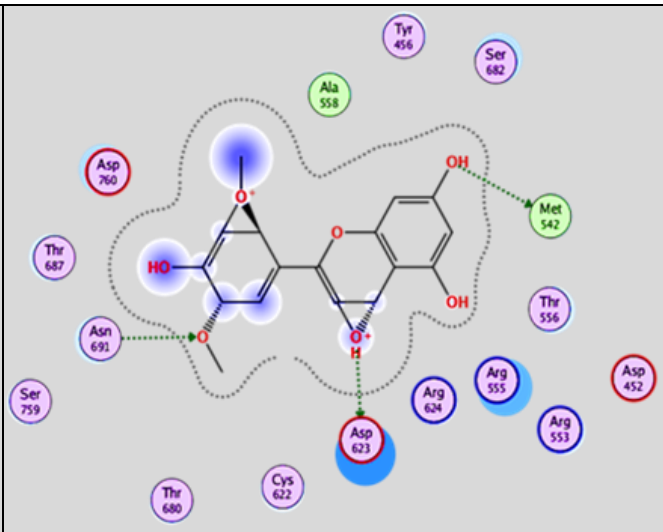
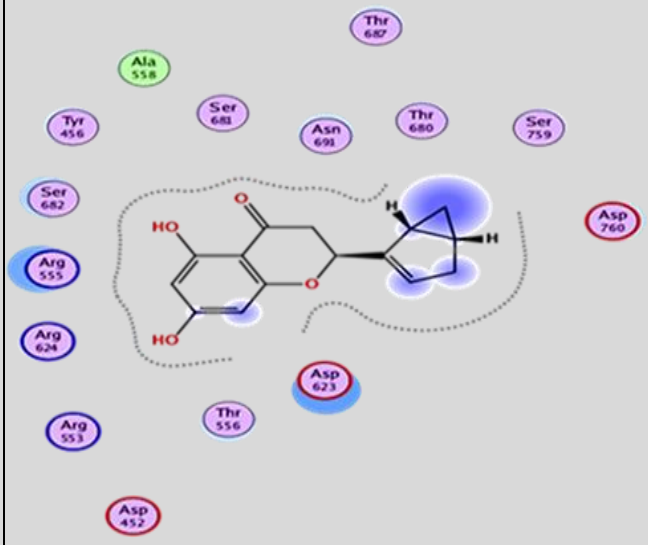
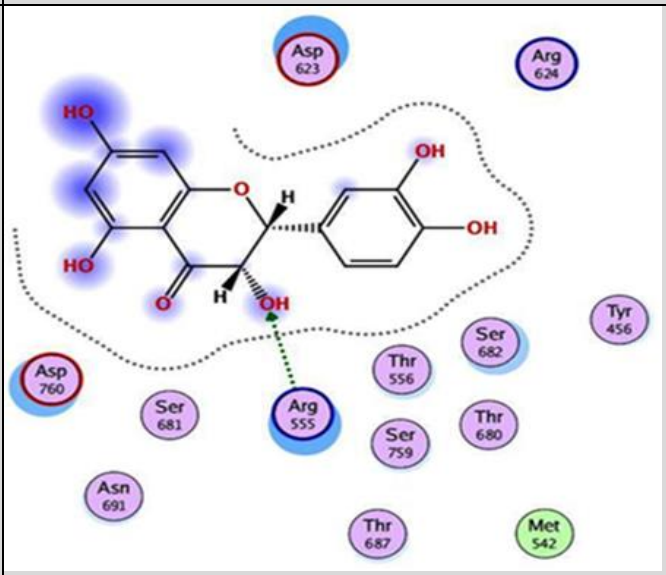
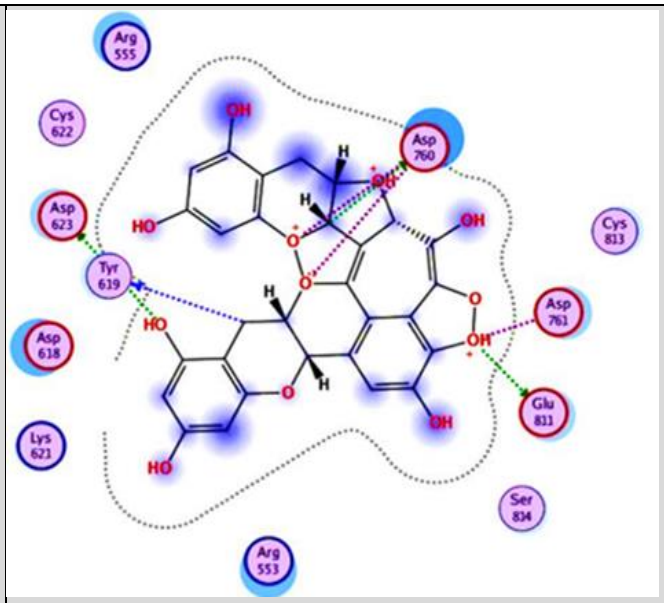
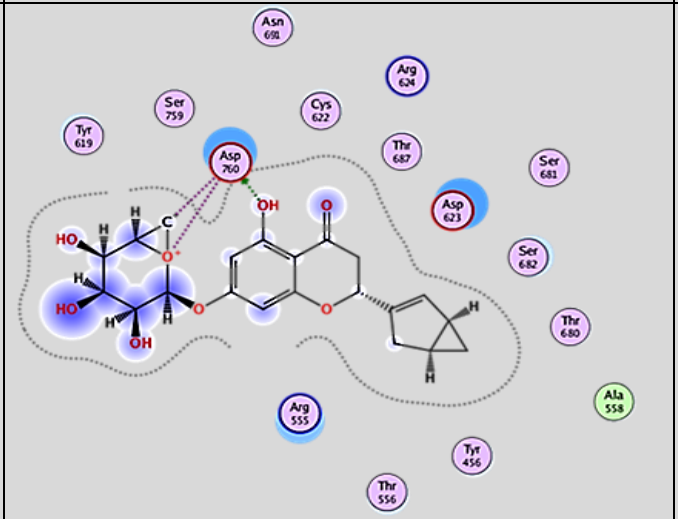
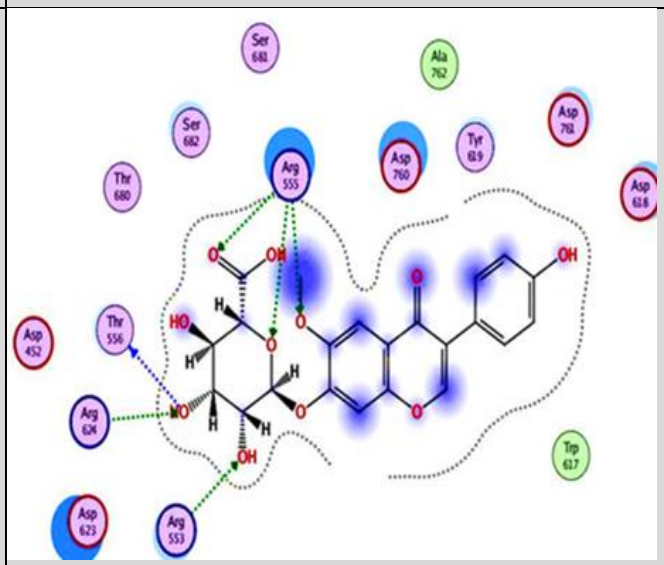
m. Myricetin3-O-rhamnoside		The (H-donor) bond formed by the amino acid TYR 268 with 3.02 A°, 2.99 A°, and 2.88A° distances and energy of -0.8, -1.0, and -1.5 kcal/mol respectively.
n.Theaflavin monogallate		The amino acid GLY 266 forming (H-donor) bond with 2.82 A°distance and energy of -3.4 kcal/mol. The amino acid TYR 268 forming (π-π) bond with 3.65 A° and energy of -0.0 kcal/mol.
o. Epicatechin-o-gallate		One (H-donor) bond by the amino acid GLU167 with 2.86 A° distance and energy of -5.0 kcal/mol.

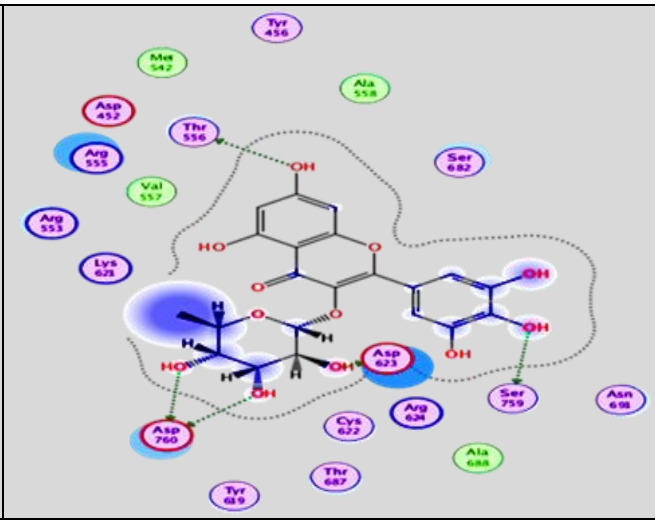
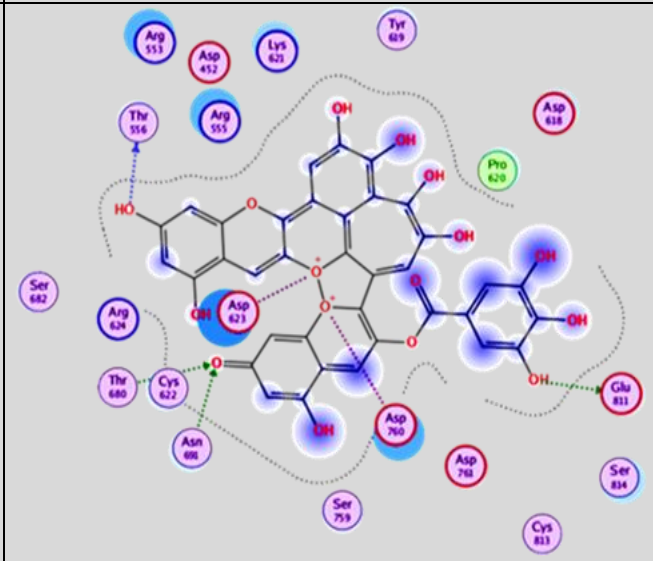
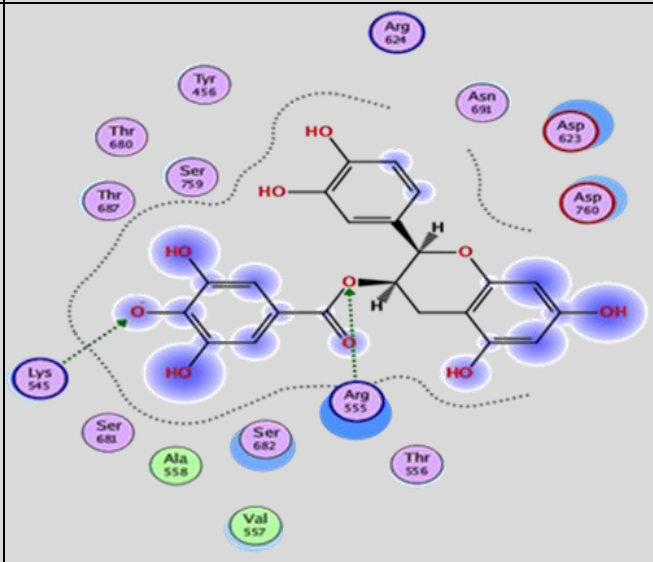
Table 8: The theoretical binding complex is gained by docking of flavonoids and their derivatives with SARS COV2 RNA dependent RNA Polymerase(RdRp).

Selected compounds	2D possible interaction of compounds	Types of binds
a. Kaempferol		The (H- donor) hydrogen bonds formed by the amino acids ASP 760, CYS 622, THR 556, and ARG 553 with distances of 2.9A°, 4.31A°, 3.03A°, and 3.03A° and energy of -9.3, -0.7, -2.3 and-4.8 kcal/mol respectively.
b. Myricetin		The (H-donor) bonds formed by the amino acids THR 680, ASP 760, and THR 556 with distances of 3.21A°, 3.02A°, and 3.1A° and energy of -1.4, -2.0, and -2.0 kcal/mol respectively.
c. Naringenin		Two (H-donor) bonds formed by the amino acids ASP 760 and THR 556 with 3.19 A°, 2.72 A°, and 3.5 A° distances and energy of -0.8, -7.5, and -0.6 kcal/mol respectively. The amino acid THR 680 form(H-acceptor) bond with 2.86 A° distance and energy of -1.3 kcal/mol.

d. Chrysin		There were non-perceptible interactions, only electrostatics (Van der Waals) interactions are perceptible.
e. Epicatechin		Two (H-donor) bonds by the amino acids TYR 619 and ASP 761 with 2.77A° and 2.82 A° distances and energy of -9.1 and -3.8 kcal/mol respectively. And two Ionic bonds formed by the amino acid ASP760 with 2.98 A° and 2.73 A° distances and energy of -4.6 and -6.6 kcal/mol respectively.
f. Glycitein		The amino acid ASP760 form 3 bond one (H-donor) bond with 2.81 A° distance and energy of -3.4kcal/mol. And two ionic bonds with 3.6 A° and 3.13 A° and energy of -1.5 and -3.5 kcal/mol respectively.

g. Malvidin		The (H-donor) hydrogen bonds formed by the amino acids ASP 623 and MET 542 with 2.7A° and 4.11 A° distance and energy of -6.5 and -4.11 kcal/mol respectively. The amino acid ASN 691 form (H-acceptor) hydrogen bond with 3.08 A° distance and energy of -1.1 kcal/mol.
h. Pinocembrin		The possible interaction of with the viral protein as shown there is non-perceptible interaction, only electrostatics (Van der Waals) interactions are perceptible.
i. Taxifolin		The amino acid ARG 555 that forms (H-acceptor) hydrogen bond with 2.93 A° distance and energy of -3.6 kcal/mol.

j. Theaflavin		(H-donor) bonds formed by the amino acids ASP 760, TYR 619, GLU 811, and ASP 623 with a distance of 3.06 A°, 3.41 A°, 2.51 A°, and 3.4 A° and energy of -2.7, -0.8, -26.7, and -0.6 kcal/mol respectively. Ionic bonds three of this bonds formed by the amino acids ASP 760 and one by ASP 761 and one by GLU 811 with a distance of 3.65 A°, 3.04 A°, 3.25 A°, 3.03 A° and 2.51 A° and energy of – (1.4, 4.2, 3.0, 4.3 and 8.7)kcal/mol respectively.
k. Pinocembrin-o-rhaminoside		The amino acid ASP 760 forming one (H-donor) bond and two Ionic bonds with distances 2.98 A°, 2.76 A°, and 3.34 A° and energy of – (1.9, 6.6 and3.6) kcal/mol respectively.
l.Glycitein-o-7glucorenoid		Four (H-donor) bonds formed by the amino acids ASP 623, TYR 456, THR 556, and CYS 813, the distance for the bonds are 3.48 A°, 3.01 A°, 3.37 A°and 4.25 A° with the energy of – (0.7, 1.1, 0.8 and 0.7 kcal/mol) respectively. Two (H-acceptor) bonds formed by the amino acids SER 682 and ARG 624 with a distance of 3.27 A° and 2.8 A° and energy of -0.7 and 2.0 kcal/mol respectively.

m. Myricetin 3-O-rhamnoside		Five (H-donor) bonds formed by the amino acids ASP 760, THR 556, and SER 759 with distances of 2.83 A°, 2.81 A°, 2.87 A°, 3.24 A°, and 3.09 A°, with the energy of – (4.7, 3.7, 5.1,1.4 and 1.9 kcal/mol) respectively.
n.Theaflavin monogallate		Two (H-donor) bonds formed by the amino acids GLU 811 and THR 556 with distances of 2.78 A° and 2.85 A° and energy of -5.0 and -1.0 kcal/mol respectively. Two (H-acceptor) bonds formed by the amino acids THR 680 and ASN 691 with distances of 3.53 A° and 2.99 A° and energy of -0.8 and -1.7 kcal/mol respectively. Two ionic bonds formed by the amino acids ASP 760 and ASP 623 with distances of 3.45 A° and 3.65 A° and energy of -2.1 and -1.4 kcal/mol respectively.
o. Epicatechin-o-gallate		The two (H-acceptor) bonds by the amino acids ARG 555 and LYS 545 with distances of 2.96 A° and 3.12 A° and energy of -1.8 and -2.1 kcal/mol respectively.

DISCUSSION

Under the search for any means that can be used to inhibit or lessen the harmful effect of Coronavirus, the present study tried to introduce some commonly available compounds as resources can help us to face the pandemic. In the current study, we chose two SARS-CoV2 proteins according to the extensive study on SARS-CoV2 which show that there is a multiple of Coronavirus proteins have been recommended as a possible target for antiviral drugs like envelope protein, spike protein, nucleocapsid protein, membrane protein, 3CL protease, and papain-like protease [10]. One of the attractive antiviral drug targets is the SARS-CoV papain-like protease (PLpro) is part of (nonstructural protein) NSP3, and this papain-like protease domain is responsible for the release of NSP1, NSP2, and NSP3 (which are essential for viral replication) by the hydrolysis of the peptide bond from the N-terminal region of polyproteins 1a and 1ab, the latter expressed by the first coronavirus gene (Open Reading Frame 1ab) [21]. Furthermore, the studies showed that SARS-CoV-PLpro harbors a proteolytic activity by removal of ISG15 (interferon-induced gene 15) ubiquitin-like protein as well as ubiquitin (Ub) from proteins of the host cell, Due to this action, the SARS-CoV2 PLpro enzyme performs a significant role in the innate immune response during viral infection by inhibiting the production of cytokines and chemokines which are responsible for the activation of the host innate immune response against viral infection[13,22,23]. In addition to the SARS-CoV2 papain-like protease, the RNA dependent RNA polymerase is another viral protein also known as NSP12 catalyzes the synthesis of viral RNA and thus plays a vital role in the replication and transcription cycle of COVID-19 virus, possibly with the assistance of NSP7 and NSP8 as cofactors, Therefore, NSP12 is considered a primary target for nucleoside analog antiviral inhibitors such as Sofosbuvir which acts as a defective substrate for RNA-dependent RNA polymerase that is essential for the transcription of Hepatitis C viral RNA and for its high replicative, and Remdesivir, which shows potential for the treatment of COVID-19 viral infections [11,12], in our study we try to take only the NSP12 without the NSP7 or NSP8 or any compound to examine the direct effect of flavonoid and their derivatives on RdRp protein.

From our results in Table 5 and 6, we can notice that the antiviral drug and viral inhibitor reported very high scores of binding with SARS-CoV2 PLpro enzyme and RdRp ranging from -6.2 to -8.2 kcal/mol despite that the natural Flavonoids like Theaflavin as well as the Flavonoids derivatives gave also high scores some times better than the antiviral drugs as shown in table 5 and 6. The Theaflavin and Glycitein 7-O-glucuronide reported a binding score with PLpro enzyme better than both the Sofosbuvir and Darunavir antivirus drugs, and the Theaflavin monogallate has a binding score with RdRp higher than that of both antiviral drugs, which means some Flavonoids like Theaflavin and their derivatives have a high affinity to bind with the COVID-19 viral protein as reported by (Peterson, 2020) [24]. And that also means consumption of food or drink which are rich with flavonoids or their derivatives like black Tea which contains Theaflavin, Kaempferol, Myricetin, and Quercetin, etc. can inhibit the viral infection or accelerate patient cure by inhibiting viral proteins [25].

Additionally, the results in table 6 show that the Flavonoid derivatives specially glycosylated flavonoids, for example, Pinocembrin7-O-Rhamnoside and Myricetin 3-O-Rhamnoside gained a better binding score with both chosen COVID-19 viral proteins than the Flavonoids themselves as shown in Table 7 and 8 and that's maybe related to the sugar's moiety (like Rhamnose which increases the compound's affinity to bind with viral proteins [26]. And from the Table 7 and 8 can be shown that the other Flavonoids derivatives like Epicatechin o-gallate, Theaflavin monogallate, and Glycitein 7-O-glucuronide all these flavonoids have highly reactive acidic groups like Glucuronic acid and gallic acid which enable them to binds with the viral protein tightly, the Glucuronic acid in some cases work as a minor component in particular sulfated fucans that isolated from brown algae and showed a wide variety of biological activities, such as inhibitors of human pathogenic viruses including HIV, herpes simplex virus (HSV) and human cytomegalovirus (HCMV) [27]. while The gallate compounds (esters of gallic acid) are widely employed as antioxidants and other biological activities mainly the anticancer, antibacterial, and antifungal properties and anti-herpes simplex virus (HSV)-2 [28].

CONCLUSION

The docking of some flavonoids and their derivatives into specific SARS COV2 proteins PLpro and RdRp form binds in energy scores -which may exceed the complex energy scores of docking the antiviral drugs with the same viral proteins-that enable us to try to use this Flavonoids in COVID-19 treatment also the infected people with COVID-19 virus can consuming nutritions which are rich with Flavonoids and their derivatives and that can participate in patients cure of viral infection by inhibiting of viral proteins.

CONFLICT OF INTEREST

None

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