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Potential antioxidative and inhibitory activity of parietin

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ИНСТИТУТ ЗА ИНФОРМАЦИОНЕ ТЕХНОЛОГИЈЕ КРАГУЈЕВАЦ

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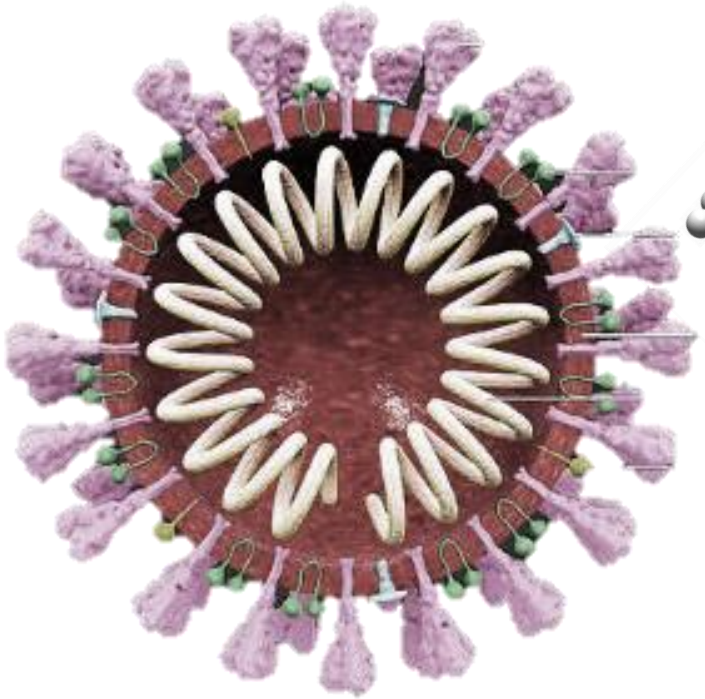
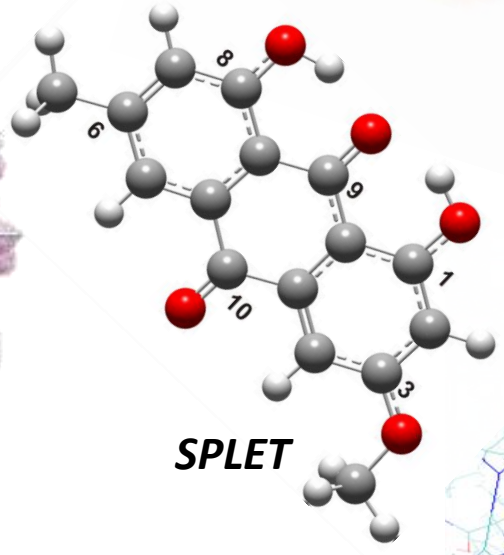
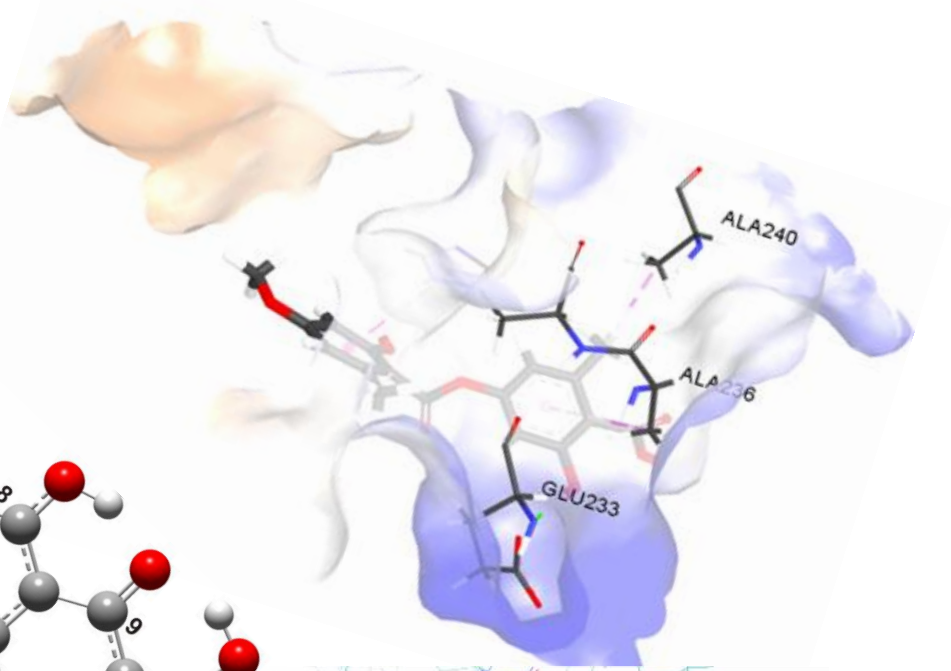
Potential antioxidative and inhibitory activity of parietin

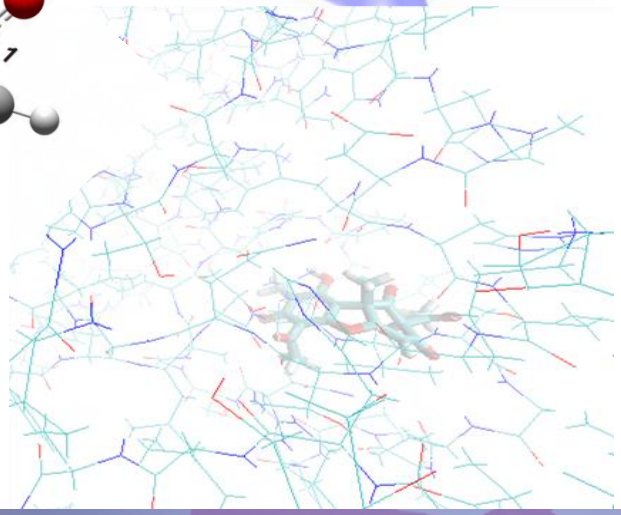
Graphical Abstract





SPLET





Abstract: The anthraquinones are a large group of natural compounds, and one of the compounds from that group is 1,8-dihydroxy-3-methoxy-6-methyl-anthracene-9,10-dione (parietin, known as physcion as well). It is well known that parietin possesses antitumor activity, antioxidant activity, antimutagenic activity, topoisomerase II inhibitory activity, in vitro antiviral activity against poliovirus, and antifungal activity. Knowing these facts it can be supposed that they can found application in medicinal chemistry. A study was conducted to explore the antioxidative and inhibitory potency of parietin. Density functional theory (DFT) is a powerful tool used for examining the antioxidative mechanisms. The Gaussian 09 program package is used to perform all electronic calculations. The equilibrium geometries of the parent molecule of parietin, its radical cation, radicals, and anions are calculated using the B3LYP-D3BJ functional in conjunction with the 6-311++G(d,p) basis set. The influence of water as a polar solvent was estimated using the CPCM solvation model. Inhibitory potency of parietin is estimated by applying molecular docking simulations. For this purpose AutoDock 4.0 software is used, and inhibitory potency of parietin is estimated toward main protease M^{pro} from SARS-CoV-2.

Keywords: antioxidative mechanisms, inhibitory potency, SARS-CoV-2

Introduction

Free radicals and other reactive species are constantly generated in the human body.

- Oxygen is crucial for aerobic organisms, but it produces reactive oxygen species (ROS).

Oxidative stress is caused by an imbalance between the production of reactive oxygen and a biological system's ability to readily detoxify the reactive intermediates or easily repair the resulting damage.

There are also some external factors including dietary substances, such as flavonoids, phenolic acids, vitamins C and E, hydroquinones and various other natural occuring compounds which help in preventing free radical damage.

It is considered that oxidative stress plays an important role in the pathogenesis of many diseases:

- inflammation, cancer, hypertension, diabetes mellitus, atherosclerosis, ischemia/reperfusion injury, neurodegenerative disorders, rheumatoid arthritis, and ageing.

- The anthraquinones are a large group of natural compounds, and one of the compounds from that group is 1,8-dihydroxy-3-methoxy-6-methyl-anthracene-9,10-dione (Fig. 1., parietin, known as physcion as well).

- The parietin is produced by various plants such as *R. crispus* and *R. japonicus Houtt.*, as well as many fungi such as *Aspergillus spp.*, *Penicillium spp.*, and *Alternaria spp*.

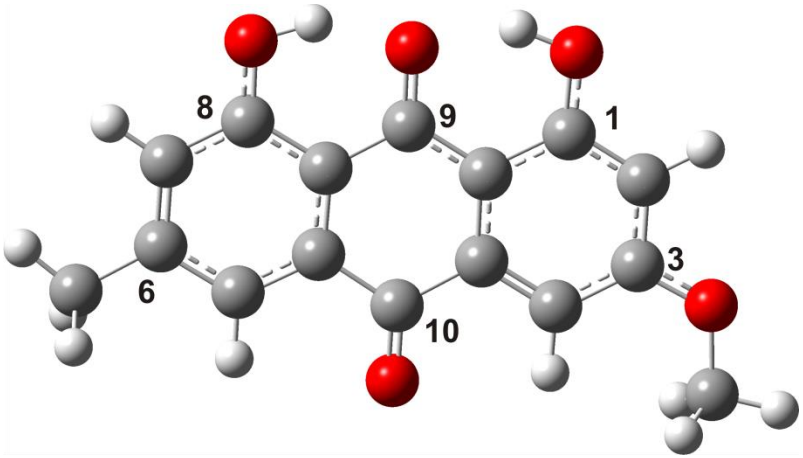


Fig. 1. The structure and labelling of molecule of parietin.

- It is well known that parietin posses antitumor activity, antioxidant activity, antimutagenic activity, topoisomerase II inhibitory activity, *in vitro* antiviral activity against poliovirus, and antifungal activity. Knowing these facts, it can be expected that they can find application in medicinal chemistry.

- Investigated mechanisms of antioxidant activity:

Hydrogen Atom Transfer - **HAT mechanism**

$R^{\bullet} + ArOH \rightarrow ArO^{\bullet} + RH$

Single Electron Transfer-Proton Transfer- **SET-PT mechanism**

$R^{\bullet} + ArOH \rightarrow R^{-} + ArOH^{\bullet +} \rightarrow RH + ArO^{\bullet}$

Sequential Proton Loss Electron Transfer-**SPLET mechanism**

$ArOH \rightarrow ArO^{-} + H^{+}$

$ArO^{-} + R^{\bullet} \rightarrow ArO^{\bullet} + R^{-}$

Inhibitory potency

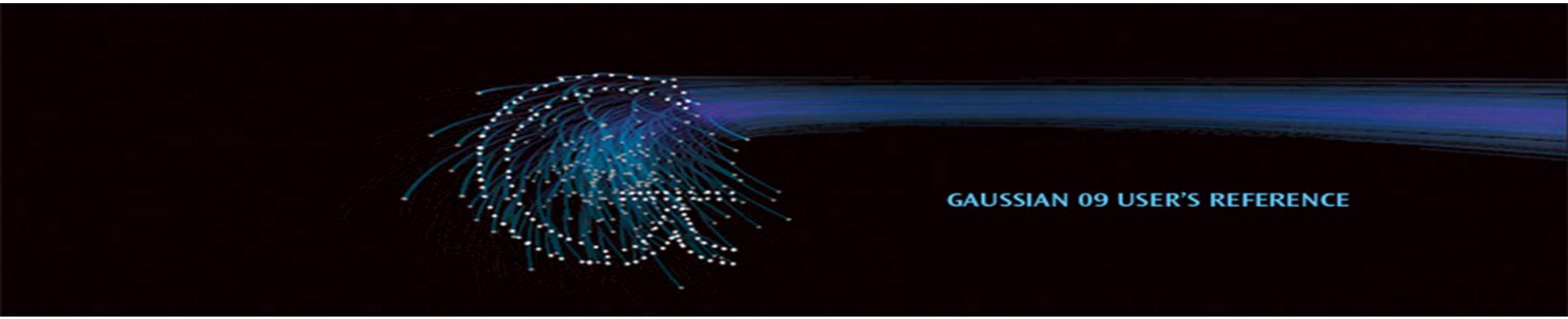
- The emergence of the pandemic of COVID-19 put in the foreground research of potential drugs for the treatment of SARS-CoV-2.

- Bearing in mind that in the literature are found the results of the antitumor activity, antioxidant activity, antimutagenic activity, topoisomerase II inhibitory activity of parietin, it is examined its inhibitory potency against main protease M^{pro} from SARS-CoV-2 (COVID-19 major protease) by molecular docking analysis.

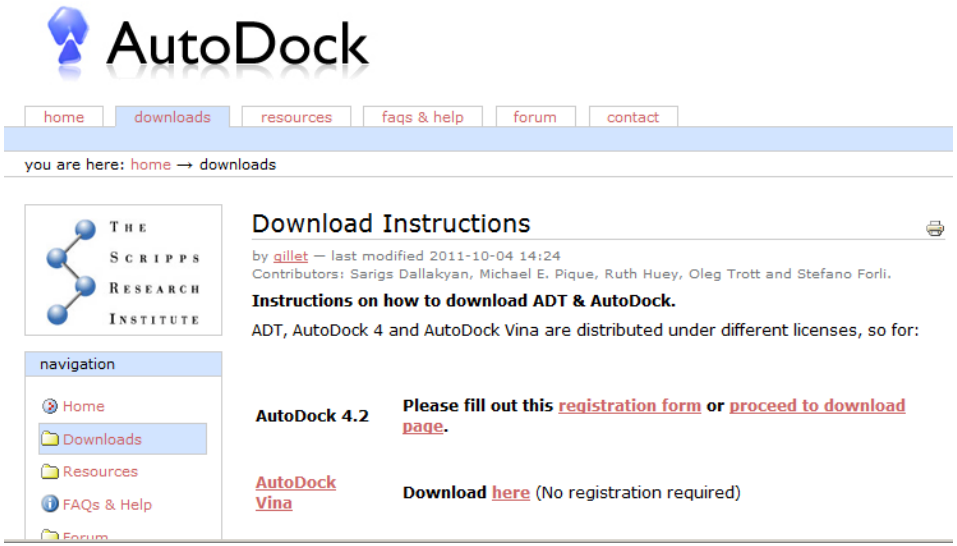
- In regard to the values of binding energy and inhibition constant K_i, it can be expected that parietin will show good inhibitory potency.

- The smaller values of the K_i indicate the greater binding affinity and the smaller concentration of medication needed in order to inhibit the activity of receptor.

Applied softwares and methods for estimation of antioxidative and inhibitory potency:



- Level of theory: B3LYP-D3BJ /6-311++G(d,p)
- the CPCM solvation model: influence of water (ε = 78.36)



Results and discussion

In this study, three different mechanisms of antioxidant action are examined:

1) hydrogen atom transfer (***HAT***),
2) single electron transfer followed by the proton transfer (***SET-PT***)
3) sequential proton loss electron transfer (***SPLET***).

- It should be pointed out that the net results of all three mechanisms of antioxidant action are the same, and that is the formation of the more stable radical species, exactly the radical of an antioxidant compound, A-O$^{\bullet}$.

- The antioxidant potency and the most probable mechanism of antioxidant action of investigated compound is examined in the absence of harmful free radical species.

- ***HAT*** mechanism is characterized by the transfer of hydrogen atom, and it is the only one-step antioxidative mechanism of three investigated antioxidative mechanism in this study.

$$\mathbf{Ar{-}OH \rightarrow Ar{-}O^{\bullet} + H^{\bullet}}$$

$$\mathbf{BDE = \mathit{H}(Ar{-}O^{\bullet}) + \mathit{H}(H^{\bullet}) - \mathit{H}(Ar{-}OH)}$$

- In the ***SET-PT*** mechanism, a parent molecule first loses one electron thus yielding the corresponding radical cation, and then froms radical cation in the process of deprotonation the corresponding radical is established.

$$Ar{-}OH \rightarrow Ar{-}OH^{\bullet+} + e^{-} \qquad IP = H(Ar{-}OH^{\bullet+}) + H(e^{-}) - H(Ar{-}OH)$$
$$Ar{-}OH^{\bullet+} \rightarrow Ar{-}O^{\bullet} + H^{+} \qquad PDE = H(Ar{-}O^{\bullet}) + H(H^{+}) - H(Ar{-}OH^{\bullet+})$$

- The last examined mechanism of antioxidant action, ***SPLET*** mechanism, is described with deprotonation of the parent molecule in the first step, and then, the so-formed anion loses an electron and the corresponding radical is formed.

$$Ar{-}OH \rightarrow Ar{-}O^{-} + H^{+} \qquad PA = H(Ar\ {-}O^{-}) + H(H^{+}) - H(Ar{-}OH)$$
$$Ar{-}O{-} \rightarrow Ar{-}O^{\bullet} + e^{-} \qquad ETE = H(Ar\ {-}O^{\bullet}) + H(e^{-}) - H(A\ {-}O^{-})$$

Position	Water				
	HAT	***SET-PT***		***SPLET***	
	BDE	***IP***	***PDE***	***PA***	***ETE***
		485			
1-OH	399		101	230	355
8-OH	406		107	229	363

Table 1. Calculated reaction enthalpies (kJ mol^{-1}) for the antioxidant reactions of parietin

- The preferred antioxidative mechanism is estimated based on the bond dissociation enthalpy (BDE), ionization potential (IP), and proton affinity (PA) values.

- The lowest values indicate the most convenient mechanism of antioxidant action. BDE describes the process of homolytic breaking of O-H bond and donation of a hydrogen atom to a radical specie.

- In the case of heterolytic cleavage of O-H bond anion and proton are formed, and the thermodynamics of this process is described by IP value. The PA value describes the last examined mechanism of antioxidant action, and includes the proton exchange and formation of respective anionic species from antioxidants.

- The IP value is significantly higher than the corresponding BDE and PA values. This fact marks the SET-PT mechanism as an impractical reaction pathway for antioxidant action in polar solvent.

- The results achieved in water are analysed, it seems that undoubtedly SPLET mechanism is predominant, which can be concluded based on the significantly lower values of PA in comparison with BDE values.

- It should be highlighted, and that is values in positions 1-OH and 8-OH. Namely, the similar values of PA are obtained for both positions, are indicating that OH groups posses similar reactivity for free radical scavenging in polar solvents.

- The emergence of the pandemic of COVID-19 put in the foreground research of potential drugs for the treatment of SARS-CoV-2.

- In this study is examined parietin inhibitory potency against main protease M^{pro} from SARS-CoV-2 by molecular docking analysis.

- The 3D structure was taken from RCSB Protein Data Bank (PDB ID: 6lu7).

- The molecular docking simulations are done for predicted binding sites for targeted protein, and those are defined using POCASA.

	x	y	z
P1	-12.4	11.9	69.8
P2	-34.7	15.7	56.2
P3	-14.7	33.2	55.4
P4	-25.0	3.4	43.8
P5	-7.9	19.1	67.6

Table 2. The dimension of grid size of 6lu7 for different binding sites of (Å)

- For molecular docking simulations as ligands are used molecule of parietin and two drugs that are used in the treatment of COVID-19, and for which is confirmed that they posses the inhibitory effect against main protease M^{pro} from SARS-CoV-2.

- The binding affinity of remdesivir and chloroquine, respectively, are predicted based on the values of binding energies and inhibitory constants.

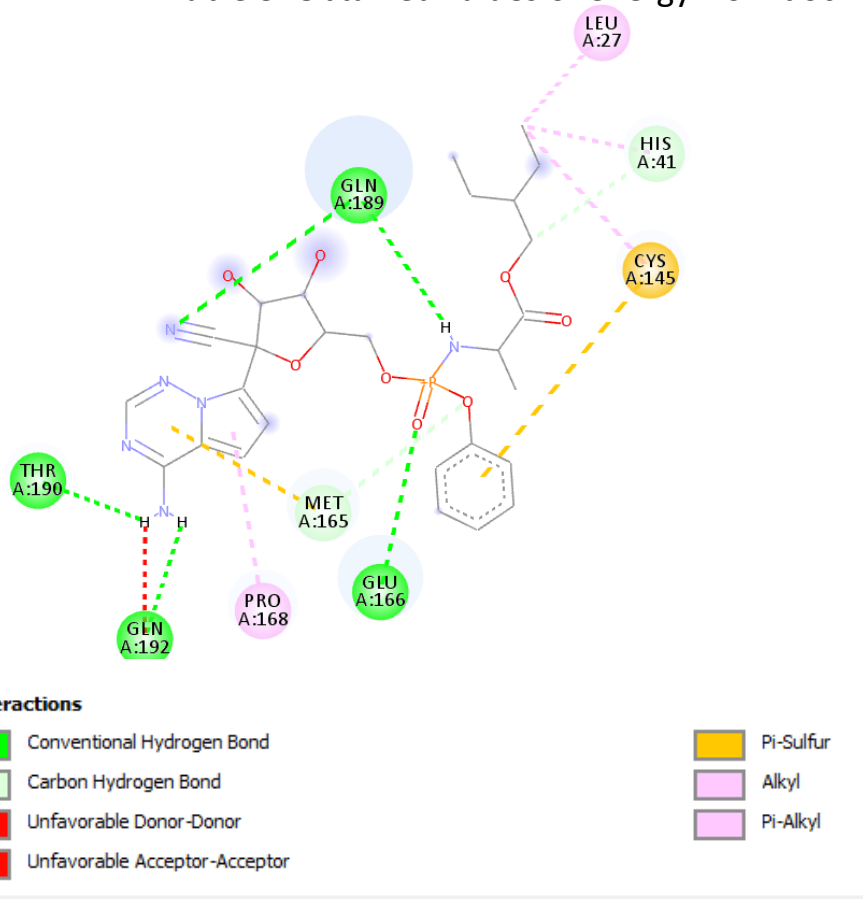
- The value of free energy of binding (ΔG_{bind}) depends on the Final Intermolecular Energy (FIE), Final Total Internal Energy (FTIE), Torsional Free Energy (TFE), and Unbound System's Energy (USE). The FIE is a summary of the Van der Waals energy, energy of hydrogen bonds, desolvation energy of the system, and electrostatic energy.

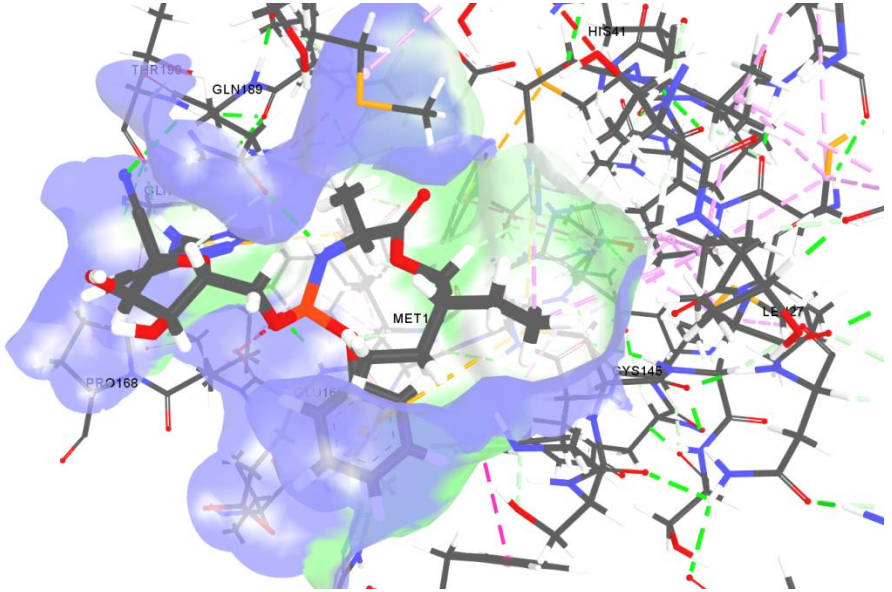
- It is worthy to mention that the values of FTIE and USE are the same when the same receptor and ligand are treated (Tables 3-5).

$$\Delta G_{bind} = [(FIE)+(FTIE)+(TFE)-(USE)]$$

	ΔG_{bind} (kcal/mol)	K_i (uM)	FIE (kcal/mol)	vdW + Hbond + desolv Energy (kcal/mol)	Electrostatic Energy (kcal/mol)	FTIE (kcal/mol)	TFE (kcal/mol)	USE (kcal/mol)
P1	-7.70	2.29	-12.77	-12.68	-0.08	-5.61	+5.07	-5.61
P2	-5.29	132.61	-10.36	-10.33	-0.03	-6.31	+5.07	-6.31
P3	-5.67	69.29	-10.75	-10.60	-0.15	-5.14	+5.07	-5.14
P4	-4.62	407.79	-9.70	-9.41	-0.28	-4.61	+5.07	-4.61
P5	-6.61	14.24	-11.68	-11.55	-0.14	-4.68	+5.07	-4.68

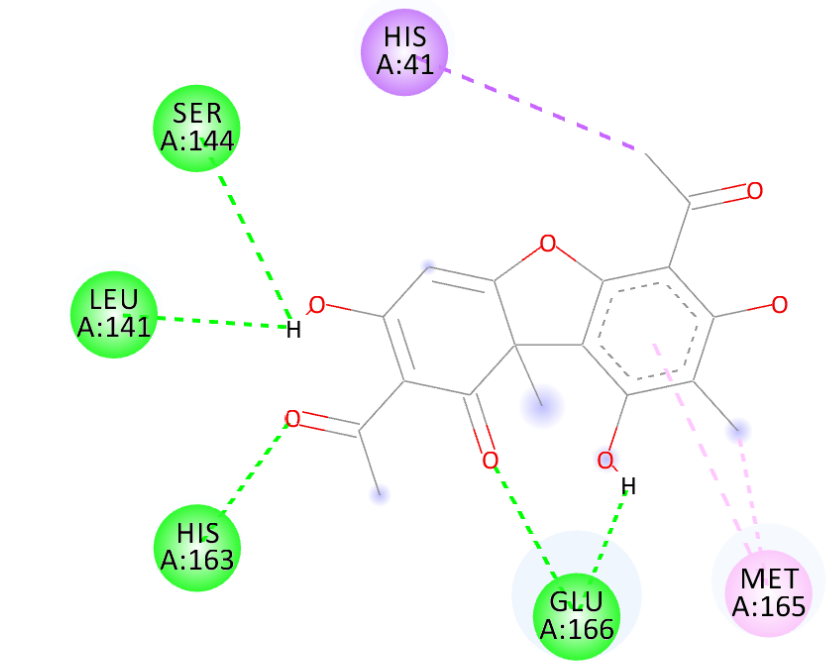
Table 3. Obtained values of energy from docking simulations between remdesivir and 6lu7

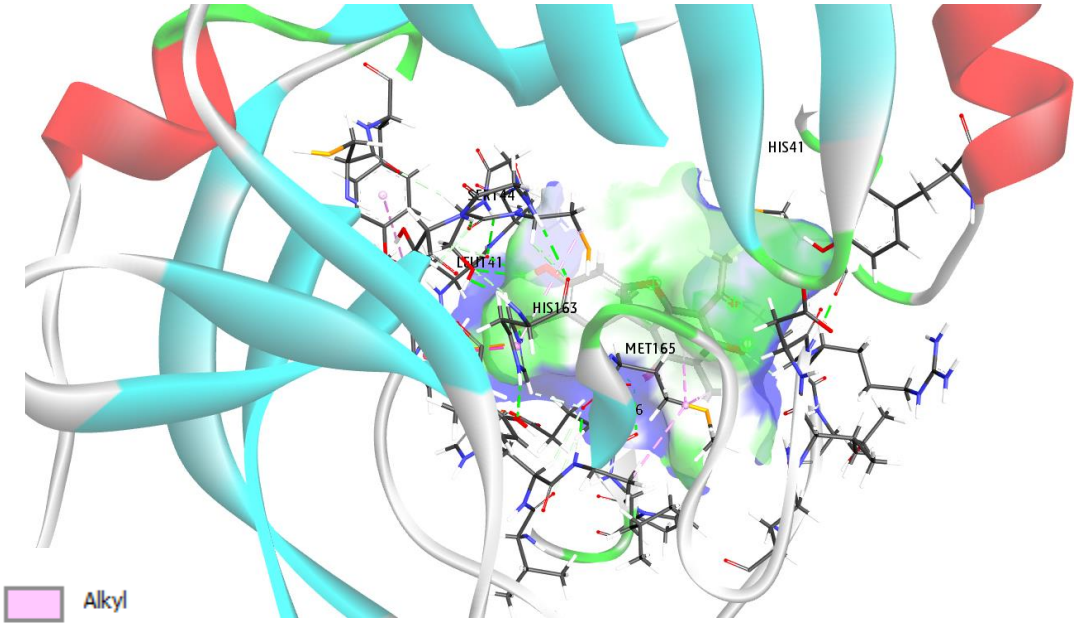




	ΔG_{bind} (kcal/mol)	K_i (uM)	FIE (kcal/mol)	vdW + Hbond + desolv Energy (kcal/mol)	Electrostatic Energy (kcal/mol)	FTIE (kcal/mol)	TFE (kcal/mol)	USE (kcal/mol)
P1	-8.19	0.99	-10.28	-10.27	-0.00	-0.72	+2.09	-0.72
P2	-5.16	164.57	-7.25	-7.32	+0.07	-1.62	+2.09	-1.62
P3	-6.89	8.97	-8.97	-8.98	+0.01	-1.04	+2.09	-1.04
P4	-5.82	53.74	-7.91	-7.92	+0.00	-1.12	+2.09	-1.12
P5	-7.50	3.16	-9.59	-9.57	-0.02	-0.68	+2.09	-0.68

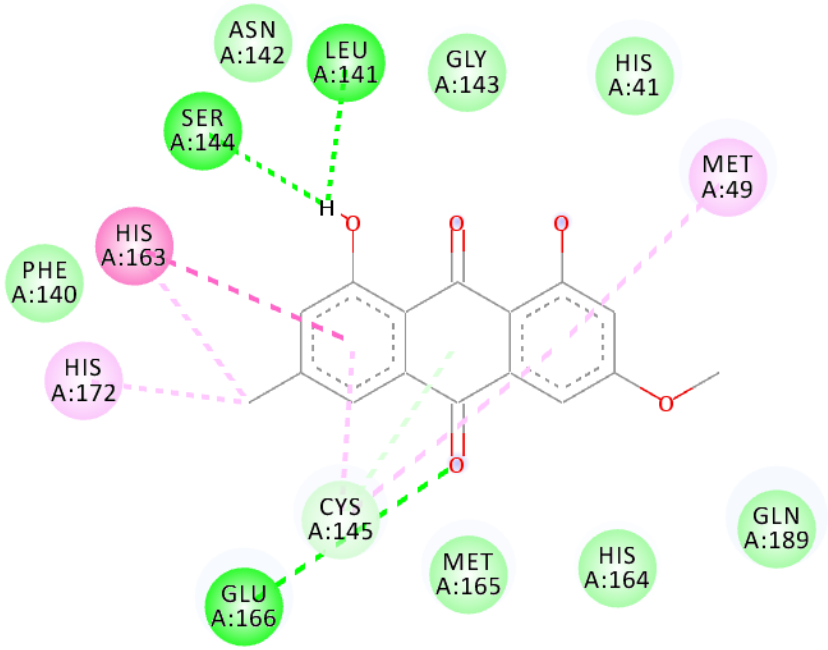
Table 4. Obtained values of energy from docking simulations between chloroquine and 6lu7

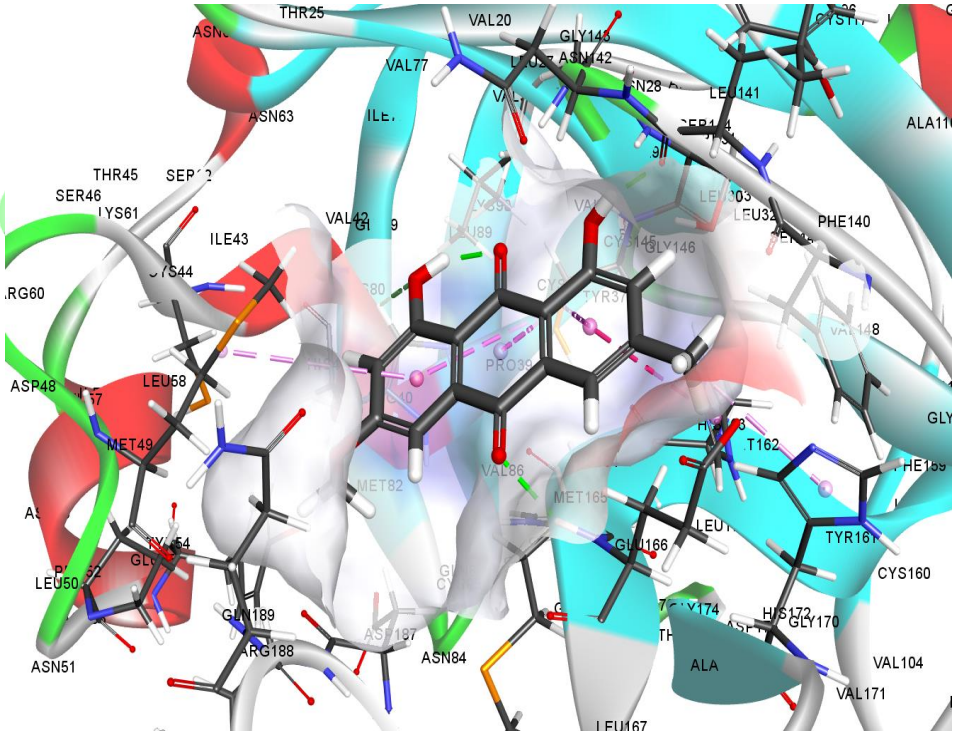




	ΔG_{bind} (kcal/mol)	K_i (uM)	FIE (kcal/mol)	vdW + Hbond + desolv Energy (kcal/mol)	Electrostatic Energy (kcal/mol)	FTIE (kcal/mol)	TFE (kcal/mol)	USE (kcal/mol)
P1	-6.83	9.85	-7.73	-7.64	-0.09	-1.38	+0.89	-1.38
P2	-6.03	38.25	-6.92	-6.68	-0.24	-1.37	+0.89	-1.37
P3	-7.29	4.51	-8.19	-7.86	-0.33	-1.40	+0.89	-1.40
P4	-5.47	97.75	-6.37	-6.16	-0.21	-1.29	+0.89	-1.29
P5	-7.45	3.47	-8.34	-8.13	-0.21	-0.76	+0.89	-0.76

Table 5. Obtained values of energy from docking simulations between parietin and 6lu7





Conclusions

- The evaluation of antioxidative activity of parietin is performed using the DFT method.
- The calculations are done in water with the aim to evaluate the effects of polar solvent.
- SET-PT mechanism is not thermodynamically favourable mechanism of antioxidantive action.
- The dominant mechanism of antioxidative action in water is SPLET.
- The molecular docking simulations are done to predict potential inhibitory potency of parietin toward COVID-19 targeted protein (COVID-19 main protease).
- The inhibitory potency of parietin is compared with the inhibitory potency of remdesivir and chloroquine.
- From obtained results is imposed conclusion that parietin can inhibit M^{pro} from SARS-CoV-2, but its inhibitory potency is lower that inhibitory potency of remdesivir and chloroquine.

Acknowledgments

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