

Facing COVID-19 via anti-inflammatory mechanism of action: Molecular docking and Pharmacokinetic studies of six anti-inflammatory compounds derived from *Passiflora edulis*

Aristote Matondo

University of Kinshasa

Jason T Kilembe

University of Kinshasa

Domaine T Mwanangombo

University of Kinshasa

Beaudrique M Nsimba

University of Kinshasa

Benjamin Z Gbolo

University of Kinshasa

Gedeon N Bongo

University of Kinshasa

Koto-te-Nyiwa Ngbolua

University of Kinshasa

Dorothée D Tshilanda

University of Kinshasa

Damien S T Tshibangu

University of Kinshasa

Virima Mudogo

University of Kinshasa

Pius T Mpiana (✉ ptmpiana@gmail.com)



University of Kinshasa

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Abstract

SARS-CoV-2 is the causative agent of the COVID-19 disease. Pathophysiologically, high levels of proinflammatory cytokines in the serum of SARS-CoV-2 patients are reported, which is so-called the cytokine storm. In this study, molecular docking calculations of six bioactive compounds from *Passiflora edulis* with anti-inflammatory activity in interaction with the main protease of SARS-CoV-2 were performed, and their pharmacokinetic properties were predicted. The results of their molecular simulations and the ADME-T profiles of each ligand (Absorption, Distribution, Metabolism, Excretion and Toxicity) suggest their use as potential treatment for SARS-CoV-2. Among the six investigated compounds in which four flavonoids and two alkaloids, the best docked ligands are quercetin (-8.2 kcal/mol), chrysin (-8.0 kcal/mol), kaempferol (-7.9 kcal/mol) and luteolin (-7.7 kcal/mol), both flavonoids compounds. Their pharmacokinetic studies using SwissADME, preADMET and pkCSM Web servers establish the good ADMET profile for each ligand.

Introduction

Other than vaccine development, people around the world are waiting for the famous news from researchers: a molecule against the Severe Acute Respiratory Syndrome 2 (SARS-CoV-2) has been found. The SARS-CoV-2 is the causative agent of the novel β -Coronavirus (2019-nCoV) or the Corona Virus Disease (COVID-19) that is a pneumonia infection characterized by the hyperproduction of mainly proinflammatory cytokines (IL-1, IL-6, TNF- α , etc) [1]. In the active research of finding molecule that can treat COVID-19, two approaches are currently being used. One is to find molecules that can be used as potential treatment against COVID-19 among several FDA-approved drugs [2-3], while the other is to identify from plants biodiversity potential inhibitors (phytochemicals) of SARS-CoV-2's main protease using molecular modeling approaches [4-5].

During molecular modeling approaches of finding potentials inhibitors, particular emphasis is placed on the significance of binding affinity of ligand-protein complexes and on their drug-likeness properties [4,6]. However, it should be mentioned that the biological activities of these molecules are as well very important [7]. Further, the most common trend is that an anti-COVID-19 molecule might be derived from a plant endowed with antiviral properties [8-11]. Nevertheless, what is abundantly clear in this moment is that the most important cause of COVID-19 related deaths is respiratory failure which is due to pneumonia (an acute inflammatory lung injury), which itself varies depending on the disease severity level, but also alveolar damage that can precipitate acute respiratory distress syndrome (ARDS) [12]. The innate immune response is then to produce pro-inflammatory cytokines and chemokines to contain and stop the infection. Pathophysiologically, previous studies have reported high levels of various cytokines (the so-called cytokine storm) and chemokines in the serum of SARS-CoV-2 patients [13-14]. In addition, Fidan and Aydoğdu recently reported that various pro-inflammatory cytokines such as IL-6, IL-1, the tumor

necrosis factor (TNF- α) induce a migration of leukocytes into lungs, that then secrete the reactive oxygen species and proteases that damage capillary endothelium and alveolar epithelium [15].

Based on the relevant clinical characteristics, phytochemicals derived from *Passiflora edulis* whose isolated molecules have several therapeutic properties such as anti-inflammatory, antioxidant, anti-microbial, anti-cancer... can be used for the treatment of COVID-19 as supported in the following lines:

- *Passiflora edulis* (*P. edulis*), also known as passion fruit (1), exhibits potential effects for the treatment of inflammation. Several mechanisms, including the inhibition of proinflammatory cytokines: TNF- α and IL-1 β levels, enzyme: myeloperoxidase (MPO) and mediators: bradykinin, histamine, substance P, nitric oxide (NO) release and/or action, appear to account for *Passiflora edulis*'s actions. Interestingly, in a comparative study, Montanher *et al.* found that *Passiflora edulis* was more effective than dexamethasone (0.5 in inhibiting both MPO and NO levels) [16]. This latter, which is considered as an important steroidal anti-inflammatory drug, might hold the promise for the treatment of COVID-19 as recently reported by Ledford [17]. Cazarin and co-authors reported in 2015 the anti-inflammatory activity of *P. edulis* leaves [18]. In a dextran sodium phosphate caused mice colitis model, *P. edulis* peel flour was found to reduce TNF- α , IL-1 β , IL-6, IL-12, and IL-17 [19]. Molecules responsible for this effect could be compounds like C-glycosyl flavonoids vicianin, orientin, chrysin, vitexin and kaempferol [20]. Finally, Harmol and harmine, two fluorescent harmala alkaloids showed anti-inflammatory activity by significantly inhibiting the NF- κ B signaling pathway [21-22].
- With regards to the reactive oxygen species that are secreted by leucocytes, several studies highlighted the antioxidant activity of *edulis* fruit and leaf which can eliminate free radicals or inhibit the activity of free radicals [23-24].
- Aqueous and ethanolic leaves extracts have shown *in vitro* effect on some viruses species including Herpes Simplex Virus Type 1 and 2, Varicella-Zoster Virus, etc. [25].

Methodology

2.1. Literature review

Based on information reported above, six phytochemicals derived from *P. edulis* with anti-inflammatory activity are chosen for this study. Chrysin or 5,7-dihydroxyflavone (5,7-dihydroxy-2-phenyl-4H-chromen-4-one), kaempferol or 3,5,7-trihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one), luteolin or 2-(3,4-dihydroxyphenyl)-5,7-dihydroxychromen-4-one, quercetin or 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one, harmol or 1-Methyl-2,9-dihydropyrido[3,4-*b*]indol-7-one and harmine or 7-Methoxy-1-methyl-9H-pyrido[3,4-*b*] indole. The four first compounds are flavonoids while the two latter compounds are alkaloids. Chemical structures of compounds were retrieved from literature sources. Their

2D structures have been sketched using Marvin JS and their 3D structures retrieved from PubChem/NLM. Bibliographical references were made using a bibliographical software "Mendeley".

2.2. Molecular Docking

The structure of the 3-Chymotrypsin-Like protease (3CLpro) or the COVID-19 virus main protease (M^{pro}) which is among the most studied SARS-CoV-2 proteases was obtained from PDB (Protein Data Bank) database (PDB ID: 2GTB) and imported into chimera for visualizing the binding domain of the complex and identifying the amino acids in the binding pocket as well. The hydrogen atoms were added to the protein in order to correct the ionization and tautomeric states of the amino acid residues. Furthermore, the water molecules and complexes bound to receptor molecule were removed before the docking. Incomplete side chains were replaced using Drunbrack rotamer library. In addition, the protein was subjected to energy minimization by applying the AMBER 14SB force field, and AM1-BCC was used for other residues with a maximum number of 200 steps at RMS gradient of 0.02. The optimized protein was saved in pdbqt format and imported to PyRx for molecular docking which was carried out by means of Autodock Vina virtual screening tool [26]. The validation of the docking study was performed by re-docking the reference ligand into an appropriate protein cavity. Re-docking is accepted if the root mean square value (RMSD) < 2.0 Å. **Figure 2** displays schematic structure of the SARS-CoV-2 M^{pro} /3CLpro (a) and the complex formed between the SARS-CoV-2 M^{pro} and 2GTB as a potential drug target for the new coronavirus-2 (b). According to Xu and co-workers, 2GTB is the main protease found in the coronavirus associated with the severe acute respiratory syndrome (SARS), and that the main protease in 2019-nCoV shares 96% similarity with that in SARS [27].

2.2.1 Generation of ligand dataset and pharmacokinetic profiles

The selected compounds derivatives from various literature resources [20, 28] were drawn using Marvin JS. **Figure 3** shows the 3D structures of the sketched compounds retrieved from PubChem/NLM. The 3D ligands were then saved in .sdf format. Ligands optimization was performed by using universal force field (UFF) with conjugate gradients algorithm of 200 Steps, and then analyzed for pharmacokinetic properties. Bioinformatics resources have been employed in the prediction of ADME properties (Absorption, Distribution, Metabolism and Excretion) using the SwissADME database [29]. During the early stages of drug discovery, the ligand to be selected as a hit must be non-carcinogenic and non-hepatotoxic. The toxicity assessment (ADMET, T for Toxicity) that allows to predict the mutagenicity (Ames test) and carcinogenicity of the potential ligands was made using the preADMET server, Korea [30], while the hepatotoxicity and the oral rat acute toxicity were assessed using the pkCSM server [31].

Results And Discussion

3.1 Energetics and geometries

Noncovalent interactions, mainly H-bonds [32], van der Waals and π - π interactions (stacked/parallel and T-shaped/perpendicular conformations) [33] are forces that drive and determine the binding of ligand-

protein interactions. The most common tool to evaluate the strength of binding between ligand-protein interactions is molecular docking. The docking results obtained using AutoDock Vina virtual screening tool between ligands **1-6**, the native or reference ligand with the SARS-CoV-2's main protease (M^{pro} or 3CLpro) are gathered in **Table 1**.

Table 1: Binding affinity (kcal/mol) of 2GTB and Ligands 1-6 with SARS-CoV-2 M^{pro}.

Receptor PDB ID	Ligands	Binding Affinity (ΔG in Kcal/mol)
2GTB	Lopinavir	-8.4
	Nelfinavir	-8.1
	1	-8.0
	2	-7.9
	3	-7.7
	4	-8.2
	Ref. Ligand	-7.4
	5	-6.7
	6	-6.4

Since Lopinavir and Nelfinavir, two FDA approved drugs for the treatment of human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome patients can represent potential treatment options [34], they were used as drug standards for comparison.

The binding affinity values of 6 ligands ranging from -6.40 to -8.22 kcal/mol place the four flavonoids compounds as the best docked ones to the SARS-CoV-2 main protease. The most strongly bound to the protease cavity is ligand **4** or quercetin (-8.22 kcal/mol), followed by ligand **1** or chrysin (-8.04 kcal/mol). The overall trend of complexes stability follows the pattern: ligand **4** > ligand **1** > ligand **2** > ligand **3** > ligand **5** > ligand **6**. Based on data presented in this table, the binding energies of the four flavonoids compounds are somewhat close to those of Lopinavir/Nelfinavir and higher than that of the reference ligand. However, as part of principles that drive drug discovery, this does not mean that ligands **1-6** can automatically inhibit the virus action, or ligands **5** and **6** cannot be considered as hits, without establishing the pharmacokinetic properties of each ligand.

Turning next to the types of noncovalent interactions established between ligands and the SARS-CoV-2 M^{pro}, one can see in figure 4 below that the complexes are mainly stabilized by hydrogen bonding interactions, but also supported by van der Waals and π/π interactions. At this stage, the stability of ligands **1-4** which are flavonoids compounds over ligands **5** and **6** can be explained by the presence of multiple OH groups that can act simultaneously as hydrogen bonds acceptors (HBA) and donors (HBD) [35].

In addition, the presence of three aromatic rings in flavonoids compounds offer much possibilities to π - π interactions to take place. Such interactions are mainly stabilized by dispersion or van der Waals forces, important in the ligand-protein interactions [33].

H-bonds parameters (distances and angles) between the protein target and ligands **1-6** along with the involved groups (ligands) and the amino acids residues of the M^{Pro} engage in H-bonding interaction are summarized in **Table 2**.

Table 2. Hydrogen-bonds parameters derived from docking of ligands **1-6** with SARS-CoV-2 M^{Pro}

Ligand	AA residues	Ligand group	δ (Å)	θ (°)
1	GLU166	O-H	1.99	155
	HIS189	O-H	2.17	163
	THR180	O-H	2.01	142
	ASP187	O-H	2.18	140
	HIS41	O=C ₂	2.17	153
2	HIS41	O-H	2.30	163
	ASP187	O-H	2.29	135
	GLU166	O-H	1.86	153
	THR190	O=C ₂	2.24	158
	GLN189	O-H	1.97	160
3	THR190	O-H	2.15	145
	THR190	O-H	2.15	150
	GLN192	O-H	2.36	144
	HIS164	O-H	2.32	130
	ASP187	O-H	2.00	170
4	GLN192	O-H	2.10	144
	THR190	O-H	2.20	155
	THR190	O-H	2.22	150
	HIS164	O-H	1.99	140
	ASP187	O-H	1.78	165
5	ARG188	H-N	2.06	145
	THR190	H-O	1.83	165
	MET165	H-N	2.04	151
6	TYR54	H-N	2.18	160

It can be seen that ligands **1**, **2**, **3** and **4** form five conventional hydrogen bonds with the active site of the SARS-CoV-2 main protease, whereas the two weakest complexes are three and one hydrogen bonds for ligand **5** and ligand **6**, respectively. The strongest (shortest) hydrogen bonding interaction is established between the residue of the amino acid ASP187 of the M^{Pro} with the O-H group of the quercetin ligand (1.78 Å). The two adducts form the strongest complex.

3.2 Physicochemical properties and ADME-T profiles

Physicochemical property is an important parameter of a molecule that influences efficacy, safety or metabolism which could be predicted by using Lipinski's rule of five (RO5) that is: molecular mass < 500; Hydrogen-bond donors (HBD) ≤ 5 ; Hydrogen-bond acceptors (HBA) < 10; and Log P < 5 [36]. Prediction of *in silico* physicochemical parameters of the 6 ligands are grouped in **Table 3**.

Inspection of **Table 3** shows that all ligands meet every single criterion of Lipinski's rule of five and thus fully obey the rule. Consequently, all the investigated ligands are predicted to be easily absorbed and have good permeability and bioavailability. According to Ghose and co-workers, the molecular refractivity is a ubiquitous parameter for a drug molecule that cannot exceed $130 \text{ m}^3.\text{mol}^{-1}$ and not to be under $40 \text{ m}^3.\text{mol}^{-1}$ [37].

Table 3. Predicted *in silico* physicochemical parameters using SwissADME online tool

Ligand	Formula	MW (Da)	Log P	HBD	HBA	PSA (Å)	Refractivity ($\text{m}^3.\text{mol}^{-1}$)	Violations	Log S
1	$\text{C}_{15}\text{H}_{10}\text{O}_4$	254.24	2.27	2	4	70.67	71.97	0	-4.19
2	$\text{C}_{15}\text{H}_{10}\text{O}_6$	286.24	1.70	4	6	111.13	76.01	0	-3.31
3	$\text{C}_{15}\text{H}_{10}\text{O}_6$	286.24	1.86	4	6	117.31	76.01	0	-3.71
4	$\text{C}_{15}\text{H}_{10}\text{O}_7$	302.24	1.63	5	7	131.36	78.03	0	-3.16
5	$\text{C}_{12}\text{H}_{10}\text{N}_2\text{O}$	198.22	1.68	2	1	48.65	61.39	0	-2.18
6	$\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}$	212.25	2.07	1	2	37.91	65.06	0	-4.05

With MW= Molecular weight, Log P = Lipophilicity, PSA = Polar Surface Area, Log S = water solubility

None violation is observed here for all the investigated ligands as can be seen in **Table 3**. Finally, as pointed out by Cerqueira and co-authors, for optimal drug absorption and distribution, the polar surface area (PSA) values cannot be higher than 140 Å [38]. Once again, none violation is observed here. Three potential candidates for the inhibition of the SARS-CoV-2 3CLpro have PSA values almost two to three times less than the recommended value (ligands **1**, **5** and **6**), while ligands **2**, **3** and **4** have PSA value higher than 100 Å .

The next step to deal with is to establish the ADME/T profiles of each ligand. In fact, a major issue after identifying stables complexes, that is, lead or hit compounds, is to evaluate their ADME parameters and cardiotoxicity.

These pharmacokinetic properties are very important parameters in the computer-aided drug discovery since they allow one to retract some hit from early-stage trials. The ADME properties are evaluated by using SwissADME and pkCSM servers, but other parameters such as the Blood-Brain Barrier (BBB), the Human Intestine Absorption (HIA) and the skin permeability come from the preADMET server. The selected endpoints for toxicity are Ames test and Rodent Carcinogenicity (rat) in preADMET server, hepatotoxicity and oral rat acute toxicity (LD₅₀) in pkCSM server. These parameters are gathered in **Table 4**.

Table 4. ADME-T profile of ligands **1-6**.

Parameter	Ligand 1	Ligand 2	Ligand 3	Ligand 4	Ligand 5	Ligand 6
Absorption & Distribution						
BBB	0.933	0.286	0.368	0.173	0.320	3.798
HIA (%)	92.644	79.439	81.132	77.207	94.263	92.827
Skin permeability (log K _p)	-3.346	-4.323	-4.280	-4.433	-4.662	-4.386
Bioavailability score	0.55	0.55	0.55	0.55	0.55	0.55
Metabolism						
CYP2D6	No	No	No	No	No	Yes
CYP3A4	Yes	No	No	No	No	Yes
Excretion						
Total clearance	0.48	0.50	0.50	0.41	0.59	0.62
Renal OCT2 substrate	No	No	No	No	No	No
Toxicity						
Ames test	Yes	No	No	No	Yes	Yes
Hepatotoxicity	No	No	No	No	No	No
Carcinogenicity (rat)	Negative	Positive	Negative	Negative	Negative	Negative
oral rat acute toxicity (LD ₅₀ , in mol/kg)	2.486	2.197	2.455	2.471	2.781	2.999
	1243	1099	1228	1236	1391	1450

Values in bold are expressed in mg/kg

According to the binding affinity values, it was derived the following decreasing order in the complexes formed between ligands and the SARS-CoV-2 3CLpro or Mpro: Ligand **4** > Ligand **1** > Ligand **2** > Ligand **3** > Ligand **5** > Ligand **6**. This order only reflects the thermodynamic stability of complexes. However, the stability over time of the ligand in a protein interaction site depends on other factors. For a ligand to be

used for therapeutic purposes, its absorption, distribution, metabolism, excretion and toxicity are aspects to take into account. To pursue further, it is worthy to point out that first of all, such a ligand must be non-hepatotoxic and non-carcinogenic [39].

Scrutiny of toxicity outcomes in **Table 4** reveals that all potential ligands are non-hepatotoxic. With regards to the carcinogenicity, the results predict the carcinogenic activity only for the ligand **2**. This encouraging result of toxicity assessment allows us to go back to ADME properties. The ability of a drug molecule to cross into the brain is an important propriety to improve the efficacy of drugs (reduce side effects and toxicities). The BBB values for the potential candidates are all positive and the lowest value is found in ligand **4** (0.173) which forms the strongest complex with the SARS-CoV-2 main protease. The probability of intestinal absorption by human is very high, and in the other hand almost the same for ligands **1**, **5** and **6**; and on the other hand almost the same for ligands **2**, **3** and **4**. Ligand **4** has the smallest probability (79.44 %) of being absorbed by human intestine, in contrast with its binding affinity with the COVID-19 protease. The recommended value of the skin permeability or $\log K_p$ for a drug molecule is set at more than -2.5 cm/h. Interestingly, the computed $\log K_p$ values range from -3.3 to -4.7 cm/h. Finally, the bioavailability score which is evaluated to 0.55 confirms that ligands **1-6** have good absorption and distribution since all potential candidates may have more than 10% of bioavailability in rat [40].

The Cytochrome P450 inhibition as metabolic indicators including CYPs: 1A2, 2C19, 2C9, 2D6 and 3A4 are predicted. Nevertheless, only CYP2D6 and CYP3A4 are responsible for drug metabolism [41-42]. Interestingly, the three best candidates according to their binding affinity are found to be non-inhibitors of CYP2D6 and CYP3A4 except hits **1** and **6** that affect the CYP3A4, and hit **6** which in addition affects the CYP2D6. This result rules the ligand **6** out from the list of potential candidates for the inhibition of the SARS-CoV-2 main protease, a result which is moreover in good agreement with its lower free enthalpy (-6.40 kcal/mol).

Turning next to excretion also called elimination, the total clearance is directly linked to the renal OCT2 (organic cation transporter 2) substrate that offers helpful information on potential contraindications. The selected 4 flavonoids and 2 alkaloids compounds are predicted to be not renal OCT2 substrates. This means that all the 6 phytocompounds can be eliminated through the OCT2 substrate. Surprisingly, the total clearance values of the investigated compounds vary almost inversely with their binding affinities values. In addition, ligands **2** and **3** which have the same molecular weight of both chemical formula $C_{15}H_{10}O_6$ have exactly the same total clearance.

Closing finally the ADME-T profiles of the six compounds, their oral acute toxicity (LD_{50}) are classified in category or class 4, meaning that they are slightly toxic (Globally Harmonized System: $300 < \text{Category 4} \leq 2000$) and can thus be considered as safe.

Summary And Conclusion

Bacteria, fungi, viruses can cause serious infections and diseases in the world. Some of these infections and diseases are curable while other are not. Even for those that are curable, there is sometimes multiple drug resistance. Since humanity exists, plants have been one of man's best friends. While it is obvious that plants are a source of vitamins, proteins, minerals, they are as well source of phytochemicals containing excellent therapeutic properties: antioxidant, anti-inflammatory, antifungal, antimicrobial, antitumor activities. *Passiflora edulis*, also known as passion fruit, passion flower, purple granadilla, or "maracuja" (DR Congo or Brazil), is widely cultivated for its edible fruit. With numerous biological activities, the passion fruit also contains vitamins A, C, E, K, minerals such as Zn (0.10 g), Mg (29 mg), K (348 mg), Ca (12 mg), etc [41]. On one hand, vitamins A and K could help to fight the COVID-19 [42]. On the other hand, these chemical elements mainly Zn, although indispensable as enzymatic co-factors, a slight increase in their intracellular concentration inhibits the replication of retroviruses including SARS-CoV-1 [43] important in the management of COVID-19. Owing to its numerous therapeutic activities, *P. edulis* has traditional or ethno medicinal uses in many countries. Of complex phytochemistry, its secondary metabolites have numerous health benefits and very recently, as stated above, Jabareen and co-workers reported in an experimental study the antiviral activity of *P. edulis* leaves on some viruses' species including Herpes Simplex Virus Type 1 and 2, Varicella-Zoster Virus, etc [25]. Since *P. edulis* exhibits anti-inflammatory capabilities essential to stem the cytokine storm, this study is conducted in order to identify potential inhibitors from a set of 6 phytochemicals endowed with anti-inflammatory activity. The 6 selected compounds (four flavonoids and two alkaloids) reacted with the SARS-CoV-2 3CLpro or Mpro, and an order of thermodynamic stability was obtained.

Compared with Lopinavir and Nelfinavir that are protease inhibitors recommended for the treatment of SARS and MERS, the binding affinities of the four top compounds, both flavonoids, are very close to those of two anti-HIV drugs, and even a bit higher to that of the ligand reference. Indeed, the ligand 1 or chrysin has anti-inflammatory, antibacterial and antioxidant activities [44-45], while ligand 2 or kaempferol exhibits antitumor, antioxidant and anti-inflammatory capabilities [46]. In fact, our previous studies showed that *aloe vera* represents potential treatment for COVID-19 [47], and three of its phytochemicals were identified as potential inhibitors of SARS-CoV-2 main protease, in which two compounds exhibit anti-inflammatory effect [5]. The anti-inflammatory activity of luteolin in experimental animal models was reported by Ziyen and co-workers [48], and recently, a study by Lesjak and co-authors showed antioxidant and anti-inflammatory activities of quercetin and its derivatives [49].

One can remember that the hyperproduction of proinflammatory cytokines is the main reason that causes morbidity and mortality in SARS-CoV-2 patients. Thus, the application of anti-inflammatory molecules is a mechanistically-sound strategy for treatment development [50]. The established ADME-T profile of each ligand suggests that the four flavonoids (chrysin, kaempferol, luteolin and quercetin) might be used as potential treatment of SARS-CoV-2.

In conclusion, the strategy adopted in this work consisted in exploring the inhibitory power of six phytochemicals derived from *P. edulis*. Given the cytokine storm, six compounds exhibiting anti-inflammatory activity, among which four flavonoids and two alkaloids, were each paired with the SARS-

CoV-2 main protease in order to evaluate first their thermodynamic stability. The docking affinity scores showed that ligands 1-4 (flavonoids) are more stables than ligands 5 and 4 (alkaloids). Then, the Lipinski's rule of five and the pharmacokinetic studies using SwissADME, preADMET and pkCSM showed that these phytochemicals have good ADME-T profiles, mainly the flavonoids compounds. Consequently, chrysin, kaempferol, luteolin and quercetin as the four top compounds can be used via anti-inflammatory mechanism of action to fight the overproduction of proinflammatory cytokines in SARS-CoV-2 patients.

Declarations

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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Figures



Figure 1

Leaves and Flowers (left) and yellow passion fruits (right) of *P. edulis*

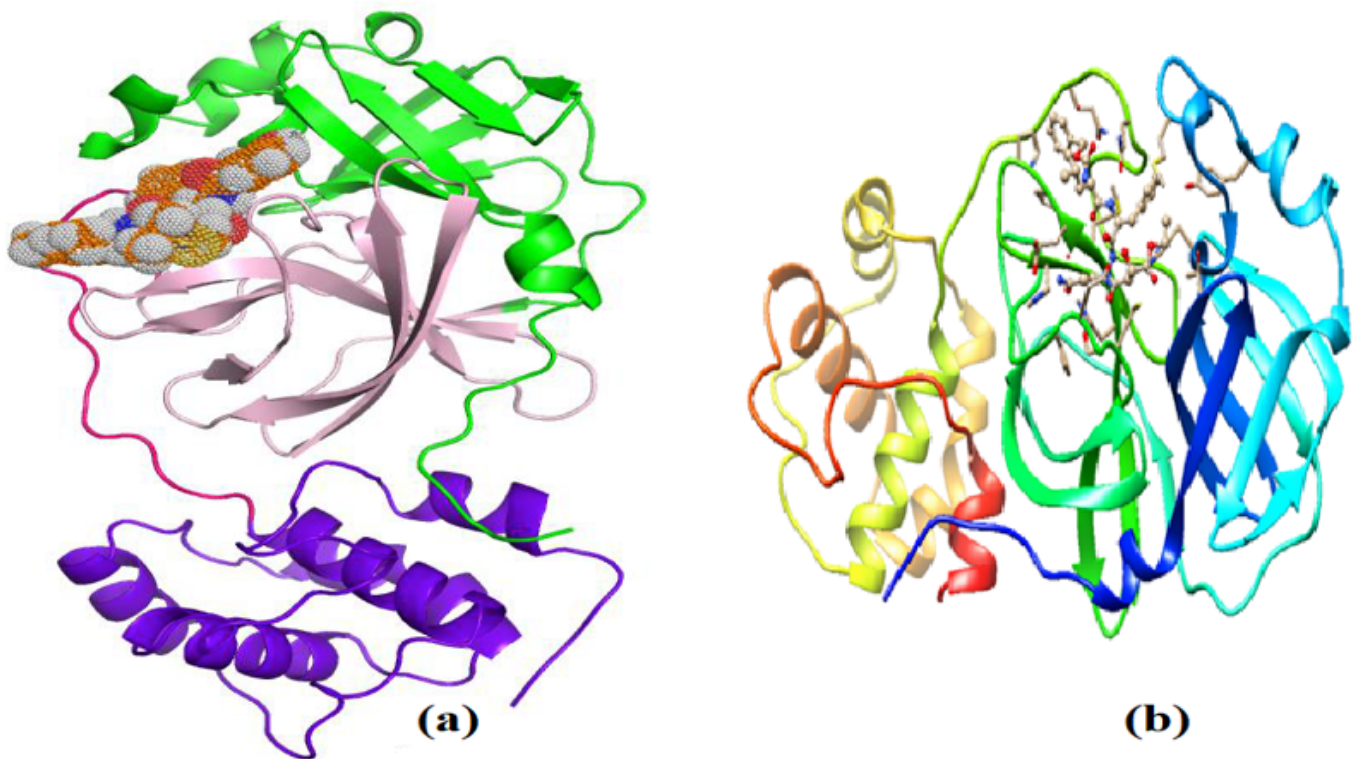


Figure 2

Schematic structure of the SARS-CoV-2 Mpro (a) and the complex formed between the SARS-CoV-2 Mpro and co-crystallized inhibitor 2GTB (b)

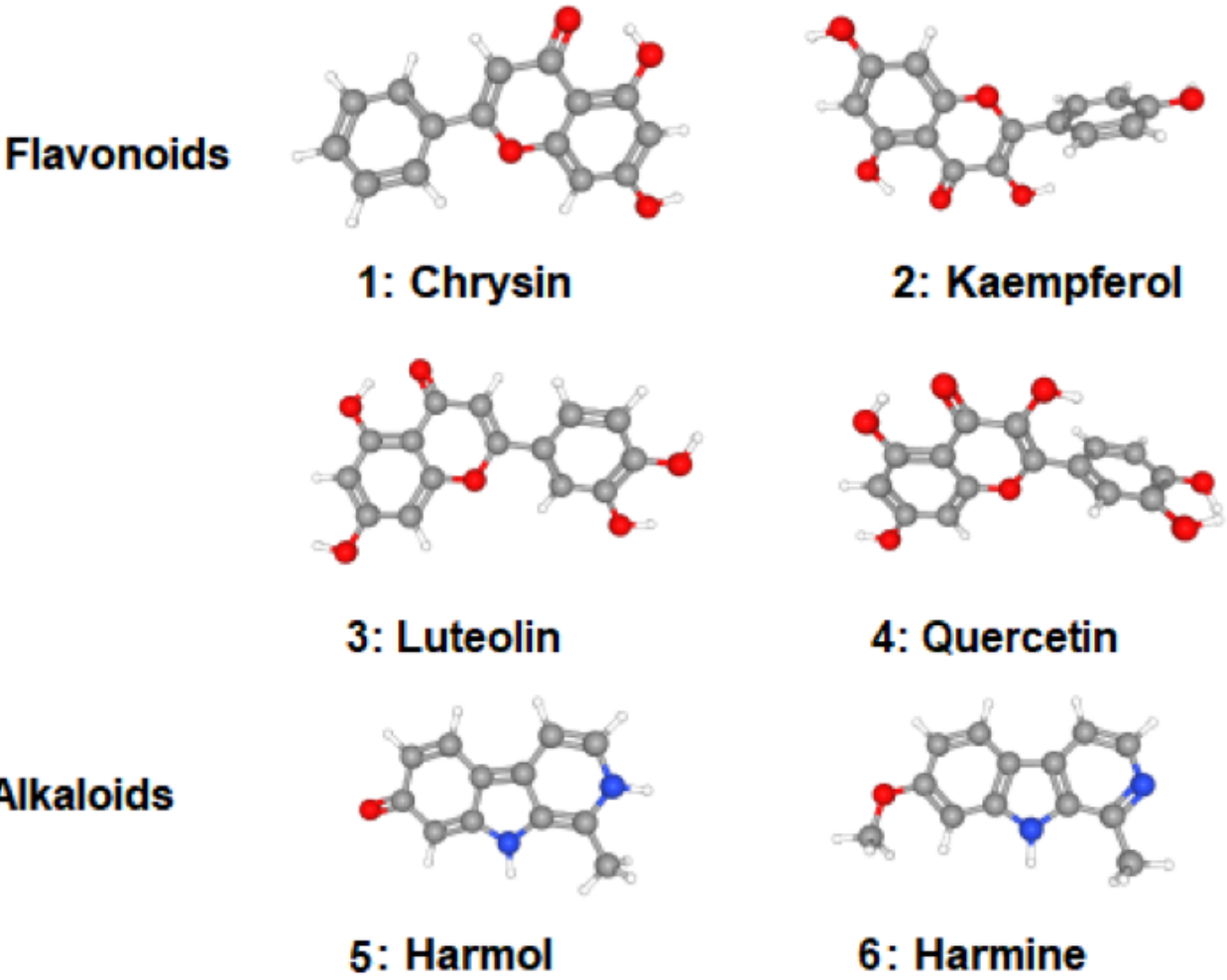


Figure 3

3D Structures of selected flavonoids and alkaloids compounds 1–6 derived from *P. edulis*.

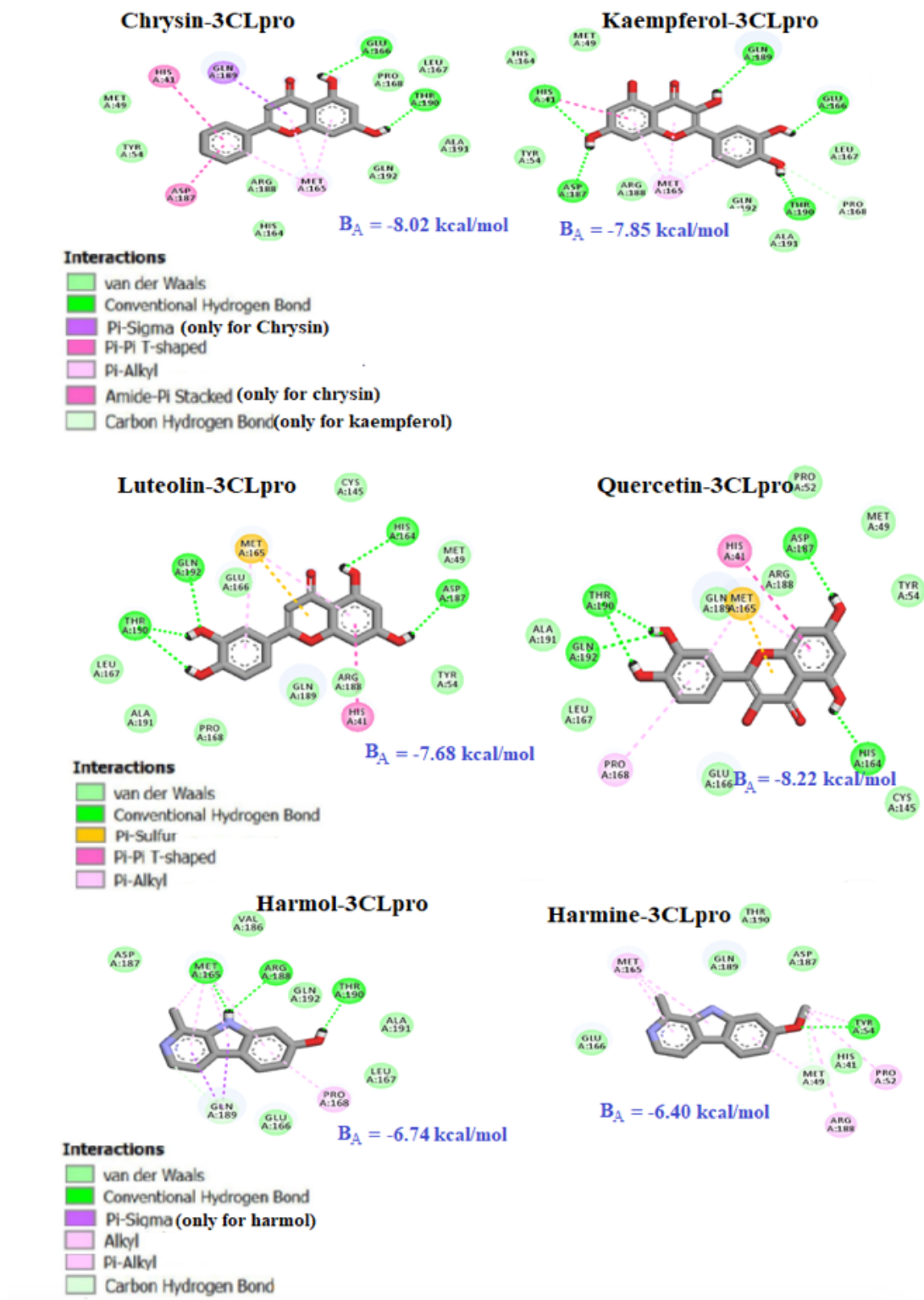


Figure 4

Interaction map of ligands 1-6 with the main protease of coronavirus 3CLpro