Theoretical Molecular Docking Study of the Structural Disruption of the Viral 3CL-Protease of COVID19 Induced by Binding of Capsaicin, Piperine and Curcumin Part 1: A Comparative Study with Chloroquine and Hydrochloroquine Two Antimalaric Drugs

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Abstract

The global pandemic caused by infections of the new coronavirus (COVID-19) makes it necessary to find possible less toxic and easily accessible therapeutic agents. In this study, we used strategies docking and molecular dynamics to analyze phytochemical compounds against FDA-approved antimalarial drugs recommended for the treatment of COVID-19. The evaluation was performed with the docking scores MolDock Score and Rerank Score calculated by Molegro Molecular. The DockThor server was used to generate the complexes and myPresto for the dynamic studies. Preliminary results suggested that piperine, capsaicin, and curcumin have the best docking scores and that they are capable of promoting structural changes in the viral protease by inducing folding of the enzyme. Curcumin and capsaicin bring the enzyme to a more compact conformational state compared to the native state, compared to chloroquine. Even though, it is unknown if these induced changes in protease are related to any inhibitory effect observed both *in vitro* and *in vivo* for any of these compounds. Further studies on the mechanisms of action of these compounds of interest are required, as well as experimental demonstrations. However, these results are interesting because they can serve as a starting point for subsequent experimental or/and *in silico* studies based on chemical structure-activity relationships taking these small molecules and their possible derivatives.

Introduction

The first case of the new Coronavirus was reported December 30, 2019, in Wuhan city, Hubei province, P. R. China (Xu *et al.,* 2020), and by the beginning of March the cases amounted to 113,702 confirmed and 4,012 deaths worldwide (Jiang *et al.,* 2020) necessitating the rapid development and approval of a vaccine not yet available to date (Jiang *et al.,* 2020). However, it has been suggested that the selection of FDA-approved drugs with potential antiviral activity against related viruses may yield promising results (Chang *et al.,* 2020; Contini, 2020), reporting that older antimalarial drugs, such as chloroquine, have the ability to interact strongly in silico with viral 3CL-protease (Chang *et al.,*2020) recently crystallographed (Chang *et al.,*2020; Liu *et al.,* 2020), and with an important inhibitory effect *in vitro* and *in vivo* (Gautret *et al.,* 2020; Wang *et al.,* 2020). Reason why its use has been recommended in China and USA for the treatment of COVID–19 (Devaux *et al.,* 2020). This despite the fact that its safety has been questioned and severe adverse effects have been reported (Wang *et al.,* 2020; Kaisari and Borruat, 2020). In this sense, various bioactive compounds of plant origin have also been *in silico* studied why could they be used as alternative medicines or to develop new drugs against COVID–19 with fewer adverse effects (Khaerunnisa *et al.,* 2020; Qamar *et al.,* 2020; Sharma and Kaur, 2020; Chandel *et al.,,* 2020; Adem *et al.,,* 2020; Gentile *et al.,,* 2020; Sun *et al.,,* 2020). But little has been reported on the use of the MolDock molecular docking algorithm for the 3CL-protease study (Adem *et al.,,* 2020), in which the docking score function is an extension of the linear part potential (PLP) that includes new hydrogen bonds and electrostatic terms to improve coupling precision (Thomsen and Christensen, 2006; Wang, 2020). This being the first study to report the structural disturbance that the natural compounds considered in this study can induce in the viral protease of COVID–19. An approach that has only been applied to antiviral drugs (Alamri *et al.,,* 2020). Therefore, in the present study was performed a theoretical study with MolDock molecular docking algorithm to obtain information on the interaction of various phytochemical compounds described with potential antiviral activity directed at the COVID–19 protease.

Methods

Docking Screening: In this study, the 3CL-protease structure (PDB ID: 6LU7) was obtained from the RCSB Protein Data Bank, which was recently released on February 5th, 2020 (Chang *et al.,* 2020). Based on a literature survey, we tested eighteen phytochemical compounds with reported antiviral properties including, Allicin (Xie *et al.,*2020), Bornyl acetate (Sun *et al.,* 2020), Capsaicin (Tang *et al.,* 2020), Carvacrol (Bansal *et al.,* 2020), Catechol (Mishra *et al.,* 2020), Cinnamic acid (Silva *et al.,* 2020), Curcumin (Bonfim *et al.,* 2020), Eucalyptol (Patra *et al.,* 2020), Gallic acid (Arsianti *et al.,* 2020), Geraniol (Wei *et al.,* 2020), Linalool (Del Bosco *et al.,* 2020), Nicotinic acid (Corona *et al.,* 2020), Phytic acid (Narayanaswamy and Esa 2018), Piperine (Chandani *et al.,* 2019), Quercetin (Nile *et al.,* 2020; Lopes *et al.,* 2020; Aggarwa *et al.,* 2020), Resorcinol (Lee *et al.,* 2019), Terpinen–4-ol (Patra *et al.,* 2020) and Viridiflorene (Shayeganmehr *et al.,* 2018). Additionally, we have used as molecular docking controls, two FDA-approved old antimalarial drug, Chloroquine and Hydroxychloroquine (an analogue of chloroquine) recommended for treating COVID–19 patients (Gautret *et al.,* 2020). Molecular structures of all compounds can be seen in the table S1 of information supplementary.

We downloaded the 3D structure of each drug from the PubChem database in Structure-data file (SDF) format (Gautret *et al.,* 2020) and Online SMILES Translator (https://cactus.nci.nih.gov/translate/) to convert SDF to PDB format. To simulate binding affinity between protein and ligands, the complexes were built in Dockthor (*https://dockthor.lncc.br/v2/)* using the flexibility algorithm and the search parameters blind docking by programming 25 runs and 10^6 evaluations for each ligand (Dos Santos *et al.,* 2020). Taken the most favored position to be analyzed with Molegro Molecular Viewer 2019_7.0.0 software, MolDock Score and Rerank Score functions were calculated (Thomsen and Christensen, 2006). We also used myPresto ligand docking utilities to dock the selected drugs to the protease under default settings. myPresto is tailored for a single process execution with a single GPU (Graphics Processing Unit), in order to optimize the enhanced conformational sampling methods (Kasahara *et al.,* 2016).

Molecular dynamics (MD) simulation: MD simulations were first performed for a docking hit for two purposes: (1) studying the relative stability of the ligand residing in the binding pocket; (2) sampling a set of conformations for MM (molecular mechanics). A MD system consisted of one copy of COVID–19 protease, one copy of docked ligand and about 50 Na^+ and Cl^- ions. The whole system was neutralized. For a protein-ligand complex, the MD system was first relaxed through a series of minimization procedures. There were three phases for a MD simulation: the relaxation phase, the equilibrium phase, and the sampling phase, as recommended (Wang, 2020). In the relaxation phase, the simulation system was heated up progressively to 250 K. A 2-picosecond MD simulation was performed without any restraints or constraints. In the next equilibrium phase, the system was equilibrated at 298 K, 1 bar for 2 ps. Finally, a 2 ps MD simulation was performed at 298 K, 1 bar to produce NTP (constant temperature and pressure) ensembles. Simulations were also made at 4 ps. All MD simulations and the additional settings were performed using myPresto program.

Complementary Analysis: The Molinspiration server was used to calculate the partition coefficient (milogP) and calculation of bioactivity scores (Cheminformatics, M. 2020; Reena Roy *et al.,* 2020). Analysis of variance of a factor (ANOVA) was used as a statistical model to establish differences between the comparative parameters analyzed, including the structural changes generated by the thermodynamically most favored ligands. Tukey was applied as a means separation test and hypothesis test. All calculations were carry out using the IBM SPSS–23 program.

Results And Discussion

In Table 1, we list the results of the coupling of 20 ligands with the 3CL protease. These scores, which are the original raw results of the coupling tools, represent the relative binding affinity obtained with MolDock, and differ from those reported using Autodock 4.2, with the Lamarckian Genetic Algorithm for curcumin, allicin, and quercetin, in terms of their positions against inhibitors like lopinavir (Khaerunnisa *et al.,* 2020). But they correspond to those reported by another author for curcumin and piperine versus chloroquine using Autodock 4.2.6 (Mohammad *et al.,* 2020). 17% of the phytochemical compounds presented more favorable docking energies than hydroxychloroquine and chloroquine for both scoring functions considered. For scoring functions MolDock Score y Rerank Score, piperine (−62.467 and −54.751 kcal/mol), capsaicin (−55.224 and −52.694 kcal/mol) and curcumin (−54.727 and −46.143 kcal/mol) have the lowest docking score and thermodynamically more favorable, respectively; even outperforming the results of hydroxychloroquine (−48.737 and −39.491 kcal/mol) and chloroquine (−46.582 and −37.804 kcal/mol), respectively (see Table 1 and Figure 1), the two antimalarial drugs currently in use, and outperforming the results getting with Lopinavir (−31.959 and −30.65 kcal/mol, respectively) a potent HIV−1 protease inhibitor not considered in this study (Capparelli *et al.,* 2005), 44% of the phytochemical presented more favorable docking energies than Lopinavir according to the MolDock Score, and 28% by Rerank Score, every found effective in treating COVID−19 patients. These results seen in Table.1 are promising if we consider that the MolDock molecular docking algorithm, based on a heuristic search that combines differential evolution with a cavity prediction algorithm, in which the MolDock docking score function is an extension of the PLP that includes new hydrogen bonds and electrostatic terms improves docking precision, by introducing a re-classification scoring function, which identifies the most promising docking solution of the solutions obtained by the docking algorithm, a strategy that has allowed to increase the docking precision surpassing other algorithms used in studies related to the protease associated with COVID−19 (Thomsen and Christensen, 2006; Wang, 2020). We therefore choose piperine, capsaicin and curcumin for further investigation with the filter MM. Doing a comparative analysis with hydroxychloroquine and chloroquine (see Table 1).

Table 1. Results of the virtual screening was done on the crystal structure of COVID 19 main 3CL-protease (PDB code 6LU7). Showing 18 phytochemical compounds with reported antiviral properties, and additionally as molecular docking controls, two FDA-approved old antimalarial drug for potential treatment, Chloroquine and Hydroxychloroquine (an analogue of chloroquine) recommended in treating COVID-19 patients. Phytochemicals with better scores than controls are highlighted in bold.

Compound Name	*CID*	*MolDock Score (kcal/mol)*	*Rerank Score (kcal/mol)*	*Interactions*
Piperine	**638024**	**-62.467**	**-54.751**	Arg4 (HB, SI)
Curcumin	**969516**	**-55.224**	**-52.694**	Lys5 (SI) - Val125 (HB) - Asp289 (HB) - Lys137 (HB)
Capsaicin	**1548943**	**-54.727**	**-46.143**	Asp 153 (HB) - Lys102 (SI)
Hydroxychloroquine*	3652	-48.737	-39.491	Lys5 (HB, SI) - Glu288 (HB, SI)
Chloroquine*	2719	-46.582	-37.804	Lys5 (HB, SI)
Allicin	65036	-36.104	-31.062	Lys137 (HB, SI)
Viridiflorene	10910653	-33.190	-28.051	ND
Geraniol	637566	-31.520	-25.941	Lys102 (HB, SI) - Asp153 (HB, SI)
Linalool	6549	-31.451	-29.211	Phe3 (HB) - Arg4 (SI)
Gallic acid	370	-30.290	-30.044	Asp155 (HB) - Asp153 (HB) - Tyr154 (HB, SI)
Carvacrol	10364	-28.914	-27.170	Glu240 (HB) - Ile200 (SI)
Quercetin	5280343	-25.994	-29.412	Glu240 (HB) - Asp245 (HB) - Gln107 (SI) - Ile200 (SI)
Phytic acid	890	-24.551	-12.742	Lys5 (HB) - Glu288 (HB) - Gly138 (HB) - Lys137 (HB, SI) - Glu290 (SI)
Resorcinol	5054	-21.341	-19.120	Asp289 (HB) - Glu290 (HB) - Lys137 (SI)
Cinnamic acid	444539	-20.229	-19.724	Asp153 (HB) - Ser158 (HB) - Lys102 (SI)
Bornyl acetate	6448	-19.237	-22.198	Arg298 (HB, SI)
Eucalyptol	2758	-18.800	-20.821	ND
Catechol	289	-18.022	-18.510	Ser10 (HB) - Glu14 (HB) - Gly11 (SI)
Nicotinic acid	938	-15.083	-17.967	Arg153 (HB) - Ser158 (HB)
Terpinen-4-ol	11230	-9.254	-16.437	Lys102 (HB) - Asp153 (HB)

*, FDA-approved old antimalarial drug recommended for treating COVID-19 patients; HB, hydrogen bonds; SI, Steric Interactions; ND; not determined.

On the other hand, for the promising coupling results, we performed molecular dynamics (MD) simulations using the myPresto software package and the results obtained are shown in Table.2.

Table 2. MD simulations using the myPresto software package and calculation of the partition coefficient and bioactivity scores with the Molinspiration server. After calculating the trajectories of the different positions of the atoms of the ligand-protein complexes as a function of time, the microscopic behavior of the protein in the presence of each ligand was simulated, as well as the bioaccumulation and bioactivity of the ligands.

Compound Name	*MW (g/mol)*	*E-potential (kcal/mol)*	*Time (psec)/ E-potential*	*E-Total (kcal/mol)*	*Time (psec)/ E-Total*	*log K_{ow}*	*P Score*	*E Score*
Piperine	285.34	-8960	1.1	-2800	2.8	3.33	-0.10	0.04
Curcumin	368.40	-8930	1.1	-2800	2.0	3.29[a]	-0.14	0.08
Capsaicin	305.40	-9000	1.3	-2800	1.2	3.04[b]	-0.02	0.07
Hydroxychloroquine	335.90	-8900	1.3	-2800	3.6	4.00	0.12	0.15
Chloroquine	319.90	-8930	1.1	-2800	1.6	4.63[c]	0.05	0.11

P Score, protease inhibitor score (-0.50 – 1.50) Cheminformatics, M. 2020; *E Score,* enzyme inhibitor score (-0.50 – 1.50) Cheminformatics, M. 2020; log K_{ow}, 2 - 5 (Bhal, 2007); [a], EPA, U. (2010). Estimation Program Interface (EPI) Suite; [b], LaHann, T. R., DeKrey, L. J., and Tarr, B. D. (1989). Capsaicin analgesia: predictions based on physico-chemical properties. In Proceedings of the Western Pharmacology Society (Vol. 32, pp. 201-204); [c], Leo, A., and Hoekman, D. H. (1995). Exploring QSAR. American Chemical Society.

After calculating the trajectories of the different positions of the atoms of the ligand-protein complexes as a function of time, to simulate the microscopic behavior of the protein in the absence and presence of each ligand, we found that all the 6 main compounds generate interaction systems thermodynamically stable and similar to each other in terms of total energy ($\Delta G \leq -2800$ kcal/mol). However, it is important to note that while the protease in the native state reaches its least-energy structure at 1.6 ps (see Table 2 and Figure 3), the three candidate phytochemical compounds may induce structural disturbances that affect the thermodynamic stability of the enzyme around of 1.1 - 1.3 ps of the simulation, by like antimalarial drugs and commercial viral protease inhibitor. Specifically, capsaicin was the compound with which the most thermodynamically stable conformation was obtained at 1.3 ps, and piperine and curcumin, generated less stable structures than the native one in much less time (1.1 ps). These results show that the studied phytochemical compounds could be able to induce large structural fluctuations with respect to the native structure, generating changes in the thermodynamic stability of the enzyme in very early stages of the docking in terms of potential energy, similar to the tested drugs (see Table 2 and Figure 3).

In relation to the molecular properties and structural characteristics studied in these compounds, and which are of interest for the search for possible pharmacological objectives, it was determined that all the phytochemical ligands have a good partition coefficient (log K_{ow}: 3.04—3.29), and although they are below what was observed with antimalarials, these results suggest that the natural compounds studied are capable of bioaccumulating with a high coefficient (Bhal, 2007). Piperine and curcumin being the phytochemicals with the highest bioaccumulation capacities (Table 2). Additionally, the potential bioactivity of these compounds was studied, by means of the scoring obtained from the comparison of the phytochemicals within a calculated distribution of activity scores for protease inhibitor ligands and other enzymatic targets compared to scores for approximately 100,000 average molecules similar to drugs. The score allows the efficient separation of active and inactive molecules, finding that like antimalarials, who obtained the highest scores, all phytochemicals can be potential protease inhibitors, with capsaicin showing the best inhibition score for proteases among phytochemicals, while for curcumin the best prediction was obtained for enzyme inhibition in general (see Table 2).

Additionally, we were able to determine that all the ligands considered for the MD analyzes are capable of inducing structural disturbances in the viral protease (3CL) with a statistically significant difference in its folding or unfolding effects of the enzyme ($p < 0.001$) using as reference the distances between the residues of Arg4 and Gly138 (see Figure 2), arbitrarily chosen because they are approximately 16 Å apart from each other and at a distance of approximately 2 Å from almost all the ligands (except for capsaicin, which presents a thermodynamically more favorable docking in a cavity that bets on predicted for the rest of the ligands).

These results are promising because they show the existence of known bioactive compounds of plant origin that could be used as model drugs in more exhaustive theoretical or/and experimental studies based in structure-activity relationship to develop new drugs against COVID–19. Especially, since it has been shown that compounds such as piperine can serve for the transport of bioactives of plant origin (Izgelov *et al.,* 2020). A very important aspect because it has been reported that the active sites of SARS coronavirus proteins showing important differences in both shape and size and therefore are not compatible with the COVID–19 docking site, which may affect the efficacy of reused drugs proposed for treatment (Chang *et al.,* 2020; Bzowka *et al.,* 2020). Therefore, we are conducting a second phase of this study aimed at comparative analysis of thermodynamic, structural and conformational disturbances that are capable of inducing the compounds of interest considered in this study, including the contrast with protease inhibitor drugs.

Conclusion

Based in bioinformatics tools in this study was obtained that curcumin, capsaicin and piperine strongly binding to 3CL-protease of COVID–19 in comparison to the two antimalaric drugs and promote important structural changes in this viral protease, inducing folding of the enzyme. We propose that these three compounds could be candidates as model drugs for experimental and theoretical studies to evaluate their possible biological activity. In this sense, we recommend more studies on the mechanisms of action of these compounds of interest, as well as experimental demonstrations of the possible antagonistic effect *in vitro* on COVID–19.

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Figures

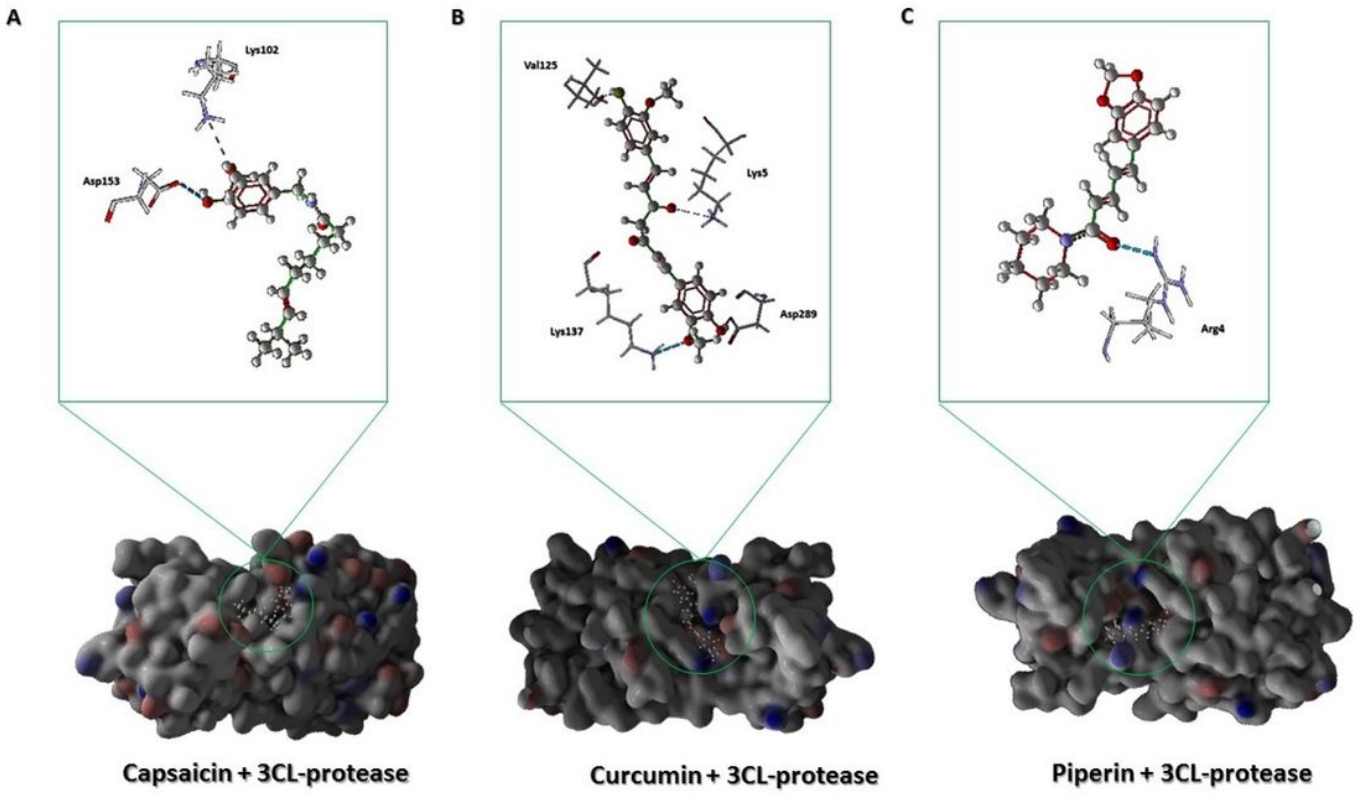

Figure 1

Visualization of the result of 3CL protease-phytochemical docking. The results of the docking of the three phytochemical compounds with better interaction energies than the antimalarial drugs considered in this study are shown. A) capsaicin, the interaction by hydrogen bridge with Asp 153 and by steric interaction with Lys 102 is shown; B) curcumin, the interaction by hydrogen bridge with Val 125, Asp 289 and Lys 137 and by steric interaction with Lys 5 is shown; C) piperin, the interaction by hydrogen bridge and by steric interaction only with Arg4 is shown.

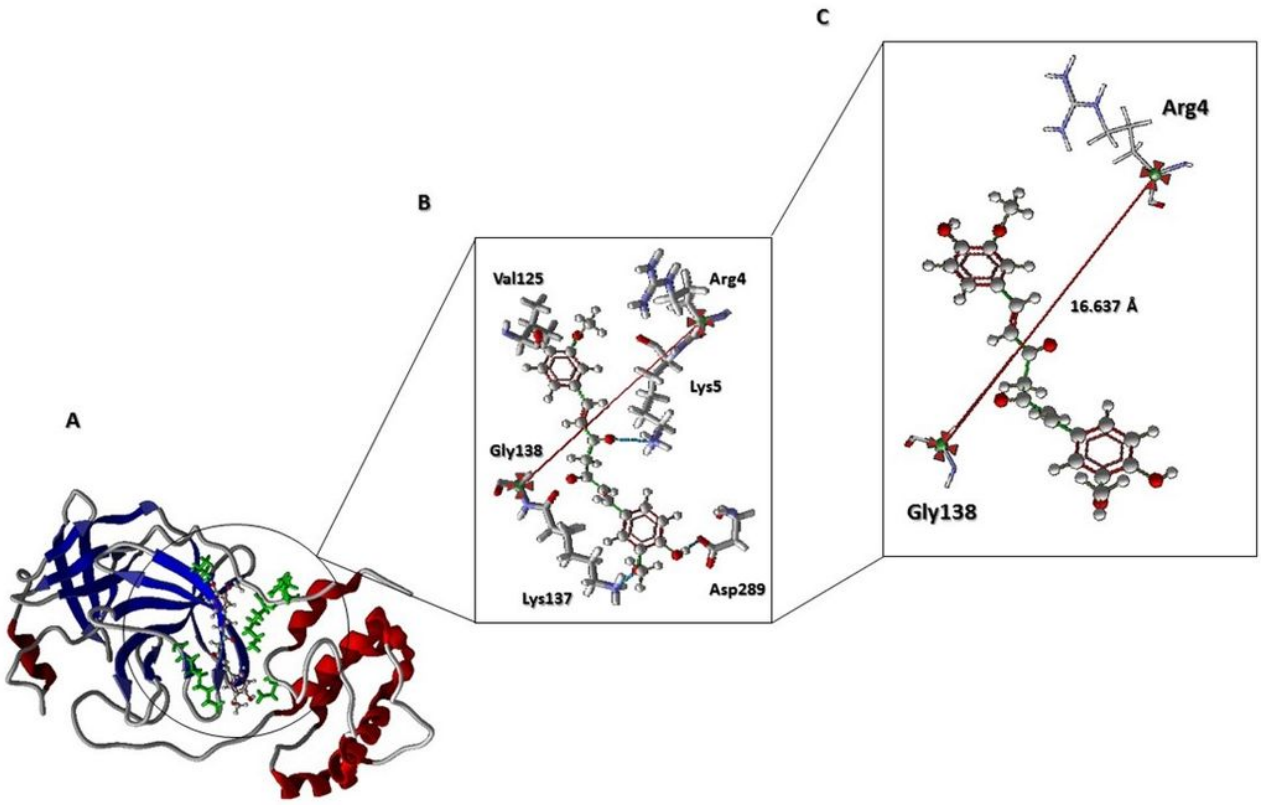

Figure 2

The location and distance between residues Arg 4 and Gly 138 are shown. They are approximately 16 Å apart from each other and at approximately 2 Å distance from almost all the ligands (except capsaicin, which presents a thermodynamically more favorable coupling in a cavity that bets for the one planned for the rest of the ligands). These residues were arbitrarily chosen to measure the conformational perturbation of the protease in the presence of each ligand. A) the figure shows the 3CL protease-curcumin docking as reference, B) as well as all the residues close to the ligand and C) the distance between the residues chosen for the MD analyzes.

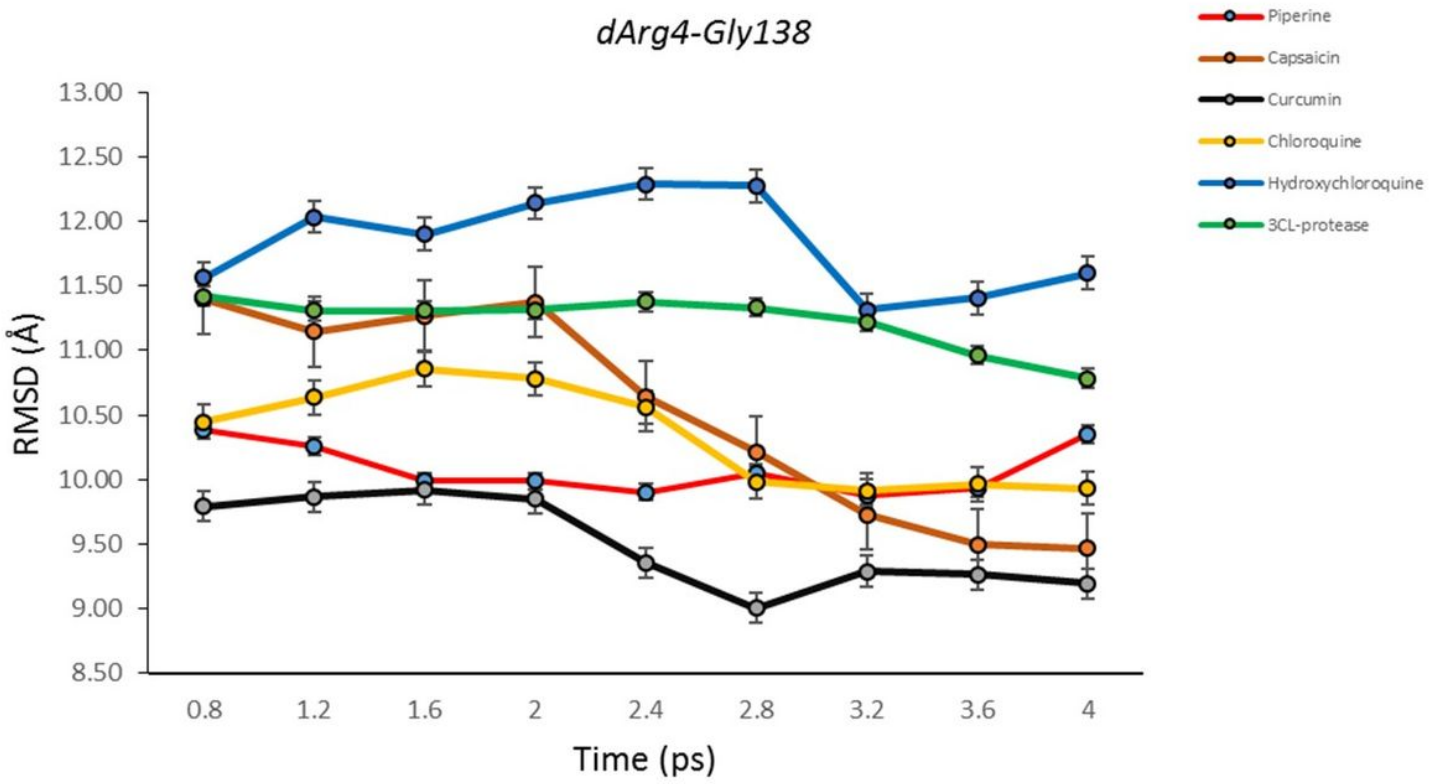

Figure 3

Conformational fluctuation and partial folding/unfolding of 3CL-protease in the presence of compounds and as a function of time. Using as a reference the distances between the residues of Arg4 and Gly138.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- InformationSupplementaryTheoreticalMolecularDockingStudyoftheStructuralDisruptionoftheViral3CLProteaseofCOVID19InducedbyBindingofCapsaicinPi