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Computaional Study on Selected Compounds in *Garcinia Kola* Seed as Potential Coronavirus Main Protease Inhibitors

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Abstract: The havoc caused by coronavirus among the old and young ones has become a serious challenge to scientists globally. The yearning by researchers to find a lasting and proficient cure to this dangerous death-causing virus remains ongoing. Thus, four selected compounds from *garcinia kola* seed were optimized using density functional theory and further subjected to molecular docking as well as molecular dynamics simulation studies to observe their biological interaction with coronavirus main protease. It was observed that all the studied compounds were active inhibitors against coronavirus main protease and performed better than the proposed standard drug (chloroquine) so far in terms of the binding energies obtained. Furthermore, compound **2** possesses a better tendency to inhibit than the standard tested and other studied compounds. It can be proposed that tested compound 2 serves as a good candidate for the design of inhibitors targeting coronavirus protease.

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Keywords: *Garcinia Kola* Seed, Coronavirus, protease, Density functional theory, Docking, Molecular dynamics simulation.

1.0 Introduction

Virus appeared to be one of the dreaded causes of death globally. Several types of diseases such as lower respiratory contamination, diarrhoea disease, human immunodeficiency virus have led to sudden human death, both in developed and developing countries.[1] Recently, an outbreak of a type of coronavirus known as COVID-19 occurred in Wuhan, China and its fast rate of spreading across the globe has become a serious concern to scientists and the entire world.[2,3] COVID-19 poses a severe danger to both the young and the old ones through respiratory infection.[4] Over two millions of people have been reported by the World Health Organization to have contracted this deadly disease while tens of thousands have been reported to be dead due to this virus.[5] Lack of efficient technique or potent drugs to fight this deadly virus has resulted in its increasing spread which has remain a challenge to the medical world.[6] The crystal structure of COVID-19 main protease bound to potent and new inhibitor named X77 was resolved recently[7] and statistics has shown that the main protease of SARS-CoV-2 is one of the most important drug targets.[8] In another study by Christian and coworkers reported chloroquine to be an effective agent to inhibit coronavirus which is a positive sign of a positive way forward.[9]

Several studies are ongoing to find potent drug candidates to inhibit this virus. Therefore, herbal products as an alternative means which helps in supporting human health and fighting diseases remain

an imperative way of treatment worldwide.[10] Chemical compounds present in herbs played a serious part in discovering and developing drug and this has drawn the attention of researchers over the years.[11] *Garcinia kola* with the family name of Guttiferae mostly exist in central and western African countries. As reported by Akintelu *et al*, 2019, *Garcinia kola* played a serious role in traditional medicine globally.[12] It has worked as an antidote to poison, antioxidant, anti-microbial and anti-antiviral agents.[13-15]

In this study, we used density functional theory (DFT), docking and molecular dynamics (MD) simulation on some selected compounds obtained from *Garcinia kola* seed in complex with the main protease of SARS-CoV-2 to answer the following objectives (i) to identify the descriptors with anti-coronavirus main protease activities using DFT (ii) to observe the binding affinities and residues involved in the interaction between the studied complexes with docking experiment and (iii) to observe the actual binding free energy of these complexes using MD.

2.0 Methodology

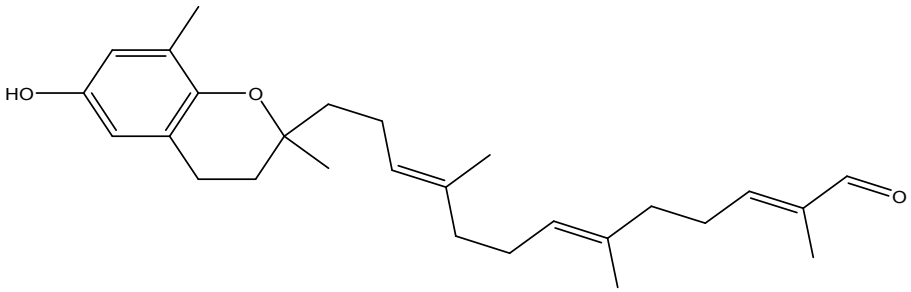
2.1 Optimization and Molecular Docking Study

The selected compounds (Figure 1) obtained from *Garcinia kola* seed were optimized using Spartan14[16] and the descriptors that described the anti-coronavirus main protease activities were obtained. The optimized compounds were docked into the active pocket of COVID-19 main protease (PDB code: 6w63[7] using AutoDock Tool 1.5.6.[17] The grid box centre was (X = -2.346, Y = 19.141, Z = -26.343) and box size (X = 68, Y = 52, Z = 70). The spacing was set to be 1.00Å. The binding affinities and the molecular interaction for each complex was observed and are comparable to that observed experimentally.[7]

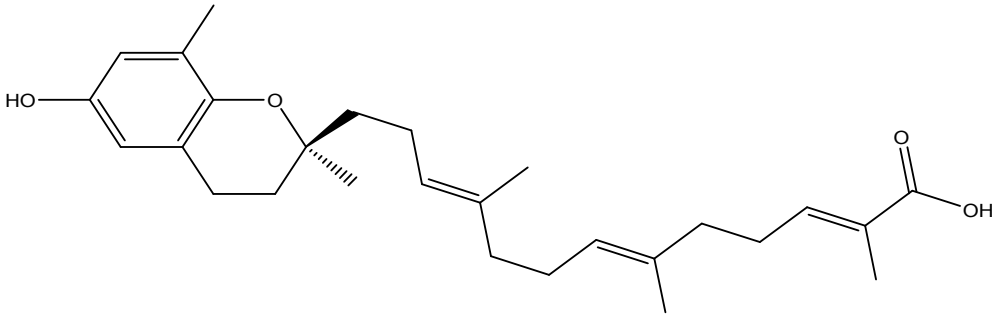
2.2 Molecular Dynamics Simulation Study

The compound with better binding affinity was selected from the docked compounds and Chloroquine was used as a standard, both were subjected to molecular dynamics simulation on AMBER14 molecular dynamics package.[18] Hydrogen atom was added to the studied complexes using a leap segment of AMBER14. The protein was described with AMBER force field 99SB while the ligand with general AMBER force field.[18, 19] To neutralize the studied complexes before solvation, the required number of counter ions were added. The solvation was implemented in a condensed octahedral cell of TIP3P[20] water molecules and 12 Å was stretched outside the protein on each side.

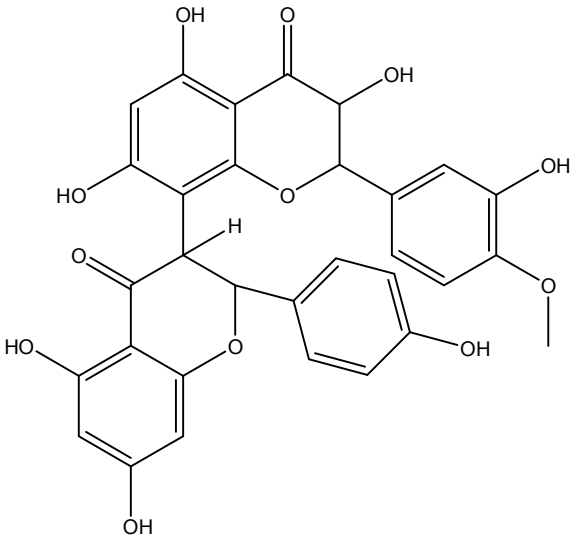
The complexes were minimized using 5000 frames of steepest descent minimization and 10000 frames of conjugated gradient minimization to eliminate bad atom interactions. The entire systems were heated at 300K and 50000ps molecular dynamics simulation was accomplished for the studied complex at 300K and 1atm via Particle Mesh Ewald method.[21] CPPTRAJ module[22] implemented in AMBER14 software was used for molecular dynamics trajectories analysis.



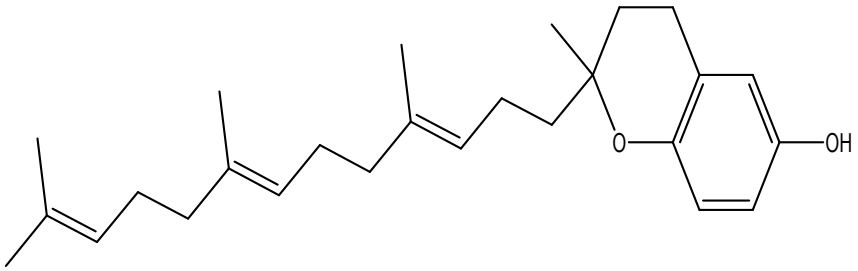
(2*E*,6*E*,10*E*)-13-(6-hydroxy-2,8-dimethyl-3,4-dihydrochromen-2-yl)-2,6,10-trimethyltrideca-2,6,10-trienal (**1**)



(2E,6E,10E)-13-[(2S)-6-Hydroxy-2,8-dimethyl-3,4-dihydrochromen-2-yl]-2,6,10-trimethyltrideca-2,6,10-trienoic acid (**2**)



(2*R*,3*R*)-8-[(2*S*,3*R*)-5,7-dihydroxy-2-(4-hydroxyphenyl)-4-oxo-2,3-dihydrochromen-3-yl]-3,5,7-trihydroxy-2-(3-hydroxy-4-methoxyphenyl)-2,3-dihydrochromen-4-one (**3**)



2-methyl-2-[(3*E*,7*E*)-4,8,12-trimethyltrideca-3,7,11-trienyl]-3,4-dihydrochromen-6-ol (**4**)

Figure 1: Structure of the selected compounds from *Garcinia kola* seed

3.0. Results and Discussion

3.1. Molecular Descriptors and Docking Study

In this work, several descriptors with potential anti-coronavirus main protease ability were obtained and reported. The obtained descriptors were subjected to Lipinski rule of five (Molecular Weight ≤ 500, HBD ≤ 5, HBA ≤ 10 and Log P ≤ 5) which every molecular compound with drug potential must exhibit. It was observed that compound **1, 2** and **4** agreed with Lipinski rule except compound **3** with higher molecular weight, HBD and HBA (Table 1).

Also, all the docked compounds have nine (9) conformations each and the calculated binding affinities were reported in Table 2 and the residues involved in the interaction were displayed in Figure 2. In this work, compound **2** with higher binding affinity proved to inhibit better than other studied compounds as well as chloroquine (Standard). The binding affinity for each of the compound was greater than the standard used, and this confirmed the potential propensity of *Garcinia kola* seed as anti-coronavirus main protease agent.

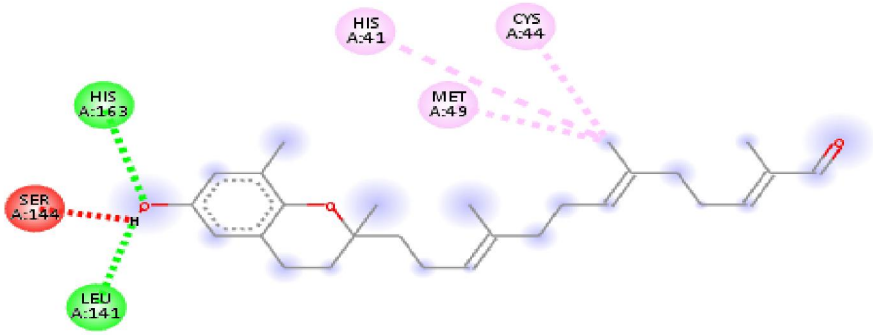
Table 1: Properties of the studied compounds

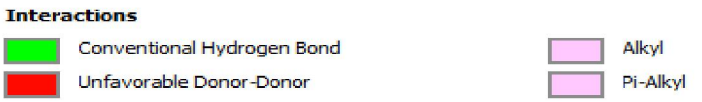
Compounds	MW (amu)	HBD	HBA	Log P
1	410.598	1	3	3.73
2	426.597	2	3	4.00
3	586.549	7	11	-5.34
4	396.615	1	2	4.93
Chloroquine	319.880	1	3	0.66

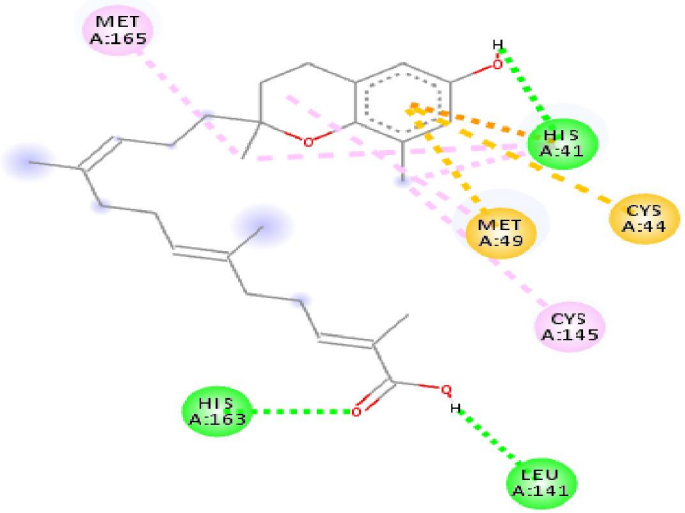
Note: MW= Molecular weight, HBD: Hydrogen bond donor, HBA: Hydrogen bond acceptor.

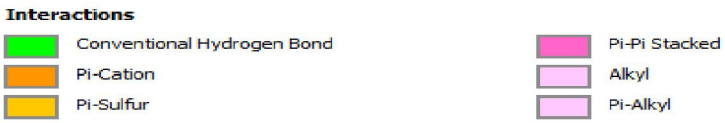
Table 2: Calculated binding affinity

	Binding Affinity (kcal/mol)
1.	-7.0
2.	**-7.9**
3.	-7.8
4.	-7.0
Chloroquine	-5.6









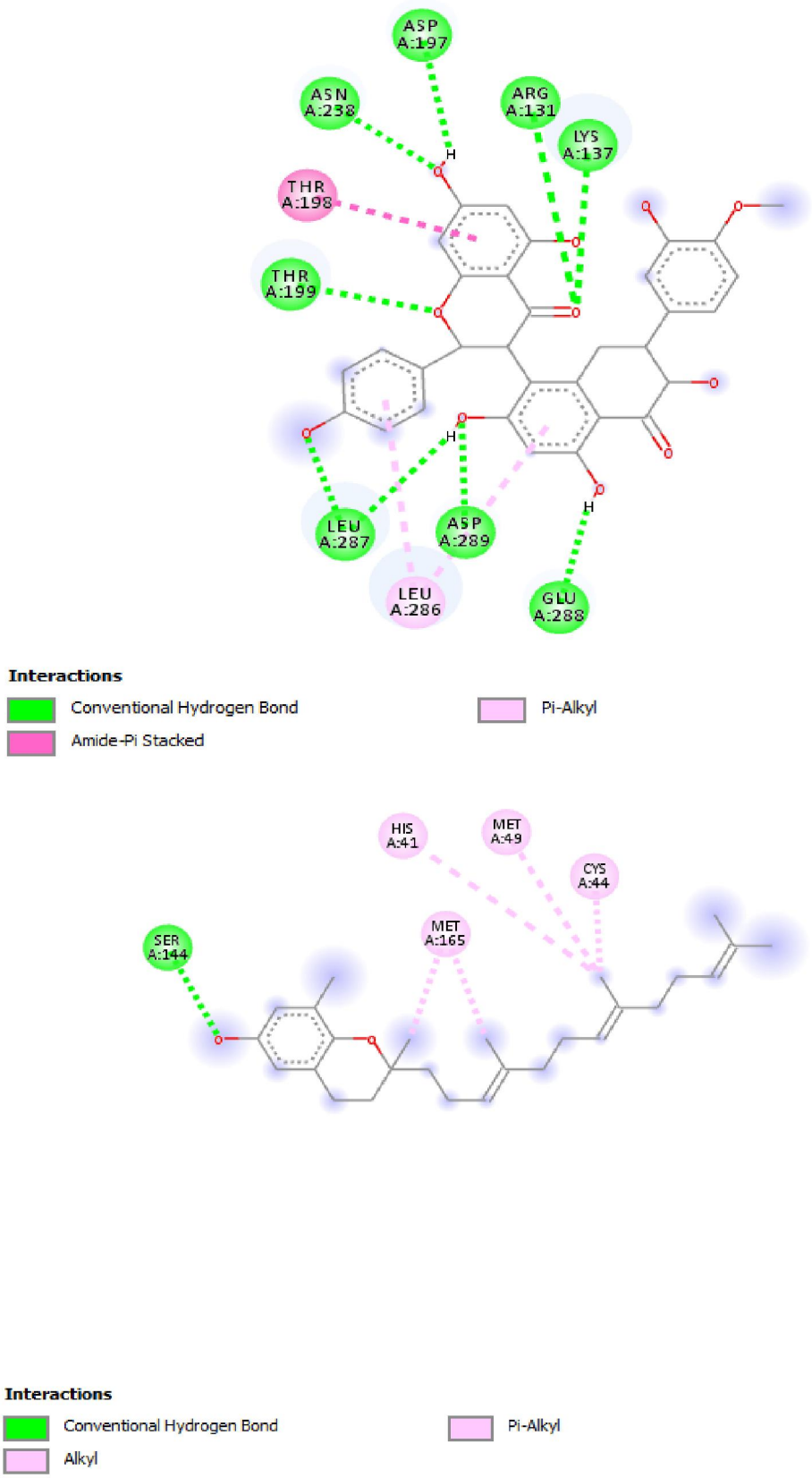


Figure 2: Interaction between compound **1, 2, 3**, and **4** with Coronavirus main protease

3.2. Molecular Dynamics Simulation of Selected Complexes

3.2.1. Root of Mean Square Deviation

Root mean square deviations (RMSD) of the Coronavirus main protease backbone atoms relative to their starting structures in complexation with compound **2** and Chloroquine during the 50 ns MD simulation were plotted as Figure 3. RMSD analysis was executed to examine the level of deviation from the initial structure upon binding and the stability of the simulated complexes.

As shown in Figure 3, stable conformation was observed for both complexes with average RMSD values of 1.13 Å and 2.15Å for Comp **2-6w63** and **Chloroquine-6w63** respectively. However, minor unsteadiness was observed for Chloroquine-6w63 at about 2000 ps and 3000ps but was later stable. The RMSD of both complexes proved to be steady particularly during the last 10 ns indicating that all systems are equilibrated well during the simulation time.

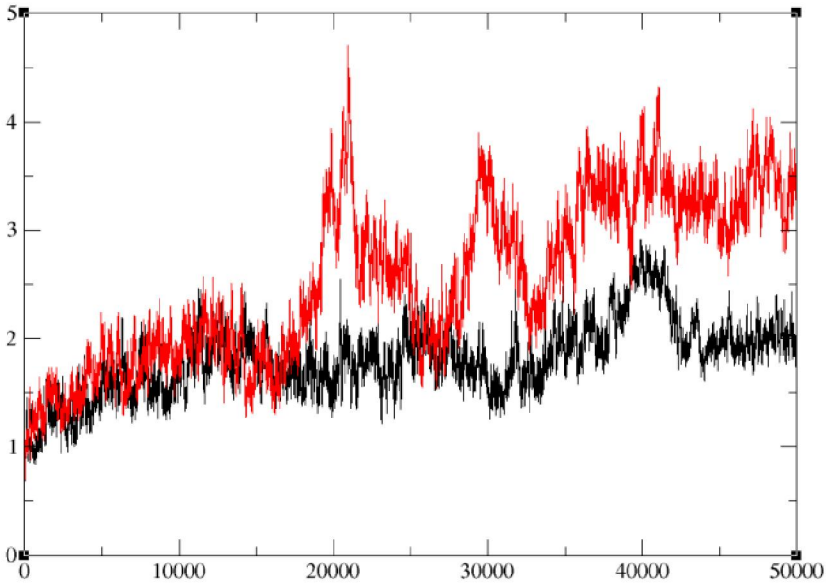


Figure 3: RMSD of **Compound 2-6w63** (black) and **Chloroquine-6w63** (red) complexes during the 50ns MD simulations.

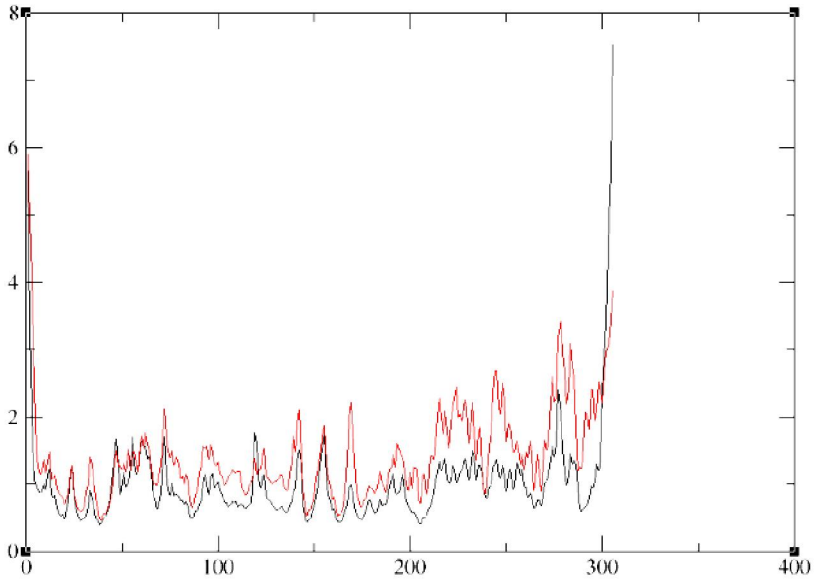


Figure 4: RMSF plots for **compound 2-6w63** (black) and **chloroquine-6w63** (red) complexes during the 50ns MD simulations.

3.2.2. Root of Mean Square Fluctuation

The calculated root mean square fluctuation (RMSF) reveals the flexibility of residues upon binding of the two compounds tested during simulation time. RMSF of the alpha carbon (Cα) was calculated along two MD trajectories. As shown in Figure 4, the RMSF plots look similar to each other in general, while the difference is the absolute configuration of the impact of binding of the two inhibitors. As supported by the better binding free energy (Table 3) of **Compound 2** to the protease in comparison to Chloroquine, viz-a-viz more residual fluctuations observed for Chloroquine. One can infer that **Compound 2** showed more residual interaction with the protease.

3.2.3. Binding free energy

The calculated binding free energies for the selected compounds are presented in Table 3 using the MMG/BSA method. The binding free energies were determined by extracting 1000 frames from the last 10 ns MD trajectories of the simulation for each complex.[23] The binding free energy for **compound 2** (-40.83kcal/mol**)** is a proof that it has better capacity to inhibit coronavirus main protease than **Chloroquine** (34.24kcal/mol) with a difference of about 6 kJ/mol. The calculated free energy includes van der Waal energy (-47.26 kcal/mol), electrostatic energy (14.86 kcal/mol), polar solvation energy (-2.54 kcal/mol), and non-polar solvation energy (-5.89 kcal/mol). This indicates that van der Waal energy, polar solvation energy, and non-polar solvation energy are favourable while electrostatic solvation energy was not favourable for the molecular binding of **compound 2** to coronavirus main protease.

Table 3: Calculated binding free energies and its components for the complexes using MM-GBSA method extracted from the last 1000 frames of 50 ns. The energy components are in kcal/mol.

Compound	ΔE_{vdw}	ΔE_{ele}	ΔG_{gas}	ΔG_{polar}	$\Delta G_{nonpolar}$	$\Delta G_{solvation}$	$-\Delta G_{bind}$
Comp 2	-47.26	14.86	-32.40	-2.54	-5.89	-8.42	-40.83
Chloroquine	-44.60	-118.56	-163.16	134.22	-5.31	128.92	-34.24

Conclusion

The selected molecular compounds obtained from *garcinia kola* seed were examined using Density functional theory method for optimization and further exposed to docking and molecular dynamics simulation studies to examine the biological interaction existing between the selected compounds and coronavirus main protease. All the studied selected compounds possess a better tendency to inhibit coronavirus main protease, however, compound **2** has a higher tendency to inhibit than other studied compounds. Also, the calculating actual binding energy for compound **2** via molecular dynamic simulation methods confirmed its ability to inhibit coronavirus main protease than other studied compounds and the standard (Chloroquine).

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Conflict of interest

The authors declare that they have no conflict of interest.

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