Advanced Journal of Science and Engineering

https://adv-j-sci-eng.com

eISSN: 2717-0705

Original Research

A Comparative *In Silico* Investigation of Curcumin, Coumarin, and Cinnamaldehyde Interactions with the MPro of COVID-19

Iqbal Hafeez[1,*], **Nazir Mahmud**[1]

[1] *Department of Chemical Engineering, University of Engineering & Technology, Peshawar, Pakistan*

[*]*Correspondence*: iqblhafeez@gmail.com (I.H.);

Advanced Journal of Science and Engineering. 2023; 4(2): 042011. https://doi.org/10.22034/advjse042011

Received: 24 September 2022 / ***Revised***: 2 January 2023 / ***Accepted***: 8 January 2023 / ***Published***: 15 May 2023

Abstract: Due to the importance of dealing with the very recent coronavirus disease (COVID-19), the current work was done to make a comparative *in silico* study on investigating the efficacy of each of curcumin, coumarin, and cinnamaldehyde ligands for interacting with the main protease (MPro) of COVID-19. The single ligand models were optimized using density functional theory (DFT) calculations and their frontier molecular orbitals (FMO) features were evaluated. Next, molecular docking simulations were performed to analyze the infarctions of each ligand towards the MPro target by formations of Ligand…MPro complexes. In this case, the models were categorized by the results of both of singular and complex states to show the strength of complexes by the interacting ligand as curcumin > coumarin > cinnamaldehyde. It was interesting that the prediction of chemical hardness and chemical potential of ligands were the same as the results of Ligand…Target complexes to show suitability of investigated ligands for approaching the purpose of new drug design issues.

Keywords: Antiviral; Coronavirus; Drug design; DFT; Inhibitor; Molecular docking.

Introduction

The appearance of coronavirus disease in the late of 2019 (COVID-19) not only shocked the people of all around the world, but it also had several adverse effects for the global human life situation [1]. In this regard, several attempts were dedicated to indicate the mystery of such an unknown disaster [2]. Indeed, the identification of main protease (MPro) of this virus helped researchers too much for exploring appropriate inhibitors [3]. To this aim, considerable efforts have been done even up to now to find the appropriate inhibitors but the success has not been certain yet and further investigations are still needed for providing more efficient treatment protocols against the continuous COVID-19 pandemic [4-6]. Examining the efficacy of available compounds against the MPro target has been found as one of the possible methods of developing treatments developments for this disease [7]. Interactions between different ligand compounds and the MPro target were accordingly investigated based on various research methods [8]. Employing *in silico* methods has been found among those most versatile research methods to explore the materials at the earliest time with a high level of precision [9]. Both of quantum chemical calculations of small ligand molecules and molecular docking simulations of interacting Ligand…Target complexes were applicable to explore new inhibitors against the MPro of COVID-19 [10].

Copyright © 2023 by the authors.
This work is licensed under a Creative Commons Attribution 4.0 International License (CC-BY 4.0).

In the current research work, three types of natural products including curcumin, coumarin, and cinnamaldehyde were investigated for interacting with the MPro of COVID-19 using the *in silico* method. In any case of developing novel treatments, natural products have been found more suitable rather than the synthetic compounds because of an expectation of lower side effects for those naturally based compounds [11]. On the other hand, the availability of such natural compounds in comparison with the synthetic requirements of other chemicals could make them more reliable for investigations [12]. But it should be noted that the toxicity is still a preventing issue for employing all types of compounds for the living systems [13]. To approach the goal of this work, the molecular models of curcumin, coumarin, and cinnamaldehyde (Figure 1) were optimized by the quantum chemical calculations and their inetractions with the MPro of COVID-19 were investigated by performing molecular docking simulations (Figure 2). The results were discussed to make a comparison for the efficacy of investigated natural products ligands towards the COVID-19 target.

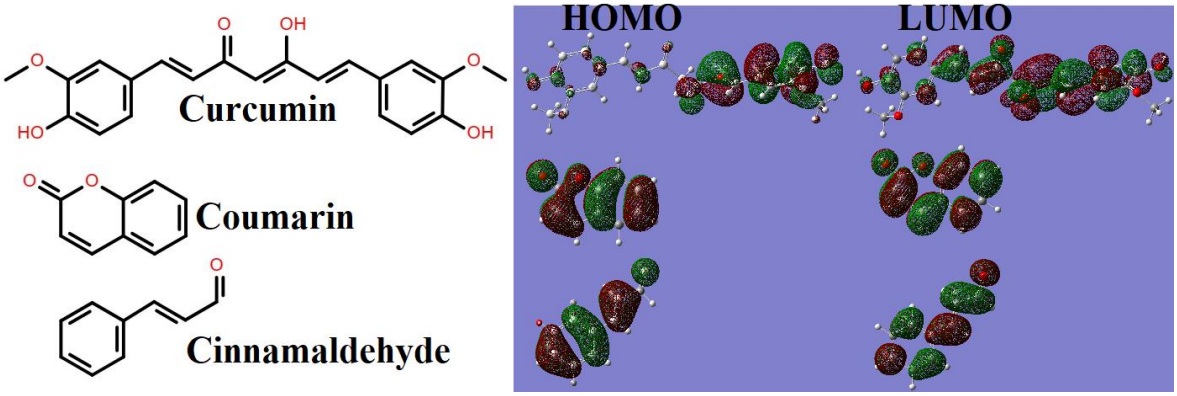

Figure 1: The investigated molecular models of natural products and their FMO patterns.

Materials and Methods

Quantum density functional theory (DFT) calculations were preformed to optimize the molecular models of curcumin, coumarin, and cinnamaldehyde using the B3LYP exchang-correlation functional and the 6-31G* Standard basis set as implemented in the Gaussian program [14]. The models of investigated natural products were initially obtained from the ChemSpider structural bank [15] and they were prepared for the optimization calculations and other electronic properties evaluations. As shown in Figure 1, the models were optimized and their frontier molecular orbital (FMO) features were evaluated in both of graphical representations and quantitative descriptions in Table 1. Distribution patterns of the highest occupied and the lowest unoccupied molecular orbitals (HOMO and LUMO) were shown in Figure 1 for the optimized states of each of curcumin, coumarin, and cinnamaldehyde models. Next, energy values of HOMO and LUMO levels were obtained and their related features were evaluated as the chemical hardness and chemical potential parameters to identify their chemical properties. Subsequently, the 3D model of MPro of COVID-19 was obtained from the PDB bank [16] with the 6LU7 identifying code. After preparing all ligands and target, they were submitted to the HDOCK webserver [17] to perform the Ligand…Target molecular docking simulation. By evaluating the results of docking score and surrounding amino acids of each ligand, the models of complexes were exhibited in Figure 2. To do such calculations and simulations, the *in silico* approach was indeed employed as a benefit of employing computational tools for exploring the chemical and biochemical related systems [18-20]. The purpose of this work for comparing the efficacy of each of curcumin, coumarin, and cinnamaldehyde for interacting with the MPro target of COVID-19 was accordingly investigated in this work using the evaluated parameters and features. The models were comparable by the assistance of each of DFT calculated and molecular docking simulated features.

Table 1: DFT calculated FMO features of optimized ligands.

Model	**HOMO** eV	**LUMO** eV	**Chemical Hardness** eV	**Chemical Potential** eV
Curcumin	-5.79	-1.75	2.02	-3.77
Coumarin	-6.50	-1.88	2.31	-4.19
Cinnamaldehyde	-6.58	-2.09	2.24	-4.33

Results and Discussion

A comparative *in silico* investigation was carried out to investigate interactions of curcumin, coumarin, and cinnamaldehyde for interacting with the MPro target of COVID-19. To this aim, the molecular models were optimized and their features were evaluated as exhibited in Figure 1 and Table 1. First it should be mentioned that the molecules had different molecular weights and formulas; curcumin with $C_{21}H_{20}O_6$ and mw = 368, coumarin with $C_9H_6O_2$ and mw = 146, and cinnamaldehyde with C_9H_8O and mw = 132, but the types of including atoms were the same for all of them as a mixture of carbon, oxygen and hydrogen atoms. Based on such different architectures, the models were found with different FMO features, in which all related parameters were different in comparison with each other. The levels of HOMO and LUMO stand for two main levels of electron transferring processes, and their variations could dictate new electronic environments for the molecular models. For approving such achievement, different values of chemical hardness and chemical potential showed the symbolic differences of such electronic systems in the models. As a result, the ligand models were suitable for being compared regarding their initial electronic features and feature activities towards the target. Curcumin had the largest mw but its chemical hardness indicated its more suitability for involving in additional reactions and interactions comparing with cinnamaldehyde and coumarin, respectively. More results on such models were dissuadable by the evaluated patterns, in which the models were variated by their patterns in comparison with each other. For curcumin, the patterns of HOMO and LUMO were in a discrete mode, but they were in a continuous mode in both of coumarin and cinnamaldehyde models. As a consequence, the models were comparable and their FMO related features affirmed the idea of performing such comparative work.

The interacting Ligand…Target complexes of each of curcumin, coumarin, and cinnamaldehyde the MPro of COVID-19 were obtained by performing molecular docking simulations as shown in Figure 2. The models were aligned by a central ligand and surrounding amino acids, in which various types of interactions were found for each of them and all of them. In the case of categorizing the strength of interactions between ligand and target, the models were assigned by a number implying for the docking score. The results indicated that the complex formation of Curcumin…MPro was at the highest suitability regarding a very better score than two other ones. Remembering the FMO results of ligands, the chemical hardness of curcumin was lower than two other ligands and an easier contribution to additional reactions and interactions was supposed for this ligand. Accordingly, the models of complexes showed a better formation of complexes between curcumin and target than other two ligands; coumarin and cinnamaldehyde. For the case of coumarin and cinnamaldehyde, although the chemical hardness of cinnamaldehyde was slightly better than that of coumarin, but a better chemical potential of coumarin made it more suitable for involving in stronger interactions. Consequently, the models of Ligand…Target complexes were categorized for curcumin > coumarin > cinnamaldehyde regarding their strengths of complex formations. The combinations of results of singular ligand molecular models through DFT calculations and Ligand…Target complexes through molecular docking simulations, it was found that the idea of exploring such natural products for developing possible antiviral inhibitors could be considered for further investigations. Not only the results of such models but also their featured properties could be expected for new opening in such drug design issues.

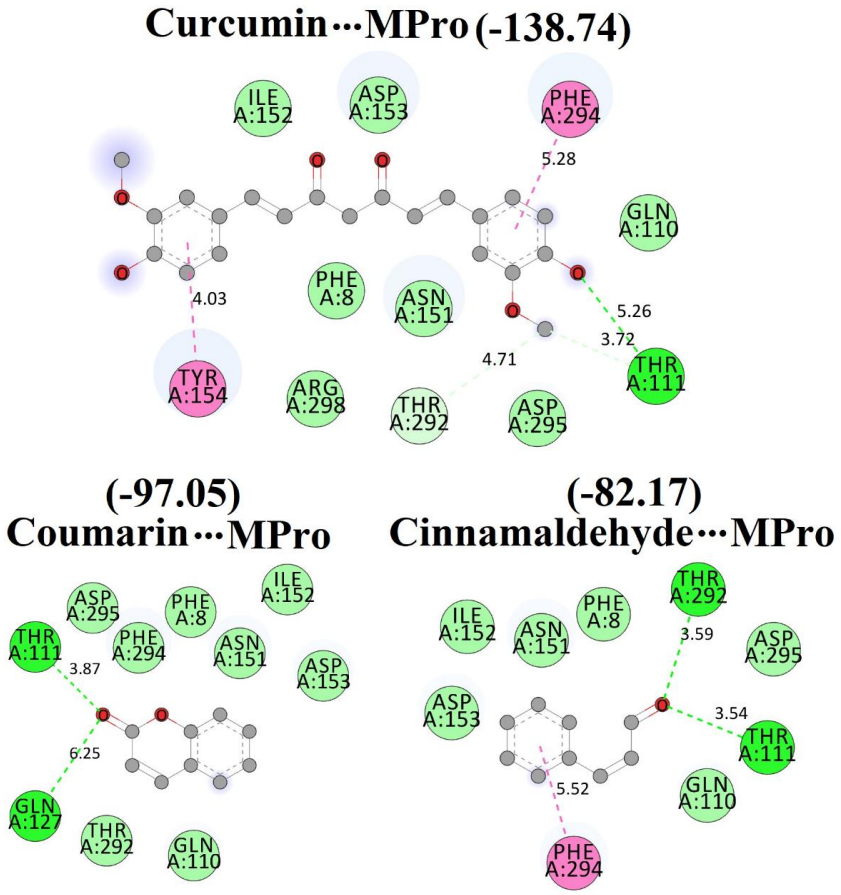

Figure 2: Interacting Ligand…Target complexes and their (docking scores).

Conclusion

The obtained results of singular ligand models and Ligand…Target complexes indicated benefits of employing the investigated ligands for inhibiting the activity of MPro target of COVID-19. The obtained FMO results showed various aspects of electronic features and the values of chemical hardness and chemical potential helped to predict a future contribution of ligand to other reactions and interactions. The complex models were analyzed based on the docking scores and the results were in agreement with already predictions of FMO results indicating the strength of complex formations; curcumin > coumarin > cinnamaldehyde with MPro target. As a final remark, further investigations of such systems for developing new antiviral drugs could be proposed.

Disclosure Statement

The author(s) did not report any potential conflict of interest.

References

1. Baker MA, Sands KE, Huang SS, Kleinman K, Septimus EJ, Varma N, Blanchard J, Poland RE, Coady MH, Yokoe DS, Fraker S. The impact of coronavirus disease 2019 (COVID-19) on healthcare-associated infections. Clinical Infectious Diseases. 2022; 74: 1748.
2. Islam M, Haque M, Rahman M, Hossen F, Reza M, Barua A, Marzan AA, Das T, Kumar Baral S, He C, Ahmed F. A review on measures to rejuvenate immune system: natural mode of protection against coronavirus infection. Frontiers in Immunology. 2022; 13: 837290.
3. Chia CB, Xu W, Shuyi Ng P. A patent review on SARS coronavirus main protease (3CLpro) inhibitors. ChemMedChem. 2022; 17: e202100576.

4. Semenov VA, Krivdin LB. Combined computational NMR and molecular docking scrutiny of potential natural SARS-CoV-2 Mpro inhibitors. The Journal of Physical Chemistry B. 2022; 126: 2173.
5. Macip G, Garcia-Segura P, Mestres-Truyol J, Saldivar-Espinoza B, Ojeda-Montes MJ, Gimeno A, Cereto-Massagué A, Garcia-Vallvé S, Pujadas G. Haste makes waste: a critical review of docking-based virtual screening in drug repurposing for SARS-CoV-2 main protease (M-pro) inhibition. Medicinal Research Reviews. 2022; 42: 744.
6. Chtita S, Belaidi S, Qais FA, Ouassaf M, AlMogren MM, Al-Zahrani AA, Bakhouch M, Belhassan A, Zaki H, Bouachrine M, Lakhlifi T. Unsymmetrical aromatic disulfides as SARS-CoV-2 Mpro inhibitors: molecular docking, molecular dynamics, and ADME scoring investigations. Journal of King Saud University-Science. 2022; 34: 102226.
7. Le QH, Far BF, Sajadi SM, Jahromi BS, Kaspour S, Cakir B, Abdelmalek Z, Inc M. Analysis of Conocurvone, Ganoderic acid A and Oleuropein molecules against the main protease molecule of COVID-19 by in silico approaches: molecular dynamics docking studies. Engineering Analysis with Boundary Elements. 2023; 150: 583.
8. Shree P, Mishra P, Kumar P, Pandey H, Giri R, Chaube R, Garg N, Tripathi YB. In silico screening of Pueraria tuberosa (PTY-2) for targeting COVID-19 by countering dual targets Mpro and TMPRSS2. Journal of Biomolecular Structure and Dynamics. 2022; 40: 11611.
9. Gupta Y, Savytskyi OV, Coban M, Venugopal A, Pleqi V, Weber CA, Chitale R, Durvasula R, Hopkins C, Kempaiah P, Caulfield TR. Protein structure-based in-silico approaches to drug discovery: guide to COVID-19 therapeutics. Molecular Aspects of Medicine. 2023; 91: 101151.
10. Singh MB, Jain P, Tomar J, Kumar V, Bahadur I, Arya DK, Singh P. An in silico investigation for acyclovir and its derivatives to fight the COVID-19: molecular docking, DFT calculations, ADME and td-molecular dynamics simulations. Journal of the Indian Chemical Society. 2022; 99: 100433.
11. Swain SS, Hussain T. Combined bioinformatics and combinatorial chemistry tools to locate drug-able anti-TB phytochemicals: a cost-effective platform for natural product-based drug discovery. Chemistry & Biodiversity. 2022; 19: e202200267.
12. Ali S, Alam M, Khatoon F, Fatima U, Elasbali AM, Adnan M, Islam A, Hassan MI, Snoussi M, De Feo V. Natural products can be used in therapeutic management of COVID-19: probable mechanistic insights. Biomedicine & Pharmacotherapy. 2022; 147: 112658.
13. Ali Abdalla YO, Subramaniam B, Nyamathulla S, Shamsuddin N, Arshad NM, Mun KS, Awang K, Nagoor NH. Natural products for cancer therapy: a review of their mechanism of actions and toxicity in the past decade. Journal of Tropical Medicine. 2022; 2022: 5794350.
14. Frisch MJ, Trucks GW, Schlegel HB, Scuseria GE, Robb MA, Cheeseman JR, et al. Gaussian 09 program. Gaussian Inc. Wallingford, CT. 2009
15. Ayers M. ChemSpider: the free chemical database. Reference Reviews. 2012; 26: 45.
16. Burley SK, Berman HM, Duarte JM, Feng Z, Flatt JW, Hudson BP, Lowe R, Peisach E, Piehl DW, Rose Y, Sali A. Protein data bank: a comprehensive review of 3D structure holdings and worldwide utilization by researchers, educators, and students. Biomolecules. 2022; 12: 1425.
17. Yan Y, Zhang D, Zhou P, Li B, Huang SY. HDOCK: a web server for protein–protein and protein–DNA/RNA docking based on a hybrid strategy. Nucleic Acids Research. 2017; 45: W365.
18. Ramirez Salinas GL, Lopez Rincon A, Garcia Machorro J, Correa Basurto J, Martinez Archundia M. In silico screening of drugs that target different forms of E protein for potential treatment of COVID-19. Pharmaceuticals. 2023; 16: 296.
19. Sheikhshabani SH, Amini-Farsani Z, Modarres P, Amini-Farsani Z, Feyzabad SK, Shaygan N, Hussen BM, Omrani MD, Ghafouri-Fard S. In silico identification of potential miRNAs-mRNA inflammatory networks implicated in the pathogenesis of COVID-19. Human Gene. 2023; 36: 201172.
20. Hossain MA, Rahman MH, Sultana H, Ahsan A, Rayhan SI, Hasan MI, Sohel M, Somadder PD, Moni MA. An integrated in-silico Pharmaco-BioInformatics approaches to identify synergistic effects of COVID-19 to HIV patients. Computers in Biology and Medicine. 2023; 155: 106656.

- **How to cite this article:** Hafeez I, Mahmud N. A comparative in silico investigation of curcumin, coumarin, and cinnamaldehyde interactions with the MPro of COVID-19. Advanced Journal of Science and Engineering. 2023; 4: 042011.
- **DOI:** 10.22034/advjse042011
- **Link:** https://sciengpub.com/adv-j-sci-eng/article/view/advjse042011