International Journal of Nanoelectronics and Materials
IJNeaM
ISSN 1985-5761 | E-ISSN 2232-1535

Mesoscopic view of spike glycoprotein inhibition by various size of fullerenes

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Received 26 December 2024, Revised 24 September 2025, Accepted 08 October 2025

ABSTRACT

Fullerene molecules, a class of allotropic carbon nanomaterials, were investigated for their potential to inhibit SARS-CoV-2 by targeting its spike glycoprotein through molecular docking simulations. Both blind and targeted docking methods were employed to evaluate interactions between various fullerene sizes (C_{20}, C_{28}, C_{60}, C_{78}, C_{84}) and the spike glycoprotein. In the blind docking method, with the exception of C_{84}, all fullerene interactions are distributed over the entire surface of the spike glycoprotein. In the targeted docking method, C_{78} and C_{84} interactions are closer to the actual binding sites of angiotensin-converting enzyme 2 (ACE2) on the spike glycoprotein. The most negative binding affinity value was found for fullerene C_{84}, with a value of -15.9 kcal/mol, primarily via hydrophobic interactions. Binding affinity correlated positively with fullerene size; larger fullerenes demonstrated a greater capacity to obstruct the ACE2 binding site. Smaller fullerenes (C_{20}, C_{28}) were ineffective, binding at unrelated regions. C_{60} showed moderate potential, with 85% of its binding occurring at the ACE2 site. In contrast, C_{78} and C_{84} exhibited 100% of their docking directly at the ACE2 binding site, indicating stronger inhibition potential. These findings underscore the significance of fullerene size in enhancing spike protein interaction and suggest that larger fullerenes, especially C_{84}, may serve as promising candidates for SARS-CoV-2 entry inhibition.

Keywords: *Docking, Fullerene, Inhibition, Mesoscopic, Spike glycoprotein*

1. INTRODUCTION

Fullerene is a form of allotropic carbon. The geometric forms of fullerenes include ellipsoids, balls (buckyballs), and tubes (nanotubes). Fullerenes are classified as inorganic nanoparticles due to their small size. The activity of these allotropic forms of carbon is determined by the nature of the fullerene core and its chemical modifications. The fullerene core exhibits a high degree of hydrophobicity, while the functional groups attached to the core contribute to the complexity of the fullerene molecule's behavior [1]. The C_{20} is the smallest member of the fullerenes family and consisting exclusively of pentagons [2]. C_{28} is the smallest fullerene that has been discovered through experimental means. It is highly active and capable of forming stable endohedral complexes. Fullerene C_{60} exhibits a remarkable geometric affinity with icosahedral viruses [3]. Fullerene C_{60} has been demonstrated to function as an enzyme inhibitor, a drug delivery vector, a photosensitizer, and a sonodynamic therapy [4], highlighting its multifaceted therapeutic potential. The presence of double electrochemical bonds in its structure endows fullerene C_{60} with potent antioxidant properties, enabling effective binding to free radicals and exertion of anti-inflammatory, antibacterial, antitumor, neurological, and radioprotective effects within the body.

The SARS-CoV-2 is a beta-coronavirus coated with spike (S) glycoprotein, envelope (E), and membrane (M). The S1 subunit of the S protein contains a receptor binding domain that binds the peptidase domain of ACE2. In SARS-CoV-2, the S2 subunit is highly conserved and is considered a potential antiviral target [5–7]. SARS-CoV-2 uses spike glycoprotein, to bind to its receptor, and mediate membrane fusion and viral-entry protein. Inhibition of ACE-2's pocket of spike glycoprotein becomes one strategy to combat the SARS-CoV-2 pandemic.

Many works have been done to stop the SARS-CoV-2 infection through an inhibition of spike glycoprotein. Various chemical compounds either from herbal or drug repurposing strategy have been used and tested to find the most promising spike glycoprotein inhibitor [8–14]. Previous research by Ramezani *et al.* [15, 16] investigated the interaction between Carbon Quantum Dots (CQDs), which are carbon-based nanomaterials, and the SARS-CoV-2 spike glycoprotein. These CQDs, noted for their green particles and low cellular toxicity, may offer a promising alternative for antiviral activity, particularly against SARS-CoV-2. The functional groups within the CQDs play a crucial role in determining the level of interaction and effectiveness. Further research by [17, 18] has demonstrated that Graphene Oxide, another carbon-based nanomaterial, can potentially destroy SARS-CoV-2 using a thermal-based model and has a strong binding affinity to adsorb the virus.

Fullerenes, as carbon-based nanomaterials, are widely known to have antiviral potential. They are known to interact with various biological molecules due to their

unique electronic structures and properties. However, specific studies focusing on fullerenes as inhibitors of SARS-CoV-2 spike glycoprotein are still rare. In this paper, the effects of different fullerene sizes on the inhibitory potential of ACE2 active site on spike glycoprotein were evaluated using molecular docking approaches (blind docking and targeted docking). The types and strengths of interactions and the effect of fullerene size on the inhibitory potential of ACE2 were discussed from a mesoscopic perspective.

2. MATERIAL AND METHODS

2.1. Preparation of Receptor and Ligand

The present study was conducted on HP laptop with an AMD Ryzen 5 5500U Processor, Radeon Graphics at 2.10 GHz, and 8GB RAM. The laptop was equipped with a range of free software, including AutoDockTools ADT 1.5.6, AutoDock Vina v1.1.2, PyMOl 1.8.6.0, UCSF Chimera 1.14, LigPlot+, and Open Babel 3.1.0. The simulation materials included the three-dimensional structure of the SARS-CoV-2 spike glycoprotein as the receptor, which was downloaded from the Protein Data Bank (rcsb.org) with the ID 6XLU [19]. This structure was chosen due to its higher resolution as compared to other spike glycoprotein's structures, such as 6M17, 6LZG, 6M0J, 7EKF, 7WBL, 7WPB, 8H5C, and 8XN2. The fullerene structures were used as the ligand in this simulation. The illustrations of Fullerene structures were shown in Figure 1.

The receptor's file (the S1 units of spike glycoprotein), first must be cleaned from unnecessary molecules such as water by using UCSF Chimera [20]. AutodockTools [21] was utilized to incorporate polar hydrogen and gasteiger charges, as well as to configure the grid box (see Figure 2). The grid box employed in blind docking covered almost one-third of the receptor surface. The grid box's size was fixed to x=120 Å, y=126 Å, z=80 Å, while the center point was set to x=179 Å, y=194 Å, z=219 Å. The targeted docking encompassed only the receptor's important side, with the grid box size was set to x=45 Å, y=47.5 Å, z=47.5 Å, while the center point was set to x=200 Å, y=200 Å, z=240 Å. This receptor's file then saved in *pdbqt* format. The structure of the fullerenes in *xyz* coordinate was obtained from The website (https://nanotube.msu.edu/fullerene/fullerene-isomers.html) and converted into three-dimensional *sdf* format by using OpenBabel converter (https://www.cheminfo.org/Chemistry/Cheminformatics/FormatConverter/index.html) and saved in *pdb* extension. The ligand as then prepared and saved in the form of *pdbqt* extension by using AutoDockTools.

2.2. Molecular Docking Simulation

Molecular docking is a physics-based computational method that predicts the binding between ligand molecules and its receptor. In this approach, the binding affinity between the ligand and receptor is calculated using thermodynamic, rotational dynamics, and electrostatic approaches. The binding affinity is expressed by the Gibbs free energy (ΔG). The magnitude of this energy is directly proportional to the strength and spontaneity of the interaction between the ligand and the receptor. Furthermore, molecular docking simulations will recommend the optimal interaction pockets and the types of molecular interactions formed between the amino acids of the target protein and the atoms and functional groups of the ligand molecule.

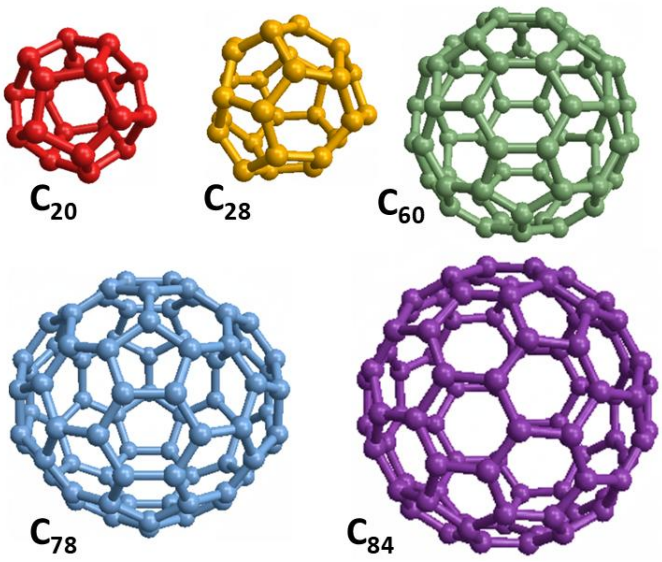

Figure 1. The illustration of fullerene structures used in this research

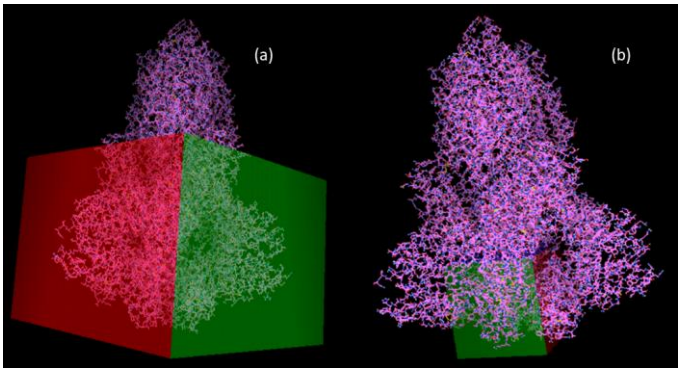

Figure 2. The grid box set up for (a) blind docking, and (b) targeted docking simulation

The molecular docking simulator employed in this study was Autodock Vina [22]. The detailed molecular interactions were displayed using LigPlot+ [23]. For the purposes of this simulation, two distinct types of grid boxes were utilized: blind docking and targeted docking. In a blind docking experiment, the grid box was set at a relatively wide width, encompassing approximately one-third of the length of the spike glycoprotein. In this scenario, interaction pockets emerged spontaneously between the ligand and receptor. In targeted docking, the interaction pocket was selected based on information about the binding location of ACE2 on the spike glycoprotein during the infiltration process of the SARS-CoV-2 virus in healthy cells [24]. The number of binding modes and the exhaustiveness of the molecular docking simulation were set to 20 and 8, respectively.

3. RESULTS AND DISCUSSION

3.1. Binding Affinity

The results of the molecular docking simulation are displayed in the form of Gibbs free energy values (binding affinity). Table 1 shows the best binding affinity values for each fullerene size in the blind docking and targeted docking approaches. It can be seen that the binding affinity value will be stronger (the value becomes more negative) as the fullerene size increases. In the smallest fullerene C_{20}, the size effect is not very obvious because the molecular size is too small, causing the binding affinity value to remain constant at -8.5 kcal/mol. Meanwhile, for C_{28} to C_{84}, the size of the fullerene will affect the strength of binding affinity.

The binding affinity of various fullerene sizes tends to remain the same in both blind docking and targeted docking approaches. Since fullerenes are closed chains of carbon atoms and without the presence of any functional groups, the bond strength of fullerenes is truly determined by the size or number of carbon atoms available. The bonds that occur between fullerenes and spike glycoprotein molecules are dominated by long-range van der Waals interaction which are above 5.0 Å and classified as a hydrophobic interaction.

3.2. Binding Poses

The binding pose of fullerene on spike glycoprotein in blind docking approach is shown in Figure 3. This figure shows the distribution of fullerene binding on the surface of the spike glycoprotein. It appears that small fullerenes such as C_{20} are widely distributed throughout the surface of the spike glycoprotein. There are five C_{20} inhibition clusters with a maximum distance difference between modes of 2.0 Å. There are five C_{28} inhibition clusters distributed on the surface of the spike glycoprotein. One of the clusters is very dominant and contains 50% of all C_{28} inhibition modes.

A different behavior appears in the C_{60} inhibition mode. Four inhibitory clusters are observed, with one cluster accounting for 60% of the inhibition mode. In C_{78}, five inhibitory clusters are observed distributed over the surface of the spike glycoprotein molecule with no cluster dominating more than 50%. In C_{84} there are four inhibitory clusters, but the distance between each cluster is not as great as the distance between the clusters in C_{20}, C_{28}, C_{60}, and C_{78}. Unlike other fullerenes, the inhibitory mode of C_{84} is

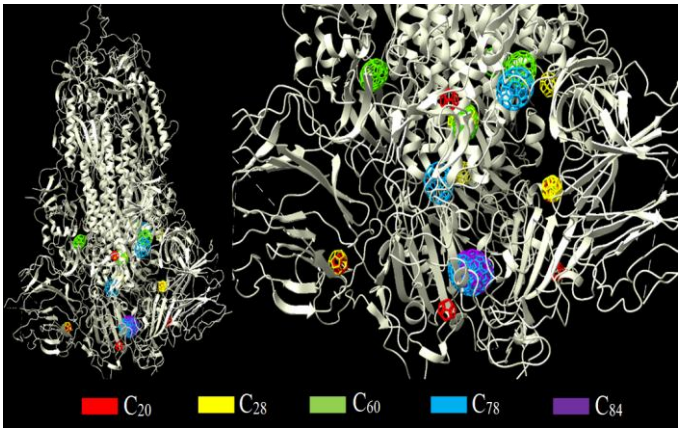

Figure 3. The binding poses of various fullerenes with spike glycoprotein in a blind docking method. The right image is zoomed to focuses on the region around the ACE2 binding site

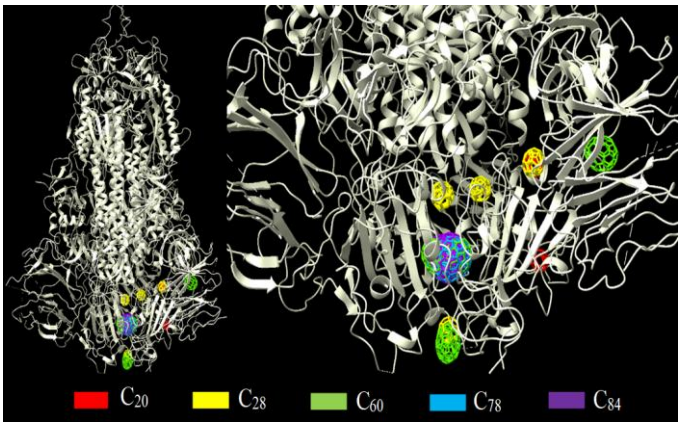

Figure 4. The binding pose of various fullerenes with spike glycoprotein in a targeted docking method

naturally more concentrated closer to the actual interaction pocket of spike glycoprotein.

The binding pose of fullerene on spike glycoprotein in targeted docking approach is shown in Figure 4. The interaction pockets are determined from the active sites of ACE2-binding to the spike glycoprotein. There are four main residues responsible for this binding, namely Arg408, Gly404, Asp405, Val503 [24]. Small fullerenes such as C_{20} and C_{28} are widely distributed throughout the surface of spike glycoprotein, but none of them are in the pocket of ACE2 binding. There are 85% (17 binding modes) of C_{60} located in the ACE2 binding site. Interesting results were found in C_{78} and C_{84}, where 100% of the fullerene binding

Table 1. The best binding affinity of various sizes of Fullerene on Spike glycoprotein in blind and targeted docking approaches

Fullerene	The best binding affinity in a blind docking approach (kcal/mol)	The best binding affinity in a targeted docking approach (kcal/mol)
C_{20}	–8.5	–8.5
C_{28}	–9.4	–9.8
C_{60}	–14.0	–12.3
C_{78}	–15.0	–15.0
C_{84}	–15.9	–15.9

modes are located directly at the ACE2 binding site. This highlights the importance of the fullerene size effect in inhibiting the ACE2 binding site on spike glycoprotein. There are many interaction pockets scattered on the surface of spike glycoprotein. Smaller molecules such as C_{20} and C_{28} are easily trapped in various interaction pockets instead of reaching the targeted interaction pocket. While larger molecules such as C_{60}, C_{78}, and C_{84} will only fall into a larger and suitable interaction pocket, namely the active site of ACE2-binding on the spike glycoprotein. This result is in agreement with [25], where in a mesoscopic scale, the size of molecules play important roles in characterizing the properties and interaction of the molecules. Figure 5 displayed the full inhibition of ACE2 binding sites on spike glycoprotein by C_{78} and C_{84} fullerene as indicated by the pink-colored closed area.

Detailed mesoscopic views of the molecular interactions of different fullerene sizes with spike glycoprotein are shown in Figure 6. The interactions are selected for the best binding affinity in the targeted docking method. As shown in the figure, the binding of fullerene to spike glycoprotein is entirely a hydrophobic interaction (long-range van der Waals interaction type). Only C_{78} and C_{84} completely inhibit and block the interaction between spike glycoprotein and ACE2 of healthy cells in the specific pocket consisting Arg408, Gly404, Asp405, Val503. The high hydrophobicity character of fullerene in this study supports the use of fullerene either as an inhibitor of ACE2 binding site or as a drug carrier through some modifications [26, 27].

To obtain a clearer picture of the interaction mechanism of fullerenes with the active site of ACE2-binding on spike glycoprotein, further studies, including the use of molecular dynamics simulations, are needed in the future. With molecular dynamics simulations, we can see the stability of the complex and the effect of fullerene binding on conformational changes that may occur in the spike glycoprotein structure.

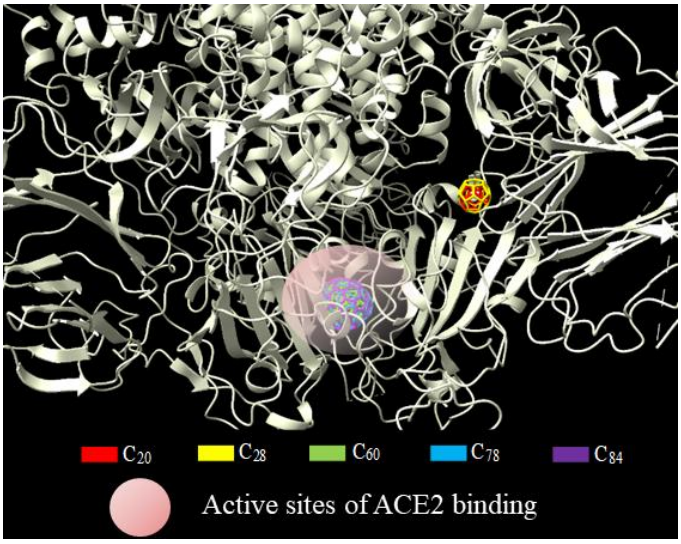

Figure 5. The binding pose of various sizes of fullerenes with spike glycoprotein (selected only for the best binding affinity in a targeted docking method). The pink-covered area refers to binding site of ACE2 on spike glycoprotein

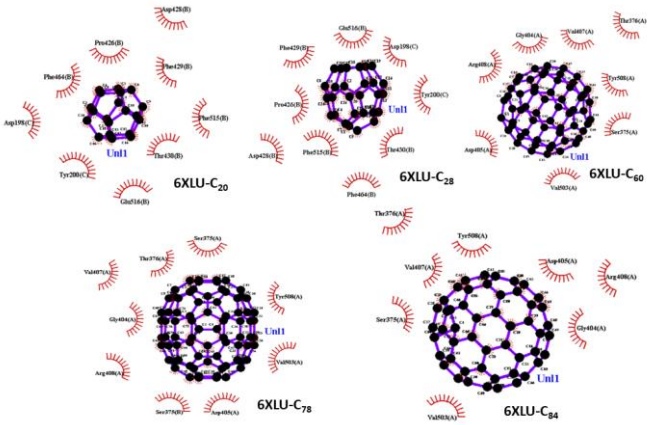

Figure 6. The binding pose of various size of fullerenes with spike glycoprotein (selected only for the best binding affinity) in a targeted docking method

4. CONCLUSION

Fullerene, a low-dimensional material composed of allotropic carbon atoms, has demonstrated the ability to inhibit the binding between the ACE2 and the spike glycoprotein. In order to develop a comprehensive understanding of the nature and type of interactions that occur, it is necessary to adopt a mesoscopic perspective. The molecular docking simulation conducted in this study offers a rationale for the impact of fullerene molecular size on the strength of the interaction and its inhibitory potential against the ACE2 binding site on the spike glycoprotein. It has been demonstrated that small fullerenes have a tendency to be readily captured and engage with amino acids that are distant from the ACE2 binding site. Meanwhile, for larger fullerene molecules, including C_{60}, C_{78}, and C_{84}, bind to amino acids situated in proximity to or directly on the ACE2 inhibition site. The results of the targeted docking simulation revealed that fullerene C_{84} exhibited the strongest binding affinity, with a binding energy of –15.9 kcal/mol. In terms of size, fullerenes C_{78} and C_{84} have the highest potential to block the ACE2 binding site on the spike glycoprotein. The observed interactions are exclusively of the hydrophobic nature, manifesting as long-range van der Waals bonds. Fullerene is a type of carbon atom bond that lacks functional groups. In comparison to other carbon allotropes, such as graphene oxide, fullerene does not exhibit the presence of hydrogen bonds. This distinction is attributed to the closed-shell structure characteristic of fullerene, which contrasts with the open-shell structure observed in graphene oxide and other carbon allotropes.

ACKNOWLEDGMENTS

Authors express gratitude to Directorate of Global Connectivity, IPB University for the funding to disseminate this research.

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