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Molecular Docking Analysis on the Antiviral Effects of Curcumin on SARS-CoV-2

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COVID-19, Curcumin, Anti-inflammatory, Conformation analysis, Molecular docking

Abstract

The structural preferences of curcumin ($C_{21}H_{20}O_6$) molecule were analyzed by MMFF method using Spartan06 program and the most stable geometry was determined. To evaluate the effects of curcumin on SARS-CoV-2, the molecular docking studies have been done on the spike glycoprotein and the apo/holo forms of the SARS-CoV-2 major protease enzyme (Mpro). The binding affinities and binding modes of curcumin targeted to the SARS-CoV-2 proteins were determined. It was discovered that curcumin had binding affinities of -7.3, -5.7, and -7.6 kcal/mol to the apo and holo forms of the major protease enzyme (Mpro) and spike glycoprotein, respectively. The findings suggested that curcumin could be a useful therapeutic agent for COVID-19 treatment.

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1 INTRODUCTION

Turmeric is used extensively as a spice in Asian cultures, it is also used in several traditional treatments.. Curcumin, found predominantly in turmeric, affects multiple signaling pathways and has chemosensitizing and radiosensitizing properties. It is also known to be anti-inflammatory, antioxidant, antimicrobial. In Asia, locals utilize it to treat respiratory illnesses including cough and sore throat [1]. Curcumin is a polyphenolic substance, obtained from turmeric, the rhizome of the plant curcuma longa, has anticancer, anti-HIV, and anti-coagulant activities [2-4]. Additionally, it reduces the growth of cancer cells by preventing nuclear factor kappa B from becoming activated. Curcumin's anti-inflammatory impact is due to its reduction in nuclear factor kappa B, cyclooxygenase 2 (COX-2), and tumor necrosis factor-a (TNF-a) [5,6]. The most obvious symptoms of the Covid-19 virus, which has become a global epidemic, are respiratory symptoms. However, some patients develop serious cardiovascular and renal complications. In order to understand why these symptoms develop and to develop treatment modalities, it is necessary to determine the mechanism of the symptoms caused by this virus. In a theoretical study published in 2020, Zahedipour et al. examined the possible effects of curcumin on virus entry, encapsulation, and viral protease, as well as its influence on cellular signaling pathways. As a result of this research, it has been seen that curcumin modulates the targets of molecules that are effective in binding SARS-CoV-2 in organs such as the liver, cardiovascular system, and kidney. Furthermore, it has been shown that it affects cellular signaling pathways such as inflammation, apoptosis, and RNA replication [7]. The antiviral properties of curcumin and its analogs were discovered in the study done by Noor et al. in 2021. The hydrogen bonding at the protein's binding site makes them potential candidate drugs for the treatment of COVID-19. They showed that hydrazinocurcumin is a promising drug for treating COVID-19 and has immunomodulatory and anti-cytokine therapeutic potential [8].

Curcumin, or the curcumin molecule, is approved by FDA. This molecule has known to have a protective effect on neurological, inflammatory, cardiovascular, lung, metabolic, and liver diseases. It has also been found by scientists to have beneficial effects on important diseases such as cancer. Due to having antiviral activity against many viruses, it has also been thought to have a therapeutic property in this global epidemic disease [9]. SARS-CoV and MERS-CoV are from the same family as this epidemic encodes papain-like proteases. The task of papain-like proteases is to inhibit the immune response. Medications recommended for the treatment of COVID-19 are primarily major protease (Mpro) inhibitors [10]. It has been suggested that curcumin has a potential effect on the Mpro as an inhibitor, and therefore may be a potential therapeutic agent. Some scientists have investigated the effect of interferon in the treatment of COVID-19 by considering this effect in their studies. Viruses such as SARS-CoV, MERS-CoV, and SARS-CoV-2 can inhibit interferon induction in humans. They can stimulate certain regulatory factors to produce a large number of antiviral cytokines. [11]. The PEDV (Porcine Epidemic Diarrhea Virus) pattern of coronavirus reproduction has been demonstrated to be suppressed by curcumin-based therapy [12]. This is accomplished by inducing the host's innate immunity and increasing the production of interferon-induced genes (ISGs) and Vero cell cytokines (IL8 and IL6).Oxidative stress is present in all serious lung injuries [13]. Curcumin can regulate glutathione expression and inhibit the formation of reactive oxygen species and malondialdehyde [14].

In this study the most stable Curcumin structure was revealed and molecular docking simulations were performed with the apo/holo forms of SARS-CoV-2 main protease enzyme (Mpro) and the SARS-CoV-2 spike glycoprotein and their binding affinities and binding modes were determined.

2 MATERIALS AND METHODS

The Spartan06 software [15] and the MMFF method [16] were used to conduct the analysis. The possible binding sites on the surface of the receptor were identified using the CAVER program [17]. Utilizing the AutoDock-Vina program, the molecular docking studies were conducted on the identified active sites [18].

3 RESULTS AND DISCUSSION

3.1 Structure

Figure 1 shows the the three lowest energy conformers of curcumin obtained by conformational analysis, and in Table 1 the relative energies of these conformers, are given.

Table 1. The relative energies of three lowest energy conformers of curcumin, obtained by conformational analysis

Conformers	*Relative energy (kj/mol)*
(I)	0
(II)	0.68
(III)	1.15

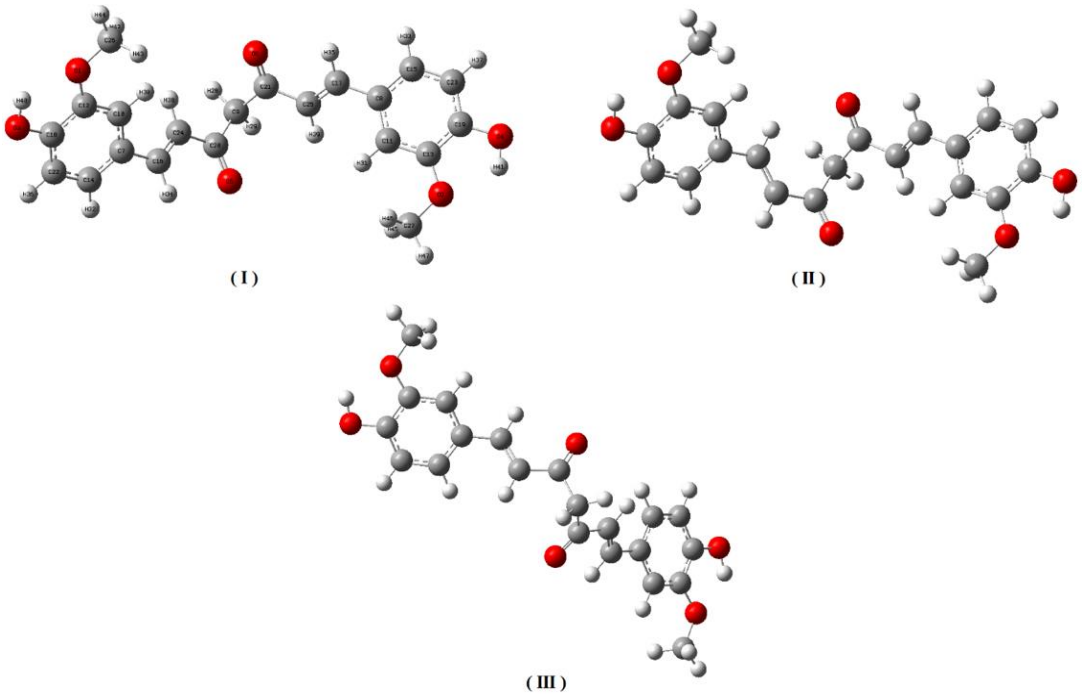

Figure 1. The three lowest energy conformers of the Curcumin, obtained by conformational analysis

3.2 Molecular Docking

Molecular docking analysis in target proteins the apo/holo forms of main protease enzyme (Mpro) of SARS-CoV-2 and the spike glycoprotein were undertaken in order to assess the anti-proliferation impact of curcumin.

The crystal structure of spike glycoprotein (PDB ID: 6VXX), apo form of Mpro(PDB ID: 6M03) and holo form of Mpro(PDB ID: 6LU7) was acquired with referring to the protein database [19-21] and the docking analysis of curcumin was carried out using AutoDockVina [18]. The most active site was determined by docking simulations of curcumin to the apo/holo forms of SARS-CoV-2 main protease enzyme (Mpro) and the SARS-CoV-2 spike glycoprotein. Figure 2 depicts curcumin docked in the most active site of the main protease enzyme (Mpro) and the SARS-CoV-2 spike glycoprotein in three dimensions. Figures 2-4 show the interactions between curcumin and the apo/holo forms of SARS-CoV-2 main protease enzyme (Mpro) and the SARS-CoV-2 spike glycoprotein complexes.

The interactions between the apo form of SARS-CoV-2 main protease enzyme (Mpro) and curcumin (shown in Figure 2) are as follows:

2.92 Å long hydrogen bond with Gln110; 2.42 Å long hydrogen bond with Thr111; 2.73 Å long unfavorable acceptor-acceptor interaction with Ile249; 5.4 Å long Pi-alkyl interaction with Pro252; 5.66 Å long Pi-Pi T-shaped interaction with Phe294; 4.89 Å long Pi-alkyl interaction with Val297.

As a result of docking simulations the binding affinity of curcumin with the apo form of SARS-CoV-2 main protease enzyme (Mpro) is found to be -7.3 kcal/mol.

The binding affinity of curcumin docked with the holo form of SARS-CoV-2 main protease enzyme (Mpro) is found to be -5.7 kcal/mol. Fig 3 shows the 3D docking representations of the curcumine in the active site of holo form of Mpro. The following interactions between the holo form of main protease enzyme (Mpro) and curcumin are revealed:

With Leu286, a 4.85 Å long Pi-alkyl interaction and a 5.42 Å long intramolecular Pi-Pi T-shaped interaction.

The docking simulations of curcumin with SARS-CoV-2 spike glycoprotein revealed the binding affinity as -7.6 kcal/mol. As seen in Figure 4, SARS-CoV-2, the interactions between spike glycoprotein and curcumin are 2.26 Å long hydrogen bond with Thr114 and 3.75 Å long carbon hydrogen bond with Gly199.

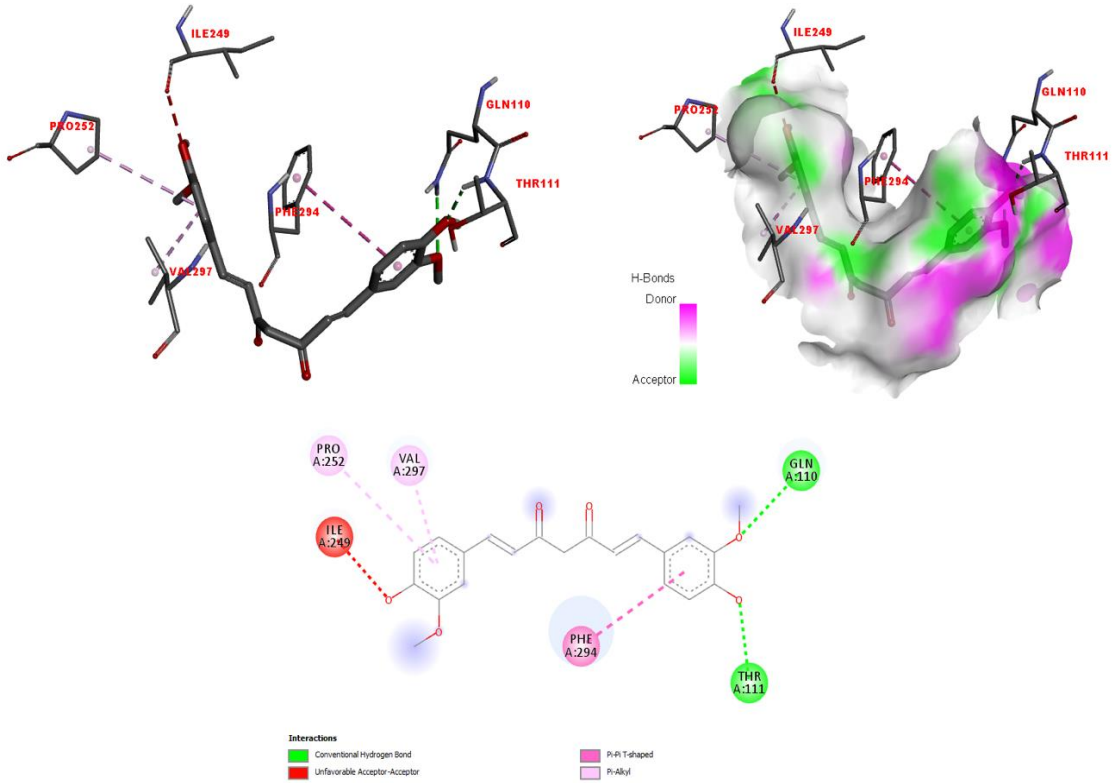

Figure 2. The 3D docked representations of the most stable conformer of curcumin in the active site of apo form of main protease enzyme (Mpro) (ΔG = -7.3 kcal/mol)

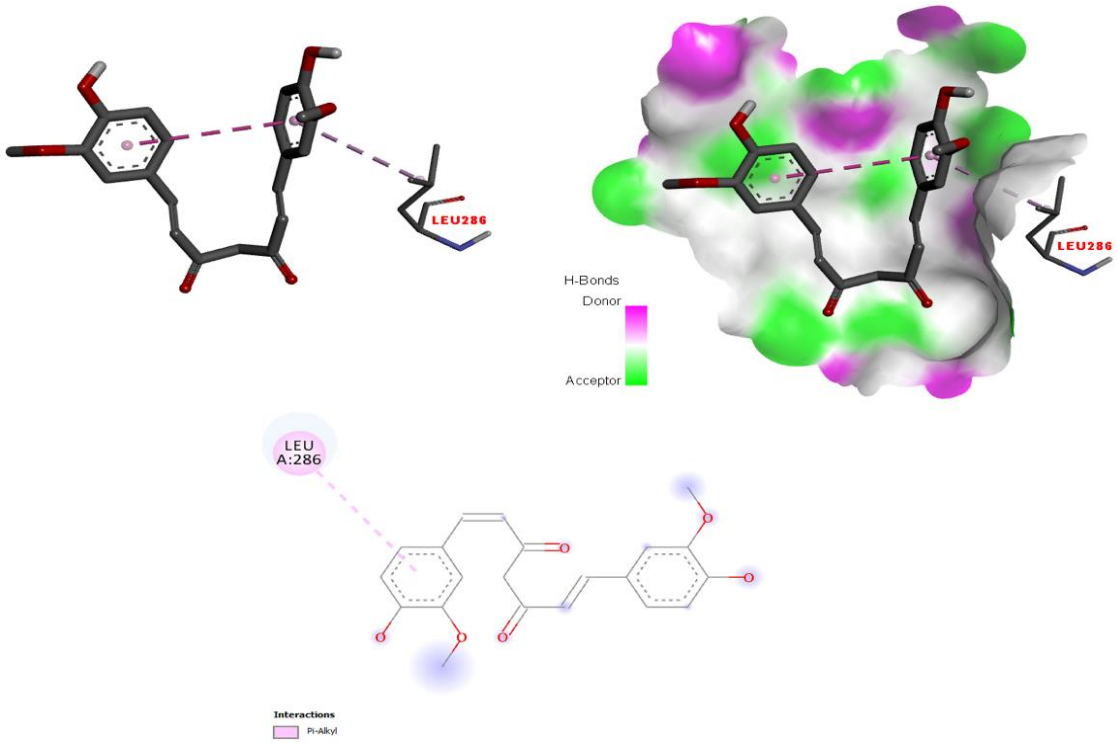

Figure 3. The most stable conformer of curcumin in the active site of holo form of COVID-19's main protease enzyme (Mpro) (-5.7 kcal/mol) in 3D docked representations

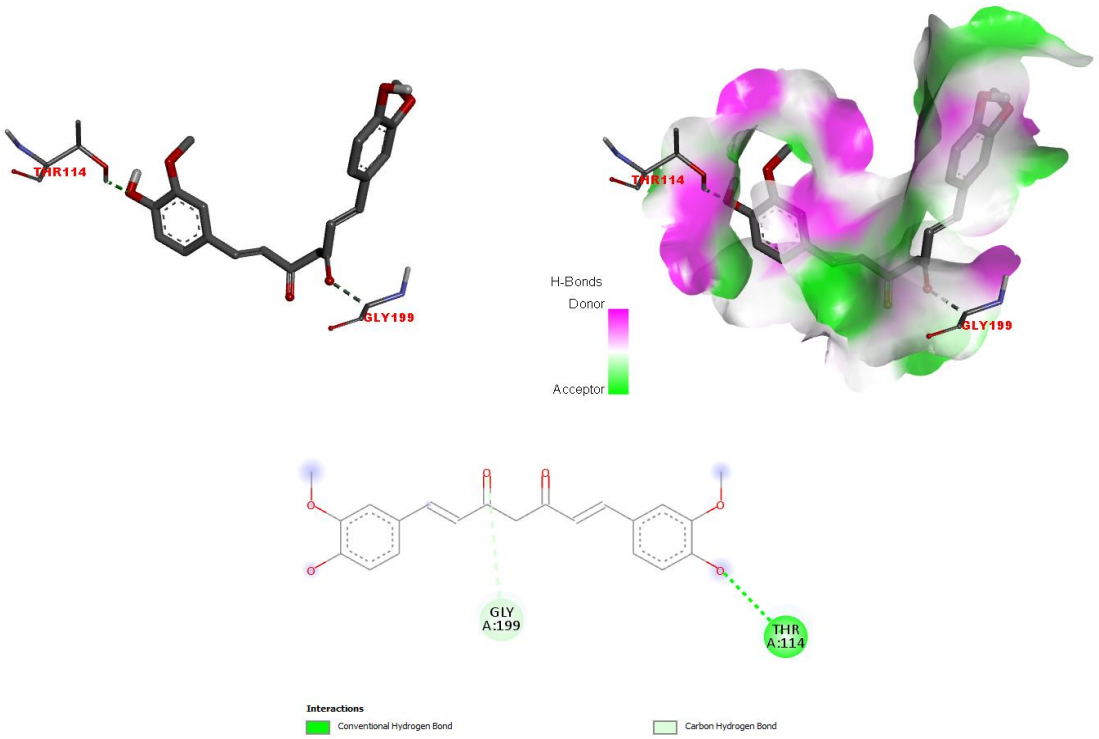

Figure 4. The Molecular docking diagram of curcumin into the active site of the SARS-CoV-2 spike glycoprotein. The interactions are shown (binding affinity -7.6 kcal/mol)

4 CONCLUSION

Since protein-ligand interactions are important in drug design, conformational analysis of curcumin was performed using MMFF to obtain the most stable conformer. Afterward, the docking simulations were performed to assess the title molecule's biological activity using its most stable conformer. The inhibitory activity of curcumin was studied by docking it with both the apo/holo forms of SARS-CoV-2 main protease enzyme (Mpro) and the spike glycoprotein. The binding affinities of curcumin to the apo/holo forms of main protease enzyme (Mpro) and spike glycoprotein were -7.3, -5.7, and -7.6 kcal/mol, respectively. In this section, the importance and effects of the study should be clearly stated. In the conclusion part, the results should not be repeated.

Author Contributions

Aliye Demet DEMIRAG: Conceptualization, Methodology, Software, Investigation, Writing - Original Draft, Writing - Review & Editing.
Sefa CELIK: Conceptualization, Methodology, Software, Investigation, Writing - Original Draft, Writing - Review & Editing, Supervision.
Aysen E. OZEL: Conceptualization, Methodology, Software, Investigation, Writing - Original Draft, Writing - Review & Editing, Supervision.
Sevim AKYUZ: Conceptualization, Methodology, Software, Investigation, Writing - Original Draft, Writing - Review & Editing, Supervision.
All authors read and approved the final manuscript.

Conflict of interest

No conflict of interest was declared by the authors.

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