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IN SILICO INVESTIGATION OF THE EFFECTS OF CURCUMINOIDS ON THE SPIKE PROTEIN OF THE OMICRON VARIANT OF SARS COV-2

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Curcumin, the dried ground rhizome of *Curcuma longa Linn*., is known as zerdeçal in Turkish, Haldi in Hindi, turmeric in English, and ukon in Japanese. Many biological active properties of this plant, which is widely used in Asian medicine, are known. Commercially known curcumin, on the other hand, contains 77 % of curcumin, along with demetoxycurcumin and bis-demethoxycurcumin. Curcumin and its derivatives belong to the group of diarylheptanoids. The effects of curcumin and its two other derivatives, which have been the subject of many studies thanks to their unique therapeutic ability, on the Spike protein of the SARS-CoV-2 Omicron variant, which caused the pandemic to be declared at the beginning of 2020, were examined within the scope of this study. According to the results obtained, the binding energies of curcumin, demetoxycurcumin, and bis-demethoxycurcumin to the Spike protein of the SARS-CoV-2 Omicron variant are -6.6, -5.5, and -6.0 kcal/mol, respectively. It was determined that curcumin, demetoxycurcumin, and bis-demethoxycurcumin interact with the Spike protein of the SARS-CoV-2 Omicron variant through hydrogen bonding, electrostatic interactions, and hydrophobic interactions. These biologically active molecules are thought to be agents that can moderately inhibit the Spike protein of the SARS-CoV-2 Omicron variant. In addition, the pharmacokinetic and toxicological properties of these three compounds were calculated with the help of online databases.

Keywords: Curcumin, SARS CoV-2, Molecular Docking, ADMET

INTRODUCTION

Curcumin is a polyphenol derived from herbal medicine and the dietary spice turmeric. It has various anti-inflammatory and anti-cancer properties following oral or topical administration. For centuries, curcumin has been used in some medicinal preparations or as a food coloring agent. In recent years, extensive in vitro and in

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vivo studies have suggested that curcumin has anticancer, antiviral, anti-arthritic, anti-amyloid, antioxidant, and anti-inflammatory properties[4]. Due to this unique biological active potential of curcumin, its effects on the coronavirus disease, which has affected the whole world since December 2019, are also a matter of curiosity. In this context, in this study, we examined the effects of curcumin against the SARS-CoV-2 Omicron variant with the help of Molecular Docking studies.

MATERIALS AND METHODS

Molecular Docking Studies

Autodock Vina[5] program was used to calculate the binding energies of the complexes. The PDB file of the spike protein of the SARS-CoV-2 Omicron variant (PDB Code: 7T9J) [6]) has been downloaded from the RCSB Protein Data Bank (https ://www.rcsb.org). Files of ligands with .pdb extension were recorded using a crystallographic information file (.cif). The structures and structures of curcuminoids are given in Figure 1. The enzyme, which will be modeled, was first optimized with the help of BIOVA Discovery Studio Visualizer 2021[7] program. With the AutoDockTools 1.5.7 program, the enzyme interacted with curcuminoids in the active site and ligand-protein interactions were visualized. BIOVA Discovery Studio Visualizer 2021 program was used in visualization studies.

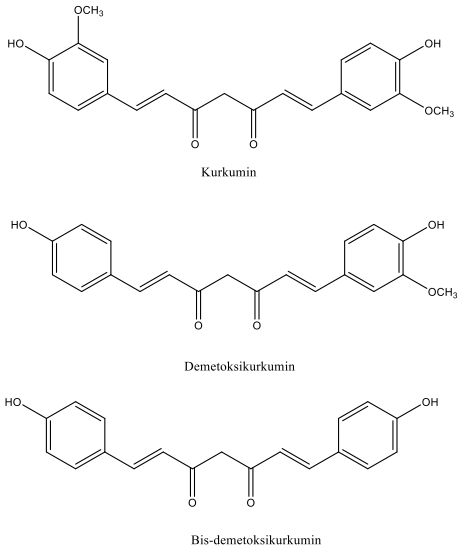

Figure 1. The structures of curcuminoids

Determination of Pharmacokinetic and Toxicological Properties

SwissAdme[8] was used to determine the absorption (bioavailability), distribution, metabolism, and excretion properties of the compounds, and Protox-II [9] online database was used to determine the toxicological properties.

Fındıngs and conclusıon

In recent years, there have been many studies conducted with Molecular Docking in computer-aided drug design. In this study, Molecular Docking studies were performed to examine the interactions of the spike protein of the Omicron variant of SARS-CoV-2 with curcuminoids and the binding energies were calculated. The binding energies (ΔG) of curcumin, demetoxycurcumin, and bis-demethoxycurcumin with the spike protein are -6.1, -5.5, and -6.0 kcal/mol, respectively. According to the results obtained, curcumin and bis-

demethoxycurcumin have the best binding affinity. Curcumin binds with the spike protein through hydrogen bonding with gln779 and val772, π-sigma with gln784, amide-π interactions with asp775, alkyl with ala1026 and val772, and alkyl interactions with lys776 (Figure 2). Demethoxycurcumin is linked with spike protein via hydrogen bonding with thr732 and his1058, carbon-hydrogen bond with asp867, π-sigma with his1058, and π-alkyl interactions with pro1057 and pro863 (Figure 3). Bis-demethoxycurcumin interacts the active site of the spike protein through hydrogen bonding with lys776, val772, and gln779 , π-sigma with gln784, amide-π with asp775 and π-alkyl interactions with lys776 and lys776 (Figure 4). When the hydrogen bond interactions were examined, the average hydrogen bond lengths between curcumin, demetoxycurcumin, and bis-demethoxycurcumin with the mentioned amino acids were determined as 2.69 Å, 2.43 Å, and 2.47 Å, respectively. Accordingly, it can be said that demetoxycurcumin and bis-demethoxycurcumin make stronger hydrogen bonds with the active site of the spike protein. When the binding energy is evaluated in terms of hydrogen bond lengths and interaction types, it is thought that the binding affinity of curcumin to spike protein is higher.

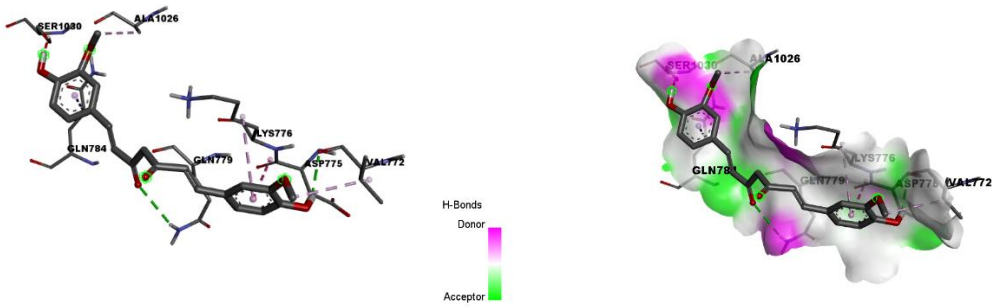

Figure 2. Two-dimensional interactions of Curcumin with amino acids in the active site of the Spike protein of the Omicron variant of SARS CoV-2 (left), and hydrogen bond interactions between Curcumin and the active site of the Spike protein of the Omicron variant of SARS CoV-2.

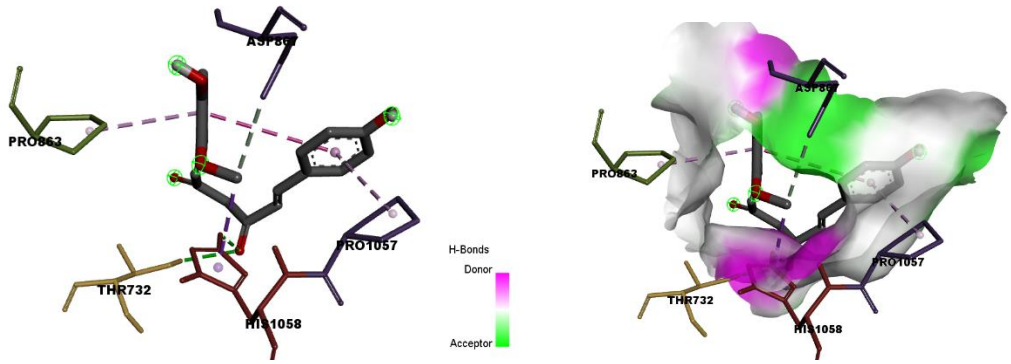

Figure 3. Two-dimensional interactions of Demethoxycurcumin with amino acids in the active site of the Spike protein of the Omicron variant of SARS CoV-2 (left), and hydrogen bond interactions between Demethoxycurcumin and the active site of the Spike protein of the Omicron variant of SARS CoV-2.

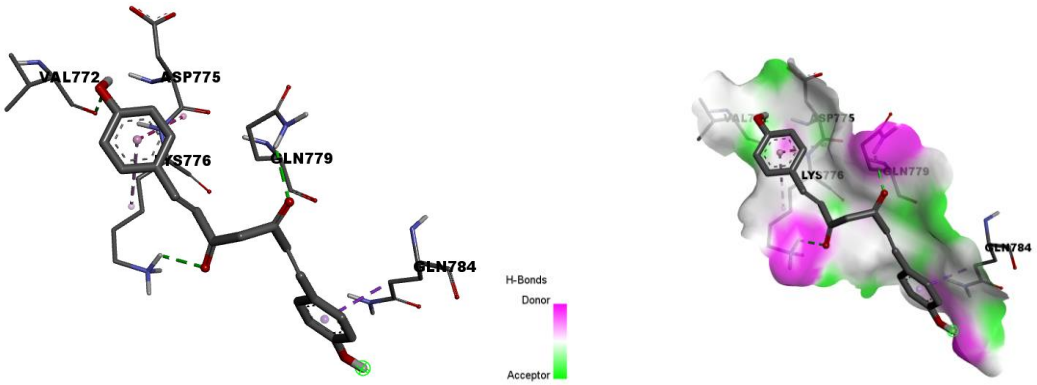

Figure 5. Two-dimensional interactions of bis-demethoxycurcumin with amino acids in the active site of the Spike protein of the Omicron variant of SARS CoV-2 (left), and hydrogen bond interactions between bis-demethoxycurcumin and the active site of the Spike protein of the Omicron variant of SARS CoV-2.

Pharmacokinetic and Toxicological Properties

The pharmacokinetic and toxicological properties of curcuminoids are given in Table 1. All three compounds were found to be compatible with Lipinski's rule of five. When evaluated in terms of its toxicological properties, it was determined that the bis-demethoxycurcumin compound was less toxic and its toxicity class was higher (5).

According to the data obtained, curcumin, demetoxycurcumin, and bis-demethoxycurcumin exhibit good binding affinity toward the active sites of the spike protein. The best binding energy value is between curcumin and spike protein. Therefore, when the interactions of the compounds with the spike protein are evaluated in terms of the structure-activity relationship, it can be said that more promising results are obtained for curcumin. The compounds interact with the spike protein of the Omicron variant of SARS CoV-2 via electrostatic, hydrogen bonding, and hydrophobic interactions. These compounds can be used for therapeutic purposes against coronavirus disease. Because it has the potential to exhibit an antagonist effect by interacting with the amino acids in the active region of the spike protein of the coronavirus. It is suggested that the effects of curcumin and its derivatives against the Omicron variant of SARS CoV-2 should be supported by further studies.

Table 1. Pharmacokinetic and toxicological properties of curcumin, demetoxycurcumin, and bis-demethoxycurcumin.

Properties	**Curcumin**	**Demethoxycurcumin**	**Bis-demethoxycurcumin**
Molecular Weight[a]	368,38 g/mol	338,35 g/mol	308,33 g/mol
Atom number	47	43	42
Heavy atom number	27	25	23
Rotatable Bonds	8	7	6
H-Bond acceptor	6	5	4
H-Bond donor	2	2	2
Molar refractivity	102.80	96.31	89.82
TPSA (Å^2)	93.06	83.83	74.60
Log $P_{o/w}$	3.27	2.78	1.75
GI absorption	High	High	High

BBB permeability	No	No	Yes
P-gp substrate	No	No	No
CYP1A2 inhibitor	No	Yes	Yes
CYP2C19 inhibitor	No	No	No
CYP2C9 inhibitor	Yes	Yes	Yes
CYP2D6 inhibitor	No	No	No
CYP3A4 inhibitor	Yes	Yes	Yes
Log K_p (cm/s)	-6.28	-6,01	-5,87
Lipinski	Compatible, 0 incompatibility	Compatible, 0 incompatibility	Compatible, 0 incompatibility
Toxicity Class [b]	4	4	5
Predicted LD_{50}	2000 mg/kg	2000 mg/kg	2560 mg/kg
Hepatotoxicity	Inactive	Inactive	Inactive
Carcinogenicity	Inactive	Inactive	Inactive
Immunotoxicity	Active	Active	Inactive
Mutagenicity	Inactive	Inactive	Inactive
Cytotoxicity	Inactive	Inactive	Inactive
MMP[b]	Active	Active	Active
[a]Molecular weight unit g/mol [b]Toxicity class 1-toxic; 6-non-toxic [c]MMP: Mitochondrial membrane potential			

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