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Evaluation of Receptor Relationships of Some Drugs Used in the Treatment of COVID-19 by Modeling Studies

COVID-19 Tedavisinde Kullanılan Bazı İlaçların Reseptör İlişkilerinin Modelleme Çalışmaları ile Değerlendirilmesi

[1]Tuğçe KARADUMAN, [1]Mehmet KARATAŞ, [2]Merve ÖZCAN TÜRKMEN

[1]Department of Molecular Biology and Genetics, Faculty of Science and Letters, Aksaray University, Aksaray, Turkiye
[2]Department of Molecular Biology and Genetics, Faculty of Science, Necmettin Erbakan University, Konya, Turkiye

Tuğçe Karaduman: https://orcid.org/0000-0003-0728-0968
Mehmet Karataş: https://orcid.org/0000-0002-1882-6500
Merve Özcan Türkmen: https://orcid.org/0000-0003-2064-4519

ABSTRACT

Objective: It is important to investigate the interactions of drugs used in the treatment process of COVID-19 with cellular mechanisms. In this study, the aim was to investigate the interactions of Dexamethasone, Favipiravir, and Hydroxychloroquine drugs used in the treatment of COVID-19 with the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2).

Materials and Methods: Within the scope of the study, firstly, 3-dimensional structures of receptors and drug molecules were formed. Then the interactions of each of the receptor and drug molecules at the binding site were examined by molecular docking studies, which is a computer-aided drug design method, and their binding affinities were evaluated.

Results: As a result of the analyses, it was determined that the drug named Hydroxychloroquine has the highest and the drug called Dexamethasone has the lowest binding affinity for all three receptors. In addition, it has been determined that Dexamethasone develops inappropriate interactions with ER and HER2 receptor active site amino acids.

Conclusions: In this study, preliminary data on how receptor interactions can occur when normal individuals and breast cancer patients use Dexamethasone, Favipiravir, and Hydroxychloroquine are presented.

Keywords: Breast cancer, COVID-19 drugs, molecular docking, receptor

ÖZ

Amaç: COVID-19 tedavi sürecinde kullanılan ilaçların hücresel mekanizmalarla etkileşimlerinin araştırılması önemlidir. Bu çalışmada, COVID-19 tedavisinde kullanılan Deksametazon, Favipiravir ve Hidroksiklorokin adlı ilaçların östrojen reseptörü (ER), progesteron reseptörü (PR) ve insan epidermal büyüme faktörü reseptörü-2 (HER2) ile etkileşimlerinin belirlenmesi hedeflenmiştir.

Materyal ve Metot: Çalışma kapsamında, reseptörler ve ilaç moleküllerinin ilk olarak 3-boyutlu yapıları oluşturulmuş, ardından reseptör ve ilaç moleküllerinin her birinin bağlanma bölgesindeki etkileşimleri bilgisayar destekli ilaç tasarım yöntemi olan moleküler kenetlenme çalışmaları ile incelenmiş ve bağlanma afiniteleri değerlendirilmiştir.

Bulgular: Yapılan analizler sonucunda, Hidroksiklorokin adlı ilacın her üç reseptöre de en yüksek bağlanma afinitesi gösteren ilaç olduğu ve Deksametazon adlı ilacın ise reseptörlere en düşük afinite ile bağlandığı belirlenmiştir. Ayrıca, Deksametazonun ER ve HER2 reseptör aktif bölge aminoasitleri ile uygun olmayan interaksiyonlar geliştirdiği tespit edilmiştir.

Sonuç: Bu çalışmada, normal bireyler ve meme kanseri hastalarının Deksametazon, Favipiravir ve Hidroksiklorokin adlı ilaçları kullanması durumunda reseptör etkileşimlerinin nasıl olabileceğine ilişkin ön veriler sunulmuştur.

Anahtar Kelimeler: COVID-19 ilaçları, meme kanseri, moleküler kenetlenme, reseptör

Sorumlu Yazar / Corresponding Author:
Tugce Karaduman, PhD,
Department of Molecular Biology and Genetics, Faculty of Science and Letters, Aksaray University, 68100 Aksaray, Turkiye.
Tel: +90-(382) 288 2217
E-mail: tugcekaraduman@aksaray.edu.tr

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INTRODUCTION

COVID-19 which is regarded as a pandemic and a global threat to public health, emerged in Wuhan, China in December 2019 and has spread all over the world as of March 2020.[1] As a result of understanding SARS-CoV-2 virology, current and effective pharmacological treatments are being investigated against COVID-19.[2] Dexamethasone (USA, PA), Favipiravir (Toyama Chemical, Japan) and Hydroxychloroquine (USA, Salisbury) are among the potential therapeutic agents used in COVID-19 treatment.[3]

Dexamethasone is a synthetic glucocorticoid used in conditions with inflammation such as lupus, rheumatoid arthritis, acute gouty arthritis and also used in allergic conditions such as allergic rhinitis, bronchial asthma, contact and atopic dermatitis.[4] In addition to these therapeutic indications, it is also recommended for the treatment of nausea and vomiting that may occur in the post-surgical period. Furthermore, it is a drug that is effective in the post-surgical period due to its effect on accelerating the wound healing process and consequently shortening the duration of hospital stay.[5]

Favipiravir is an antiviral drug that is approved in Japan.[6] Favipiravir triphosphate is a purine analog which is a competitive inhibitor of RNA-dependent RNA polymerase.[7] It has been used in many countries to treat new viral infections, including Ebola and Lassa. As an antiviral drug, Favipravir is authorized for use in the treatment of COVID-19 under emergency use recommendations in several countries, including Japan, Russia, and India.[8]

Hydroxychloroquine has been shown that SARS-CoV-2 has affinity for the protease enzyme and Hydroxychloroquine inhibits SARS-CoV-2 more effectively than Chloroquine.[9] It also considered that it accumulates in acidic environments such as lysosome and inflamed tissues, making the content basic and inhibiting viral replication.[10] It has also been predicted that Hydroxychloroquine may reduce the release of IL-1, IL -6, TNF and IFN-γ from mononuclear cells.[10,11]

Estrogen receptor (ER) and progesterone receptor (PR) are hormone receptors which are found in breast cells and receive hormone signals that result in cell growth. Similarly, positive status of breast carcinoma for human epidermal growth factor receptor-2 (HER2) indicates that the *HER2* gene produces too much HER2 protein that acts as a receptor on the cell surface, helping the cells grow and divide. Receptor studies such as ER, PR, and HER2 are routinely performed in breast cancer. This not only helps in the prognosis of the tumor, but also helps to determine the treatment strategy.[12]

This study was carried out to understand in advance how the receptor pathway may be affected *in vitro* if normal individuals and breast cancer patients have COVID-19 and use these drugs.

MATERIALS AND METHODS

Ethics Committee Approval: Since this article is a bioinformatics analysis, it does not contain any studies with human or animal subjects performed by any of the authors, there is no need for ethics committee approval.

***Preparation of Target Receptors*:** In the molecular docking study, protein database (PDB) data were used in the process of obtaining the required ER (Estrogen receptor), PR (Progesterone receptor) and HER2 (Human epidermal growth factor receptor 2) receptors. Obtained proteins, PDB IDs, resolutions and 3D structures are shown in Table 1. Water molecules in the receptors were removed, polar hydrogens were added, and the receptors were made ready for molecular docking using the Discovery Studio (Germany, 2021) program.

***Preparation of Ligands*:** The drug molecules to be docked were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) (Table 1). For the energy optimization of the molecules, the number of updates in 50 steps, MMFF94 (Merck Molecular Force Field 94)[13] and the steepest descent algorithm[14] were selected in the Avogadro (version 1.2.0) software and energy optimizations of the molecules were made so that the ligands were ready for molecular docking.

Molecular Docking: For the docking simulations of drug molecules to ER, PR and HER2 receptors, 3-way multi-readout was performed with Lamarc Genetic Algorithm[15] using AutoDock Vina (Version 1.1.2; USA California) software. As insertion sites, the ligands were removed from the receptors which are obtained with the ligands in the PDB data, and insertion simulations were made on the active sites. Images were created using Discovery Studio Visualizer (Germany, 2021) software.

RESULTS

Dexamethasone, Favipiravir and Hydroxychloroquine molecules, whose molecular docking was investigated, have developed interactions with the active sites of ER, PR and HER2 receptors. In these interactions, conventional hydrogen bonds, carbon hydrogen bonds, halogen bonds, van der Waals interactions, pi-sigma, pi-alkyl, and alkyl interactions were found. Aside from these positive interactions, it was also shown that inappropriate binding occurs between the ligand and active site of receptor. Amino acids with interactions, interaction types and bond distances are shown in Table 2.

Dexamethasone molecule, which improperly binds to ALA-350 amino acid with low affinity (4.6 kcal/mol) in the estrogen receptor (ER) active site, forms a conventional hydrogen bond with CYS-530 amino acid, while developing van der Waals interaction

Table 1. 3D structures and PDB database information of receptors, ligands and their properties.

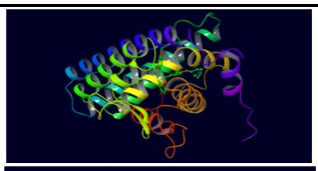
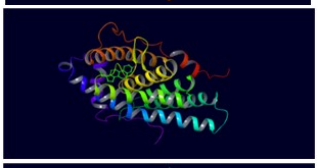
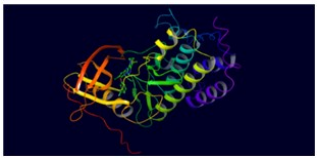
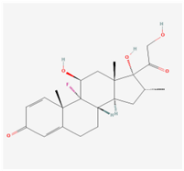
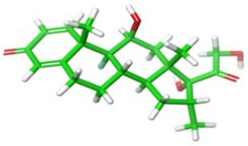
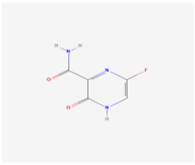
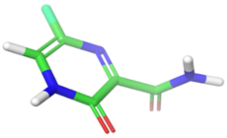
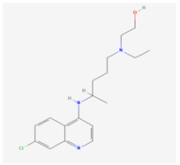
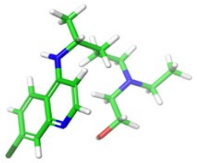
Receptor Name	PDBID	Resolution (Å*)	Method	3D**
ER	1XPC#	1,60 Å	X-Ray Diffraction	
PR	1A28#	1,80 Å	X-Ray Diffraction	
HER2	3PP0#	2,25 Å	X-Ray Diffraction	
No	Ligand	PubChem CID	Molecular Weight (g.mol-1)	2D** 3D***
1	Dexame-thasone	5743##	392.5 g/mol	 
2	Favipira-vir	492405##	157.1 g/mol	 
3	Hy-droxychl oroquine	3652##	335.9 g/mol	 

Table 2. Results of docking of drugs to receptor active sites.

Receptor	Ligands	Binding Energy (kcal/mol)	Number of Hydrogen Bonds	Amino Acid Residue
ER	Dexamethasone	4.6	1	ALA 350 - CYS 530
ER	Favipiravir	-4.9	0	LEU 346 - LEU 387 - ALA 350
ER	Hydroxychloroquine	-6.4	1	MET 343 - LEU 346 - MET 388 - PHE 404 - MET 421 - LEU 428 - HIS 524 - LEU 525
PR	Dexamethasone	-1.0	1	ASN 719 - VAL 760
PR	Favipiravir	-5.2	1	LEU 718 - PHE 778
PR	Hydroxychloroquine	-6.3	3	LEU 718 - MET 759 - MET 909
HER2	Dexamethasone	-0.6	0	VAL 734 - LEU 852
HER2	Favipiravir	-6.1	5	VAL 734 - ALA 751- LYS 753 - LEU 796 - THR 798 - THR 862 - ASP 863
HER2	Hydroxychloroquine	-5.1	0	VAL 734 - ALA 751 - LEU 852

with MET-388 amino acid. Favipiravir molecule binds to estrogen receptor (ER) active site with higher affinity (-4.9 kcal/mol) and more interaction compared to Dexamethasone molecule. Favipiravir molecule which made van der Waals interactions with five amino acids, also performed pi-sigma, pi-alkyl and halogen interactions. The hydroxychloroquine molecule also binds to the estrogen receptor (ER) active site with higher affinity (-6.4 kcal/mol) and more interaction compared to Dexamethasone molecule (Figure 1).

Dexamethasone molecule, which binds to the progesterone receptor (PR) active site with low affinity (-1.0 kcal/mol) compared to other molecules, made conventional hydrogen bond with ASN-719 and carbon hydrogen bond with VAL-760 amino acid. In addition, the Dexamethasone molecule carried out numerous van der Waals interactions in the PR active site. Favipiravir molecule binds to the PR active site with higher affinity (-5.2 kcal/mol) and with different interactions than Dexamethasone molecule. Among these interactions, there are conventional

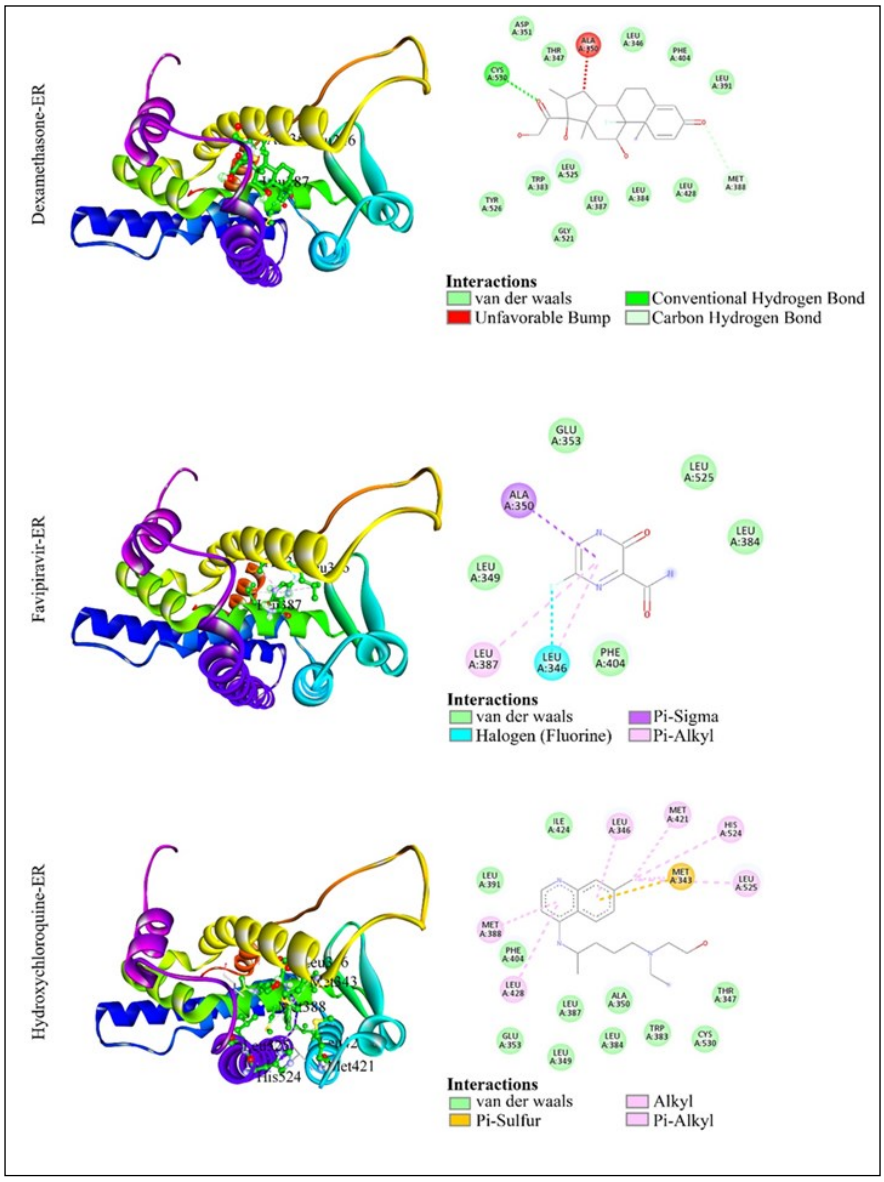


Figure 1. 3D and 2D images of the interactions of Dexamethasone, Favipiravir and Hydroxychloroquine molecules with ER, respectively.

hydrogen bonds, van der Waals interactions, and pi-pi interactions. Favipiravir molecule and Hydroxychloroquine molecule, which binds to the PR receptor active site with higher affinity (-6.3 kcal/mol) than Dexamethasone molecule, have developed van der Waals and pi-pi interactions (Figure 2).

Of these inappropriate bonds, the binding affinity of the Dexamethasone molecule (-0.6 kcal/mol), which interacts only with the HER2 receptor, was found to be lower than the other molecules, and that it showed inappropriate interactions with the amino acids VAL-734 and LEU-852. The Favipiravir molecule, which interacts with HER2 receptor, developed more proper interactions compared to Dexamethasone molecule, and binds to the receptor active site with higher affinity (-6.1 kcal/mol). Favipiravir molecule developed conventional hydrogen bonds with 3 amino acids at the HER2 receptor active site and showed van der Waals interaction with 5 amino acids. Also, the Hydroxychloroquine molecule was bound to HER2 receptor active site with proper interactions and higher affinity (-5.1 kcal/mol) compared to Dexamethasone molecule (Figure 3).

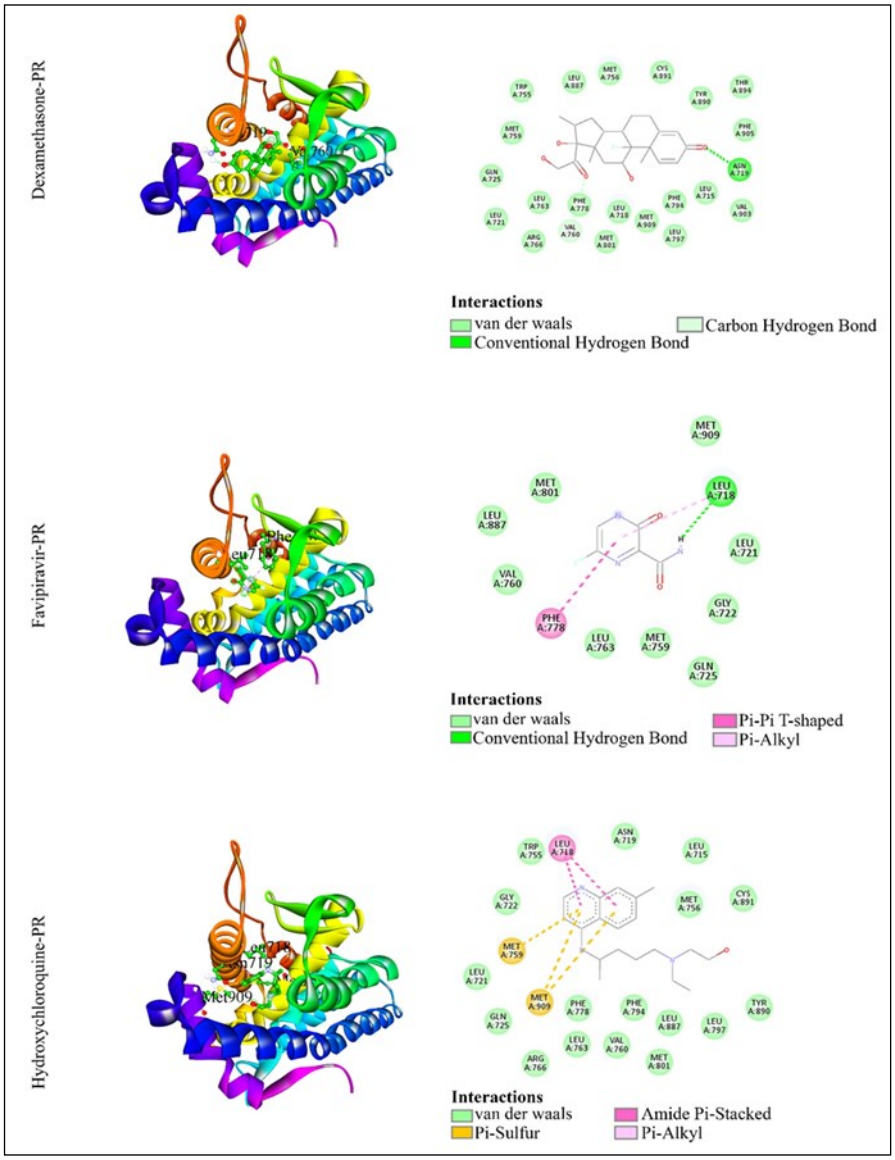


Figure 2. 3D and 2D images of the interactions of Dexamethasone, Favipiravir and Hydroxychloroquine molecules with PR, respectively.

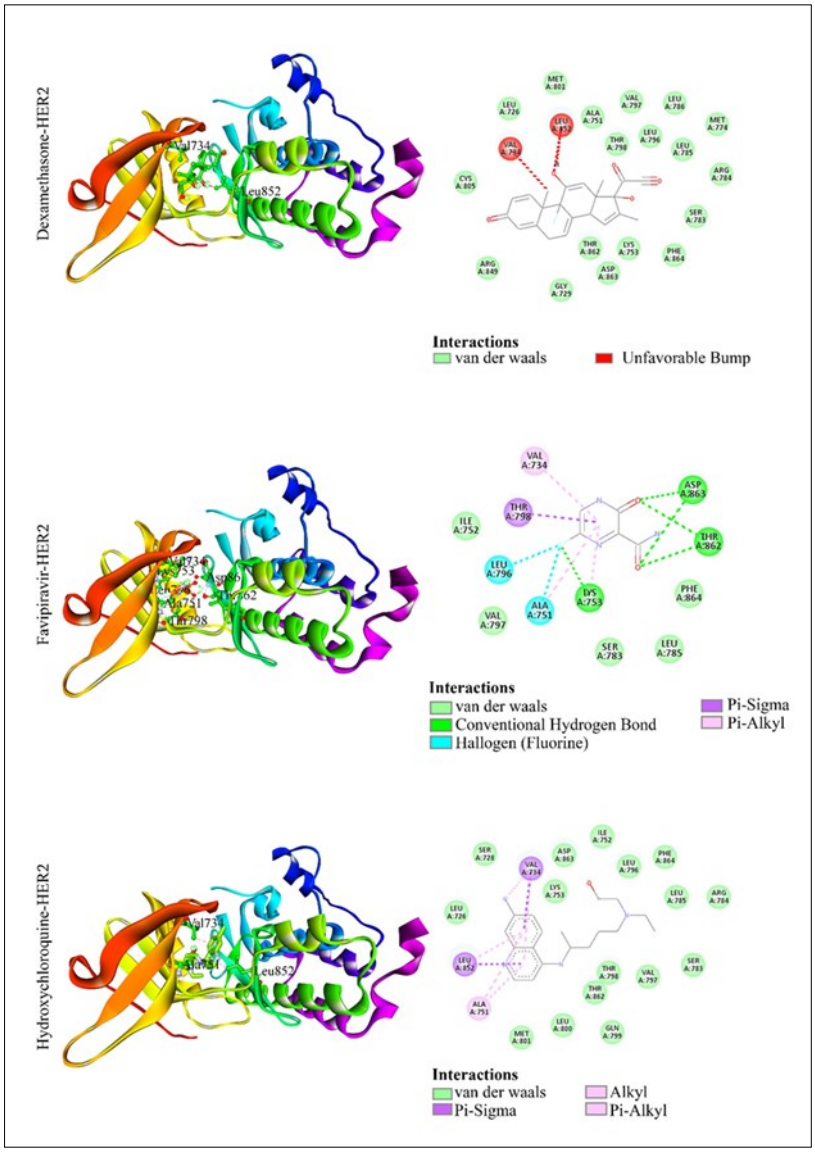


Figure 3. 3D and 2D images of the interactions of Dexamethasone, Favipiravir and Hydroxychloroquine molecules with HER, respectively.

DISCUSSION AND CONCLUSION

The studies to determine the most effective drugs in COVID-19 treatment process are still ongoing, and the effectiveness of these drugs are being investigated with computer-aided drug design methods which have been progressing along with developing computer technologies .[16,17] Molecular docking is one of the main constituents of these techniques and widely used to understand the interactions between ligands and target proteins, allowing us to predict the structure of the ligand-receptor complex.[17–19] In this sudy, molecular docking studies were performed to analyze the interactions of drugs that are Dexamethasone, Favipiravir and Hydroxychloroquine which are used in the treatment of COVID-19, with ER, PR and HER2 receptors. According to the results, hydroxychloroquine binds to all three of these receptors with the highest affinity, while Dexamethasone binds to the active sites of ER and HER2 receptors with the lowest affinity among these three drugs.

Molecular docking studies using either of these drugs in previous studies in the literature have generally investigated the binding of drugs to a SARS-CoV-2 protein.[18,20-22] Celik et al. analyzed the interactions of both hydroxychloroquine and chloroquine with proteins of SARS-CoV-2 such as SARS-CoV-2 RNA polymerase, main protease and spike proteins which play an important role in the structure, survival, reproduction, attachment and survival of the SARS-CoV-2 virus.[20] They showed that neither hydroxychloroquine nor chloroquine do not act on SARS-CoV-2 proteins however both molecules prevent the binding of SARS CoV-2 spike protein to angiotensin-converting enzyme 2 (ACE2) by inter-

acting with the allosteric site.[20] In another study, Wang et al. investigated the binding affinities of the favipiravir to SARS-CoV-2 and human coronavirus NL63 RNA-dependent RNA polymerase (RdRp) and indicated that favipiravir has similar binding affinities to these proteins.[22] In the present study, we show for the first time the interactions of these drugs with the ER, PR and HER2 receptors and evaluate their binding affinities. Thus, it will help to understand how ER, PR, and HER2 receptor pathways can be affected in cellular mechanisms in vitro when these drugs are used by normal individuals and breast cancer patients who have COVID-19.

Defects in the expression of ER, PR and HER2 and increased mutations play a role in the development of different types of cancer, primarily breast cancer.[23,24] Inhibition of these receptors, which play a role in the course of this disease, plays an important role in the treatment process.[25] During the process of cancer treatment, glucocorticoids are routinely used as adjuvant therapy.[26] Dexamethasone is a member of the glucocorticoid family and is used to mitigate the undesirable side effects of chemotherapy as well as to treat COVID-19.[3,26] Favipiravir, an antiviral drug, is an RNA-dependent RNA polymerase inhibitor and there are not enough resources in the literature showing its potential effects on breast cancer.[7] Hydroxychloroquine, a chloroquine analogue, has been shown to increase the effects of chemotherapy and radiotherapy on tumors.[23] It has been shown that the hydroxychloroquine molecule increases the anti-estrogen response, possibly via the autophagy pathway.[27] In addition, there are not enough studies in the literature showing the fate of the hydroxychloroquine molecule on HER2 and PR receptors. According to the results of molecular docking in this study, Hydroxychloroquine was found to be the drug molecule that binds to ER, PR and HER2 receptors with the highest affinity when compared to Dexamethasone and Favipiravir molecules. These three drug molecules show high and low affinities and different molecular interactions at the active sites of the three receptors. On the other hand, Dexamethasone molecule bound to the receptor active sites with the lowest affinity and also developed improper interactions with the active site amino acids.[28]

In conclusion, within the scope of this study, molecular docking studies were carried out to examine the interactions of drugs that are Dexamethasone, Favipiravir and Hydroxychloroquine which are used in the treatment of COVID-19, with ER, PR and HER2 receptors, and their binding affinities were evaluated. It was observed that hydroxychloroquine binds to all three receptors with the highest affinity, while Dexamethasone binds to the active sites of ER and HER2 receptors with the lowest affinity among the three drugs. In addition, it has been determined that Dexamethasone develops inappropriate interactions with receptor active site amino acids. Therefore, this is a preliminary clinical study conducted to understand how receptor interactions can occur when normal individuals and breast cancer patients are treated for COVID-19 using Dexamethasone, Favipiravir, and Hydroxychloroquine. However, computer simulations are the initial step in drug research and development based on predictions and algorithms; more research and clinical testing is needed.

Ethics Committee Approval: Since this article is a bioinformatics analysis, it does not contain any studies with human or animal subjects performed by any of the authors, there is no need for ethics committee approval.

Conflict of Interest: No conflict of interest was declared by the authors.

Author Contributions: Concept – TK; Supervision – TK, MK; Materials – TK, MK; Data Collection and/or Processing –TK, MK, MOT; Analysis and / or Interpretation – TK, MK, MOT; Writing –TK, MK, MOT.

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