Bölüm 7

Nobel Molecule Artemisia-Annua and T-CD8+ Receptor Bestfit Interactions

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Abstract

Effector T cells, one of the body's defense cells, have an active role in the regulation of immune responses. These T cells have assumed the role of defense between the soluble substances they produce and the ligand interactions on their surface, and the regulators of the immune system. The CD8+ cells surface receptor control intracellular pathogens. CD8+ cells directly mark cells infected with intracellular organisms. In this study, the interactions between Artemisia annua ligand molecule and CD8+ surface protein molecules were investigated. AutoDock 4 –MGLTolls package program was used for the calculations, taking into account the basic energy data by determining the best binding site of the protein to the ligand interaction.

1. INTRODUCTION

Since Chinese medicine, Artemisia annua is used as a natural supplement to reduce fever and treat malaria. Chinese chemists obtained this extract from the leaf parts of the plant in 1971. The obtained extract is a sesquiterpene lactone bearing a peroxide group. Unlike the components in the structure of many other anti-inflammatory drugs, the molecular structure of the Artemisinin plant does not have a nitrogen-containing heterocyclic ring system. This compound is both sensitive and resistant to chloroquine (1).

Artemisinin is resistant and effective against all other classes of parasites, making it the most important group of natural antimalarial drugs currently available. Some of the two most important safe classes of drugs for the treatment of severe malaria have been published in the literature as plant-

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derived cinchona alkaloids and Artemisia Annua . Cinchona is a native tree of the Amazon Rainforest. It is used to obtain quinine. This substance is an antipyretic that has been used in the prevention and treatment of malaria from the very beginning. Artemisia annua is derived from the qinghao herb, which has been documented in traditional Chinese pharmacology for the treatment of fever for over two thousand years and has a longer history of use (2-5). Artemisia annua has a complex mechanism of action and can cause widespread damage to many components of the parasite (3). Artemisia annua (Sweet wormwood) is a plant with a very characteristic features. It has a leaf structure similar to fern leaves and can reach 2 meters in length. It is used in the treatment of malaria, fever and parasitic ailments. Recent studies have discovered new areas where it can be used in the treatment of many types of cancer, as well as melanoma, brain tumors and prostate cancer (4-5).

Artemisia annua (PubChem CID: 68827) has become a key component of malaria treatment (5). Access to Artemisia annua -based drugs is still limited in most regions. However, agricultural developments, the most beneficial hybrid selection, the development of peroxides synthesized in the laboratory and microbial drug production will facilitate access to these drugs. Artemisia annua -based therapies are also recommended by the World Health Organization (WHO) for the first-line treatment of malaria (6). 2015 Nobel Prize in Medicine, Artemisia annua. It was given to three scientists doing research on Artemisia annua, which is a malaria-protective extract obtained from the extracts of the plant Artemisia annua (7). Cytotoxic T cells CD8+; (PDB ID:1CD8) protect infected cells, tumor cells and transplant cells. In addition, they target and destroy certain cells that exhibit recognizable antigens. T cells, with their different subgroups, play a key role in the control of both intracellular and extracellular pathogens. T cells expressing the CD8 surface receptor control intracellular pathogens. Stimulated T cells and CD8+ directly destroy cells infected with intracellular organisms(8).

In this study, it is thought that the interaction between the CD8 surface receptor and the Artemisia annua molecule may have positive effects on the immune system. These calculations made with Autodock 4 (9) and Chimera Package (10) Programs are preliminary information in future laboratory studies in order to determine whether the effect of Artemisia annua molecule on the immune system is positive or negative.

2. MATERIALS AND METHODS

In silico methods based on estimating the properties of drugs and other chemical substances and their effects on the body with computer models have become increasingly important in pharmacology and toxicology in recent years. Because in silico methods have important advantages. In silico methods are fast and inexpensive, allow a large amount of data to be evaluated simultaneously and with high accuracy, and provide an alternative to animal experiments and complex in vitro tests.This study was prepared in computer environment by using AutoDock4 and UCSF Chimera package programs.

2.1. Ligand and Molecule Optimization

In this study, two-three-dimensional structure data were obtained with the ligand UCSF-Chimera [10-11] software, whose chemical structure is known. Affected-penetration-pocket sites on the macromolecule surface were determined using the Autodock 4 MGL Tools (https://vina.scripps.edu/) package. Molecular calculation initial values were used from PubChem(https://pubchem.ncbi.nlm.nih.gov/) and Protein DataBank (https://www.rcsb.org/) sources. It was sterilized by wiping at the junction points so that no atoms other than the macromolecule remained. Grid-based potential functions of macromolecule and ligand interactions were determined at local minimum values. Function limits were determined by adjusting the grid values in 80×80×80 Å AutoDock 4 software.

Morris, G.M., Goodsell, D.S., Halliday, R.S., Huey, R., Hart, W.E., Belew, R.K., Olson, A.J., "Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function", Journal of Computational Chemistry, 1998, 19: 1639–1662.

From simulations, we get information about molecular energies, hydrogen bonds that can be bonded to water, and the number of hydrogen bonds whose lengths are calculated. To reduce the molecular charge of the ligand, the position of the atoms was approximated using the molecular interactions. The prepared ligand was deposited into the macromolecule force field.

Base sets were determined according to the lowest energy and strongest bonds and angles of this ligand sample with minimum energy values and coordinates.

3. RESULT AND DISCUSSION

Van der Waals Interactions occur between polar and covalently bonded atoms in different molecules. In biological systems, weak interactions between molecules are important. Some of these weak attractions are due to temporary partial charges that are created when electrons move around the nucleus. Data obtained with AutoDock4 and UCSF Chimera package programs on Artemisia annua & CD8+Interaction are shared in this section. Many iterations were made and best of 3 sellected Among the other bonding molecules, PHE107 (-6.1 kcal/Mol binding energy) can be said to be to most likely amino acid to be attached (Table 1).

Table 1. The three conformations with the strongest Artemisia annua - CD8+ surface receptor interaction were obtained with the AutoDock 4 MGLTolls package program.

Conformation bestfits	Binding_ energy (kcal/mol)	Inhi- bition constant	Intermol_ energy (kcal/mol)	H Bonds
Conformation 1	-6.1	33.79	-6.1	PHE107
Conformation 2	-6.1	33.75	-6.1	PHE107
Conformation 3	-6.1	33.89	-6.1	PHE107

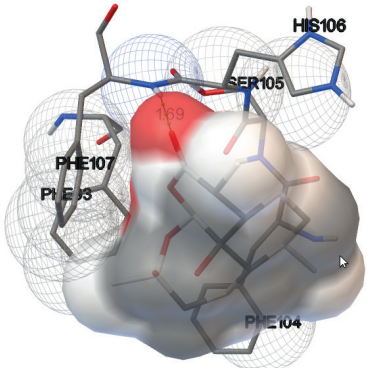

Figure 1. Conformation 1, an image in the form of Van der Waals clusters. One Hydrogen bond was observed, 1.69 Å long and bound to the PHE107 Amino acid (HIS106-SER105-PHE103

PHE104 are show weaker then A107 binding interaction) The image was obtained with the AutoDock 4 package program (11).

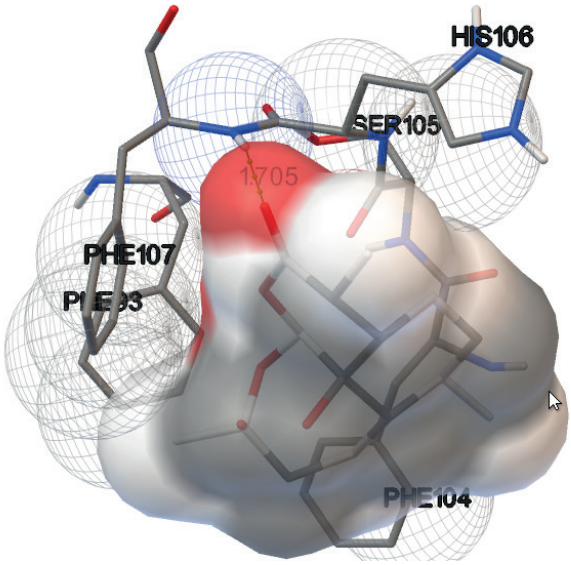

Figure 2. Conformation 2, an image in the form of Van der Waals clusters. One Hydrogen bond was observed, 1.705 Å long and bound to the PHE107 Amino acid. The image was obtained with the AutoDock MGL Tools package program.

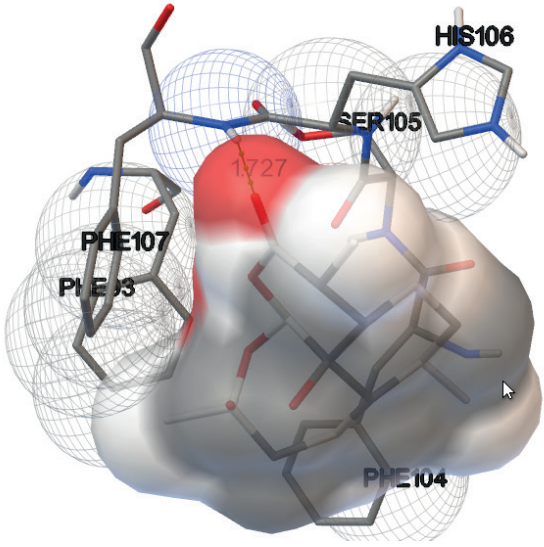

Figure 3. Conformation 3, an image in the form of Van der Waals clusters. One Hydrogen bond was observed, 1.727 Å long and bound to the

PHE107 Amino acid. The image was obtained with the AutoDock MGL Tools package program.

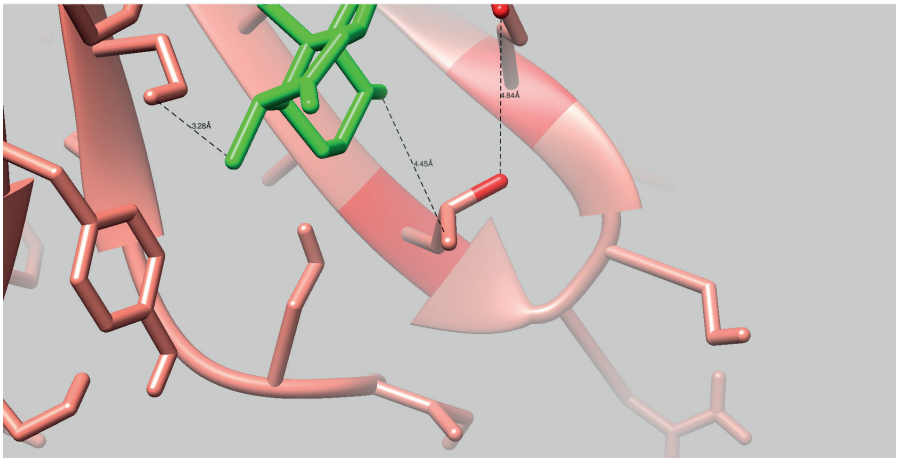

Figure 4. There are calculated bond lengths between protein-protein and protein-ligand, and the image was obtained with the UCSF Chimera package program (12). Green part: Artemisia annua substance, pink-red part: CD8+ surface receptor. The calculated nearest molecule-ligand distance is seen that 3.28 Å.

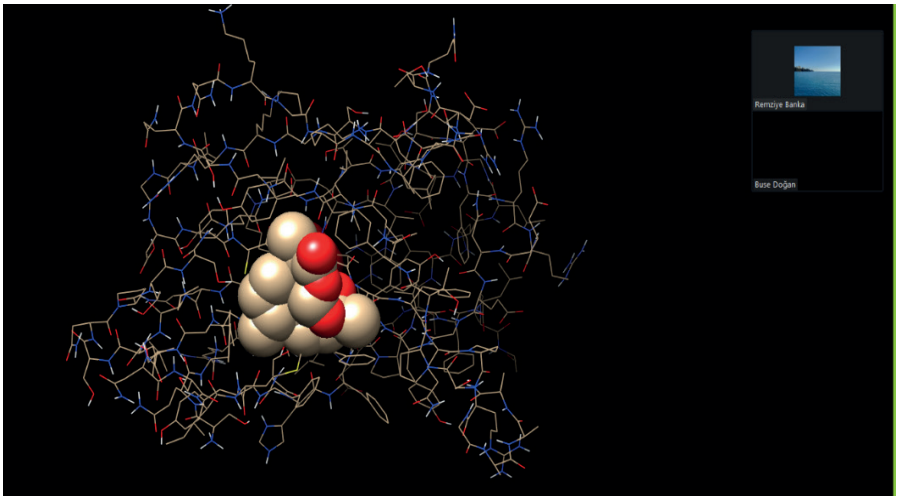

Figure 5. This image shows the size difference in the CD8+ - Artemisia annua islands. The image was obtained with the UCSF Chimera package program.

4. CONCLUSION

As a result of these calculations, interaction between ligand - CD8 surface receptor was observed and theoretical results were recorded. In the docking study, it has been proven that the Artemisia annua can bind to the CD8 surface receptor. The possibility of having positive effect on the immune system is confirmed by the results of theoretical calculations. Considering that Artemisia annua substance binds to lung cells in malaria and prevents the parasite from attaching, it is thought that in the current Pandemic, Artemisia annua substance may also bind to lung cells and prevent SARS-CoV-2 from binding. With this in-silico study, we can expect to accelerate the creation of a drug candidate targeting ligand molecule in immun system cells.

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REFERENCES

1. Klayman D.L., (1985) "*Qinghaosu (Artemisinin): an antimalarial drug from China*", **Science** 228(4703), , 1049-55.

DOI: 10.1126 / science.3887571

2. Krishna S., Uhlemann A. C., & Haynes R. K., (2004) " *Artemisinins: mechanisms of action and potential for resistance",* **Drug Resistance Updates**, *7*(4-5), 233-44.

DOI: 10.1016/j.drup.2004.07.001

3. Ariey F., Clain J., Duval R., Ménard R., Talman A.M., (2019) "*Artemisinin Bioactivity and Resistance in Malaria Parasites*", **Trends Parasitol**, 35(12), 953-63.

DOI: 10.1016/j.pt.2019.09.005

4. Bayhan Ü., Banka R.,"*CD8 Yüzey Reseptörü & Artemisinin Etkileşmesinin Doking Hesaplaması Yolu İle Belirlenmesi*" 2nd International Young Researchers Student Congress 17-19 December 2020,Abstract book, p:183 Burdur/TURKEY.

5. Miller L.H., Su X., "*Artemisinin: Discovery from the Chinese Herbal Garden*", (2011), **Science Direct**. 146(6), 855-58.

DOI: 10.1016/j.cell.2011.08.024

6. An S.S., Ariey F., Chotivanich K., Das D., Day N.P.J., Dondorp A.M., Hanpithakpong W., Herdman T., Imwong M., Lee S.J., Lindegardh N., Lim P., Lwin K.M., Nosten F., Phyo A.P., Ringwald P., Silamut K., Singhasivanon P., Socheat D., Yeung S., Yi P., Tarning J., White N.J., (2009), "*Artemisinin Resistance in Plasmodium Falciparum Malaria*", **The New England Journal of Medicine** 361;5, 455-67.

DOI: 10.1056/NEJMoa0808859

7. Croft S. L., & Ward S.,"*The Nobel Prize in Medicine 2015: Two drugs that changed global health*", **Science translational medicine** *7*(316), (2015), 316ed14-316ed14.

DOI: 10.1126/scitranslmed.aad5868

8. Bülbül Başkan E., (2013)," *T Cell Immunity*". **Türkderm** 47(1), 18-23.

DOI: 10.4274/turkderm.47.s3

9. Belew R. K., Goodsell D. S., Huey R., Lindstrom W., Morris G. M., Olson A. J., Sanner M. F. (2009), " *Autodock4 and AutoDockTools4: Automated Docking With Selective Receptor Flexiblity",*. **J. Comp.Chem.**, 16: 2785-91.

DOI: 10.1002/jcc.21256

10. Couch G.S., Ferrin T.E., Goddard T.D., Greenblatt D.M., Huang C.C., Meng E.C., and Pettersen E.F. (2004), "*UCSF Chimera- A Visualiza-*

tion System for Exploratory Research and Analysis",. **J. Comput. Chem.**, 25:1605-12.

DOI: 10.1002/jcc.20084

11. El-Hachem, N., Haibe-Kains, B., Khalil, A., Kobeissy, F.H., Nemer, G. (2017). "AutoDock and AutoDockTools for Protein-Ligand Docking: Beta-Site Amyloid Precursor Protein Cleaving Enzyme 1(BACE1) as a Case Study". In: Kobeissy, F., Stevens, Jr., S. (eds) **Neuroproteomics. Methods in Molecular Biology**, vol 1598, p:391-403, Humana Press, New York, NY.

DOI 10.1007/978-1-4939-6952-4_20