Investigating the comparative effect of Dabrafenib, Vemurafenib, Trametinib and Dacarbazine drugs on the BRAF protein by molecular docking methods

Hasti Goudarzi[1,*]
[1,*] *Department of Chemistry, Ayatollah Borujerdi University, Borujerd, Iran*

ABSTRACT

Melanoma is a type of skin cancer that originates from melanocytes, the cells responsible for producing the skin pigment melanin. It can grow rapidly and metastasize to other organs. The BRAF protein, a member of the kinase protein family, plays a crucial role in cell signaling and the regulation of cell growth and division. Approximately 40 to 60 percent of melanomas are associated with mutations in the BRAF gene, which lead to the abnormal activation of the BRAF protein. This study investigates the comparative effects of the drugs Dabrafenib, Vemurafenib, Trametinib, and Dacarbazine on the BRAF protein in melanoma using molecular docking techniques. This study investigates the comparative effects of the drugs Dabrafenib (a selective BRAF inhibitor), Vemurafenib (an enzymatic BRAF inhibitor), Trametinib (a mitogen-activated kinase inhibitor), and Dacarbazine (an alkylating agent) on the BRAF protein in melanoma using molecular docking techniques. In this study, the structure of the BRAF protein was downloaded from the UniProt database and analyzed using Chimera software. After performing several steps, including charge optimization, removal of excess ions, and water molecules, the protein was saved as the final structure. Subsequently, the three-dimensional structures of the drugs were obtained using appropriate software, and during the docking phase, the potential interactions between the drugs and the protein were assessed. The results indicated that Dabrafenib exhibited a more favorable binding energy and a better RMSD compared to the other drugs. Therefore, Dabrafenib demonstrates a superior effect on controlling the growth of cancer cells compared to Trametinib, Vemurafenib, and Dacarbazine. These findings could contribute to the improvement of therapeutic strategies in Melanoma.

Keywords: Melanoma cancer, BRAF protein, Dabrafenib, Vemurafenib, Trametinib

1. INTRODUCTION

Melanoma is a type of skin cancer that begins in melanocyte cells, which are responsible for producing skin pigment (Melanin). This type of cancer can grow rapidly and has the ability to spread to other organs. Melanoma usually occurs in areas of the skin that are exposed to sunlight, but it can also appear anywhere on the body, even in areas that are less exposed to sunlight[1].

The BRAF protein is a member of the kinase protein family and plays an important role in cellular signaling and the regulation of cell growth and division. Approximately 40-60% of skin melanomas are associated with mutations in the BRAF gene. These mutations lead to the abnormal activation of the BRAF protein, which in turn contributes to the activation of the MAPK signaling pathway. This pathway is essential for cell growth and division[2].

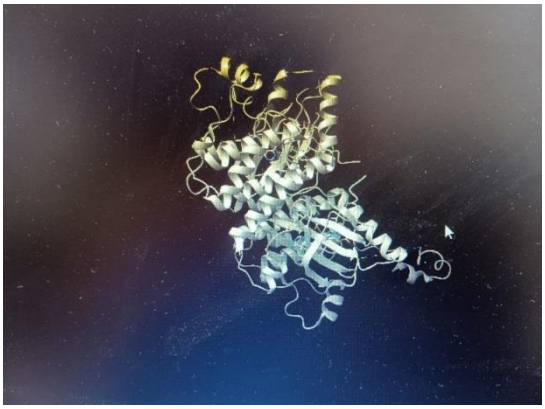

Fig. 1. *The three-dimensional structure of BRAF protein*

The drug Dabrafenib, marketed under the brand name Tafinlar, is an oral inhibitor of the BRAF protein. This drug binds competitively and selectively to the BRAF protein, preventing the phosphorylation of the Amino Acids Serine and Threonine, which in turn reduces cell proliferation [3]. The two-dimensional and three-dimensional structures with the molecular formula $C_{23}H_2OF_3N_5O_2S_2$:

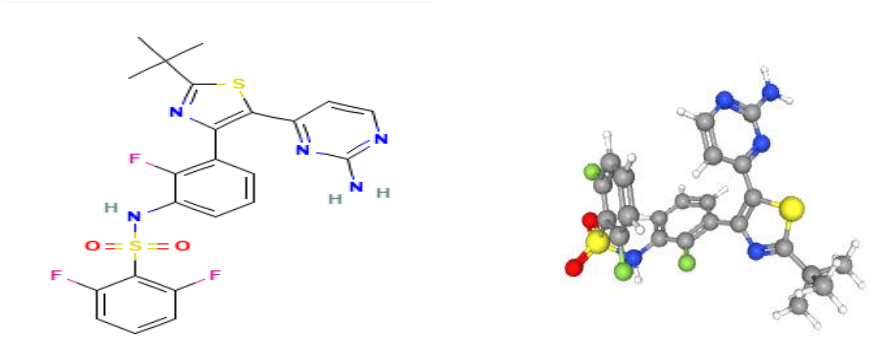

Fig. 2. *Two-dimensional and three-dimensional structures of Dabrafenib*

A Vemurafenib, marketed as Zelboraf, is an enzyme inhibitor used for the treatment of Melanoma. Vemurafenib inhibits downstream processes to suppress tumor growth and ultimately induces apoptosis[4]. The two-dimensional and three-dimensional structures with the molecular formula $C_{23}H_{18}ClF_2N_3O_3$:

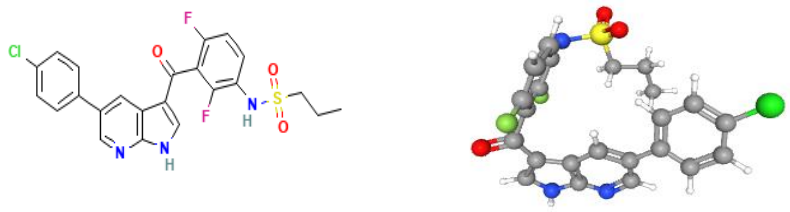

Fig. 3. *Two-dimensional and three-dimensional structures of Vemurafenib*

Trametinib, marketed as Mekinist, is an antineoplastic drug and a mitogen-activated extracellular Kinase (MEK) inhibitor that is prescribed for various cancers associated with the BRAF V600 mutation, including Melanoma, ovarian Carcinoma, unresectable or Metastatic solid tumors, and Thyroid cancer, among others. The presence of Trametinib alongside dabrafenib leads to synergy and enhances therapeutic effects [5]. The two-dimensional and three-dimensional structures with the molecular formula $C_{26}H_{23}FIN_5O_4$:

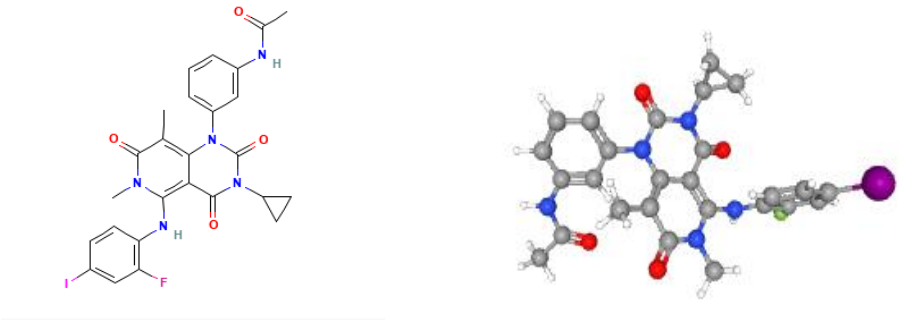

Fig. 4. *Two-dimensional and three-dimensional structures of Trametinib*

Dacarbazine, marketed as DTIC, is used for the chemotherapy of Blood cancers (Hodgkin lymphoma), Skin cancer (Malignant Melanoma), soft tissue Sarcomas, and Pancreatic carcinoma. Dacarbazine is an alkylating agent that inhibits the proliferation of cancer cells by adding an alkyl group to the DNA in the nucleus[6]. The two-dimensional and three-dimensional structures with the molecular formula $C_6H_{10}N_6O$:

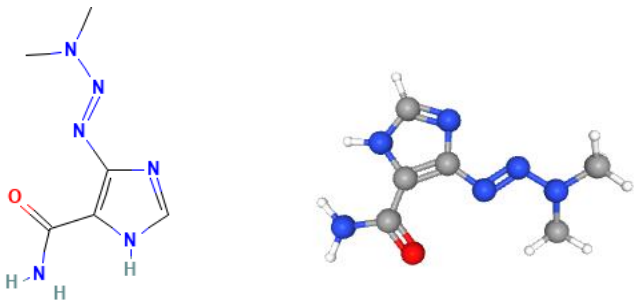

Fig. 5. *Two-dimensional and three-dimensional structures of Dacarbazine*

The aim of this study is to investigate the comparative effects of the drugs dabrafenib, vemurafenib, trametinib, and dacarbazine on the BRAF protein in melanoma using molecular docking methods.

2. METHOD

To compare the effects of the drugs Dabrafenib, Vemurafenib, Trametinib, and Dacarbazine on the BRAF protein, the structural form of the BRAF protein was first downloaded in PDB format from the UniProt website. Then, using Chimera X 1.8 software, we determined the number of chains in this protein. This protein has two chains, and we selected the larger chain as the chain of interest (A Chain). After this, we examined the protein for charge distribution, added hydrogen, removed excess ions, and eliminated water. Then, we saved it as the final protein in PDB format. Next, using the PubChem website, we saved the

three-dimensional structures of the drugs Dabrafenib, Vemurafenib, Trametinib, and Dacarbazine in SDF format. Finally, we used PyRx software to assess the possibility of drug binding to the BRAF protein.

3. RESULT

First, we selected the saved protein structure in PDB format from the File menu and chose the Load Molecule option. After doing this, we right-clicked on the protein to convert it into a micromolecule. To place the drug on the protein, we clicked on the File menu and selected the Import option, and then we imported the three-dimensional structure of the drug in the desired SDF format. Next, to change the drug format from SDF to PDB, we first clicked on Minimize and then on Convert to PDB qt. After this, we clicked on the Vina Wizard option and then selected Forward, where we examined the replacement of the drugs at various sites on the protein. In the final step, we selected forward again and waited for the docking process to complete. After the docking operation was complete, we compared the resulting data table. To compare the effect of the drugs on the protein, the more negative binding energy is greater the drug's effect on the protein.

***Table 1**. The result of the molecular docking of Dabrafenib on the BRAF protein*
Center: X:14.0247, Y:33.9369, Z:14.9775

Ligand	*Binding Affinity (Kcal/mol)*	*Mode*	*RMSD lower bound*	*RMSD upper bound*
Conformation 1	*-7.7*	*0*	*0.0*	*0.0*
Conformation 2	*-7.7*	*1*	*2.506*	*5.239*
Conformation 3	*-7.5*	*2*	*2.483*	*3.32*
Conformation 4	*-7.4*	*3*	*1.917*	*3.848*
Conformation 5	*-7.3*	*4*	*4.14*	*8.577*
Conformation 6	*-6.9*	*5*	*2.492*	*4.586*
Conformation 7	*-6.9*	*6*	*2.297*	*3.345*
Conformation 8	*-6.9*	*7*	*1.779*	*3.804*
Conformation 9	*-6.9*	*8*	*2.941*	*8.092*

Table 2. *The result of the molecular docking of the Vemurafenib on the BRAF protein*

Center X:14.0247 Y:33.9369 Z:14.9775

Ligand	*Binding Affinity (Kcal/mol)*	*Mode*	*RMSD lower bound*	*RMSD upper bound*
Conformation 1	*-7.4*	*0*	*0.0*	*0.0*
Conformation 2	*-7.3*	*1*	*4.545*	*8.49*
Conformation 3	*-7.2*	*2*	*5.11*	*8.349*
Conformation 4	*-7.1*	*3*	*4.719*	*9.294*
Conformation 5	*-7.0*	*4*	*3.521*	*4.705*
Conformation 6	*-7.0*	*5*	*4.575*	*9.563*
Conformation 7	*-6.9*	*6*	*4.768*	*9.645*
Conformation 8	*-6.7*	*7*	*4.872*	*9.638*
Conformation 9	*-6.7*	*8*	*1.956*	*2.397*

Table 3. *The result of the molecular docking of the Trametinib on the BRAF protein*

Center X:14.0247, Y:33.9369, Z:14.9775

Ligand	*Binding Affinity (kcal/mol)*	*Mode*	*RMSD lower bound*	*RMSD upper bound*
Conformation 1	*-6.3*	*0*	*0.0*	*0.0*
Conformation 2	*-6.2*	*1*	*3.488*	*6.394*
Conformation 3	*-6.2*	*2*	*4.215*	*9.255*
Conformation 4	*-6.1*	*3*	*2.686*	*5.355*
Conformation 5	*-5.6*	*4*	*4.606*	*9.283*
Conformation 6	*-5.5*	*5*	*4.674*	*9.683*
Conformation 7	*-4.9*	*6*	*3.519*	*5.267*
Conformation 8	*-3.9*	*7*	*4.043*	*5.594*
Conformation 9	*-3.3*	*8*	*3.798*	*6.42*

Table 4. *The result of the molecular docking of the Dacarbazine on the BRAF protein*

Center X:14.0247, Y:33.9369, Z:14.9775

Ligand	*Binding Affinity(kcal/mol)*	*Mode*	*RMSD lower bound*	*RMSD upper bound*
Conformation 1	*-4.7*	*0*	*0.0*	*0.0*
Conformation 2	*-4.7*	*1*	*2.008*	*3.171*
Conformation 3	*-4.6*	*2*	*1.731*	*2.807*
Conformation 4	*-4.6*	*3*	*9.769*	*11.281*
Conformation 5	*-4.5*	*4*	*2.368*	*5.087*
Conformation 6	*-4.3*	*5*	*2.322*	*5.284*
Conformation 7	*-4.2*	*6*	*2.321*	*4.993*
Conformation 8	*-4.2*	*7*	*2.586*	*5.904*
Conformation 9	*-4.1*	*8*	*1.762*	*4.439*

4. CONCLUSION

Based on the docking results, it was determined that, considering the more negative binding affinity and better RMSD values, the comparison of the effects of the drugs is as follows:

Dabrafenib> Vemurafenib> Trametinib> Dacarbazine

As a result, Dabrafenib has a better effect on the target BRAF protein compared to the other three drugs and provides a more effective response for controlling cancer cell growth.

REFERENCES

[1] *Sadeghi Urmia, A., BARATI, B., TAGHINEJAD, J. (2018). Mechanisms of developement and metastasis of malignant melanoma. Journal of Dermatology and Cosmetics, Vol. 9, no.2, P. 120-134.*

[2] *UniProtKB-P15056.BRAF_HUMAN, Function. UniProt.Avaliable:* https://www.uniprot.org/uniprotkb/P15056/entry#function.

[3] *PubChem Compound Summery CID44462760 , Dabrafenib . PubChem. Avaliable:* https://pubchem.ncbi.nlm.nih.gov/compound/44462760.

[4] *PubChem Compound Summery CID42611257 , Vemurafenib . PubChem. Avaliable:* https://pubchem.ncbi.nlm.nih.gov/compound/42611257.

[5] *PubChem Compound Summery CID11707110 , Trametinib . PubChem. Avaliable:* https://pubchem.ncbi.nlm.nih.gov/compound/11707110.

[6] *PubChem Compound Summery CID 135398738 , Dacarbazine . PubChem. Avaliable:* https://pubchem.ncbi.nlm.nih.gov/compound/135398738.