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Determination of the Interaction between HER2 Receptor and Tomentosine by Molecular Docking

Izzettin GULER[1]* and Mehmet OZASLAN[1]

[1]Department of Biology, Gaziantep University, Gaziantep, Türkiye
izzettinguler@gantep.edu.tr; ORCİD: 0000-0001-6682-7156
ozaslanmd@gantep.edu.tr; ORCİD:0000-0001-9380-4902

Sorumlu Yazar (Corresponding Author): izzettinguler@gantep.edu.tr

Abstract

Tomentosine and the HER2 gene are important molecules in cancer research. HER2 is a protein receptor on the cell surface that mediates cell growth signals. This protein encoded by the HER2 gene can cause excessive growth and spread of tumor cells, especially in some types of cancer such as breast cancer. Tomentosine, as a plant-derived compound, attracts attention with studies on its biological effects. The study evaluated the propensity of HER2 protein to bind to tomentosine and the therapeutic potential in cancer cases. The interactions of the molecules were analyzed using AutoDock 4.0. As a result, it was found that there is a multidirectional binding between HER2 and tomentosine, which was measured to be -8.47 (Gibbs free energy). These findings show that there is a high affinity and binding potential between HER2 protein and tomentosine. Therefore, it is thought that this study will provide a pioneer for future *in vitro* studies.

Keywords: HER2, Tomentosine, Cancer.

Introduction

HER2 (Human Epidermal Growth Factor Receptor 2) is a receptor protein found on the cell surface. It is coded from the HER2 gene, which is responsible for regulating cell growth and division. Overexpression or amplification of the HER2 gene leads to aggressive disease progression in various cancer types, especially breast cancer (Cheng X., 2024). HER2 has an abnormally increased expression in approximately 25-30% of breast cancer cases. HER2 positive breast cancer usually grows and spreads more rapidly, thus worsening the prognosis of the disease (Slamon et al., 2001). HER receptors exist in monomeric form and dimerize by ligand binding. Although no HER2-specific ligand has been identified, HER2 is the preferred heterodimerization partner for other HER receptors. Heterodimers containing HER2 are strong and long-lived. The strongest dimerization partner of HER2 is known as HER3 (Yarden, 2001). In normal cells, there are few HER2 molecules on the cell surface and a limited number of heterodimers are formed. Accordingly, growth signaling is weak and unregulated. When HER2 is overexpressed, more HER2 heterodimers are formed and cell signaling becomes stronger. This results in a more pronounced response to malignant growth. HER2 overexpression therefore indicates a worse prognosis in breast tumors and may be a determinant of response to treatment. HER2 has emerged as a promising target for breast cancer therapies (Rubin and Yarden, 2001).

Detection of HER2 is critical for determining treatment approaches. Traditional methods such as immunohistochemistry and fluorescence in-situ hybridization are commonly used to evaluate HER2 expression (Pathmanathan and Bilous, 2012). Both tests are effective in accurately identifying the presence and overexpression of the HER2 gene and help in determining treatment options (Wolff et al., 2018). In addition, new technologies have been developed in recent years that are more sensitive and practical, such as chromogenic in-situ hybridization (Jahanbin et al., 2023).

Tomentosine is found in some medicinal plants of the Asteraceae family, such as *Inula viscosa*. It is a compound belonging to the class of sesquiterpene lactones and its chemical formula is $C_{15}H_{20}O_3$ (He et al., 2020).

Tomentosine is a compound that shows particular potential in cancer treatment. In numerous studies, tomentosine has been observed to induce apoptosis in cancer cells and inhibit the proliferation of cancer cells. For example, it was reported that tomentosine induced apoptosis in MOLT-4 leukemia cancer cells via caspase-facilitated proapoptotic pathway and inhibited cell proliferation (Yang et al., 2021). Similarly, cell number decreased in hepatocellular carcinoma HepG2 and Huh7 cells treated with tomentosine in a dose-dependent manner. It was determined that tomentosine showed antiproliferative effect by decreasing the number of cell colonies (Yu et al., 2021). In another study, tomentosine was also effective in programmed cell death in AGS gastric cells (Yang et al., 2020).

Studies have also reported that tomentosine is effective on the cell cycle. Tomentosine induced cell cycle arrest in SiHa and HeLa cervical cancer cells in the G2/M phase in a dose-dependent manner (Merghoub et al., 2017). In addition, tomentosine was found to stop the cell cycle, inhibit proliferation and induce apoptosis in human melanoma cell lines (SK-28, 624 mel, 1363 mel) (Rozenblat et al., 2008).

Tomentosine is thought to induce apoptosis by increasing intracellular Reactive Oxygen Species (ROS) levels (Lee et al., 2019). In a study conducted in 2022 with pancreatic cancer cells, it was concluded that tomentosine increases ROS production, stimulates apoptosis, reduces migration, invasion, and colony formation abilities (Güçlü et al., 2022).

Tomentosine also draws attention with its anti-inflammatory properties. There are studies showing that tomentosine shows anti-inflammatory effects by reducing the production of inflammation-related cytokines (He et al., 2020; Park et al., 2014).

Molecular docking is a process that uses computer programs to simulate how two or more molecules will interact with each other. Through simulation, the binding site, binding strength and other interaction properties of one molecule on another molecule are predicted. This information is used to design potential drugs or to better understand biological processes (Paggi et al., 2024).

The potential of tomentosine to inhibit the HER2 receptor may be a promising area for new therapeutic strategies effective in the treatment of HER2 positive cancer. Our aim is to reveal the therapeutic potential of tomentosine, especially against cancer types caused by the HER2 receptor. For this reason, the binding affinity, and binding modes of tomentosine with HER2 protein were investigated by computer-aided molecular docking modeling.

Materials and Methods

The crystal structure of the HER2 receptor (PDB ID: 8U8X) was obtained from the Protein Data Bank (PDB, https://www.rcsb.org/). The crystal structure of the HER2 protein with a resolution of 1.69 Å was chosen as the target (receptor) molecule. The pdb file of 8U8X was prepared using chains A and B and imported into AutoDockTools. Water molecules were

removed and the pdbqt file of the 8U8X coded domain was saved. The chemical structure of the tomentosine ligand having the molecular formula $C_{15}H_{20}O_3$ was obtained from the National Library of Medicine/National Center for Biotechnology Information, https://www.ncbi.nlm.nih.gov/ (PubChem CID: 155173). The ligand files were saved in pdbqt format using AutodockTools. The best binding pose between receptor and ligand was obtained using AutoDock 4.0. The resulting binding pose was analyzed using BIOVIA Discovery Studio Visualizer 2016 (Husunet et al., 2022).

Results and Discussion

In our study, the binding energy, amino acid interactions and chemical bond types of tomentosine ligand with HER2 protein were extensively investigated. As a result of the calculations, the binding energy (Gibbs free energy, ΔG) between tomentosine and HER2 was calculated as -8.47 kcal/mol. This negative value indicates that the reaction occurs spontaneously, and the binding process is a thermodynamically stable process.

The different docking positions of the interaction between tomentosine and HER2 are shown as detailed in figures 1, 2, 3 and 4. These images clearly show how the ligand binds with the receptor and the positions of the interactions. During the interaction of the ligand with the HER2 receptor, 4 different types of chemical bonds were observed with a total of 16 different amino acids (Figure 2). These interactions demonstrate that the binding mechanism between the molecules is complex and multifaceted. The analyzed results revealed that tomentosine ligand performed several important amino acid interactions with the HER2 receptor. Tomentosine ligand established conventional hydrogen bonds with some amino acids in the HER2 receptor. These bonds were particularly observed with amino acids ASP867, ARG872 and PHE868 (Figure 2). Conventional hydrogen bonds are interactions between molecules in which a hydrogen atom bonds with an electronegative atom. In addition, van der Waals interactions were also observed between tomentosine and HER2. GLY869, TYR776, LEU845, ALA779, MET778, THR866 and SER787 are amino acids involved in van der Waals interactions (Figure 2). These bonds increase the physical proximity and stability between ligand and receptor. In addition, amino acids such as LEU873, LEU870, VAL777, ARG788, VAL781 and LEU789 formed alkyl bonds with the ligand (Figure 2). Alkyl bonds are the interactions of alkyl groups, usually containing hydrogen and carbon atoms. These bonds are one of the important factors that strengthen the interaction between molecules and make the binding more stable. The amino acid PHE868 was found to establish a Pi-alkyl bond between tomentosine and HER2 (Figure 2). Such interactions occur between aromatic rings and alkyl groups and increase the attractive forces between molecules.

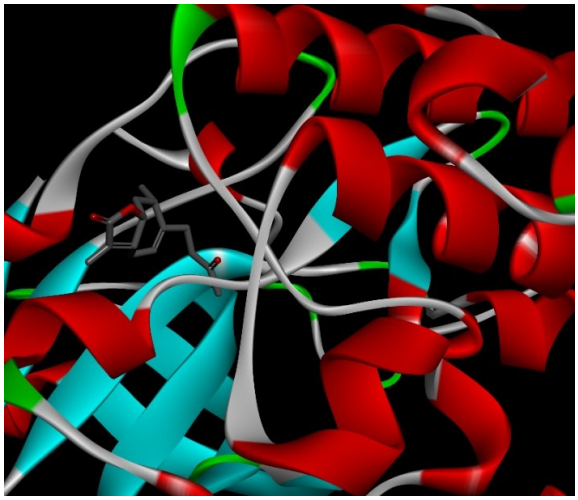

Figure 1. 3D binding pose between HER2 and Tomentosine

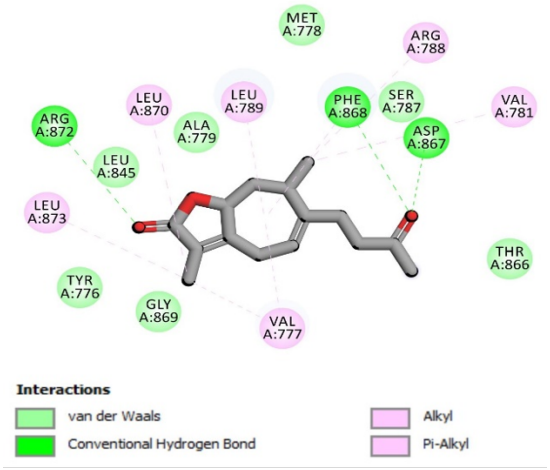

Figure 2. Amino acid interaction and chemical bond types between HER2 and Tomentosine

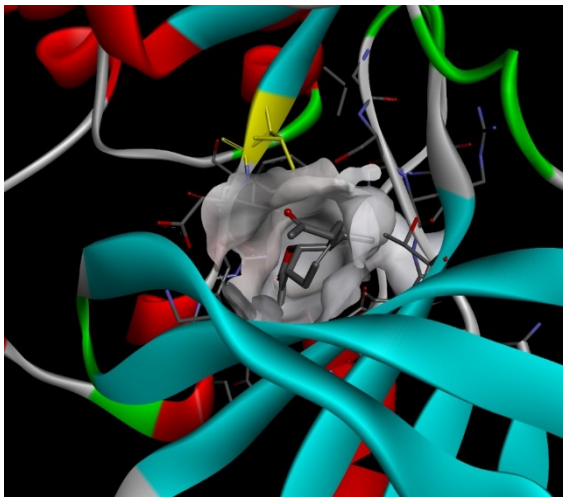

Figure 3. Electric field interaction between HER2 and Tomentosine

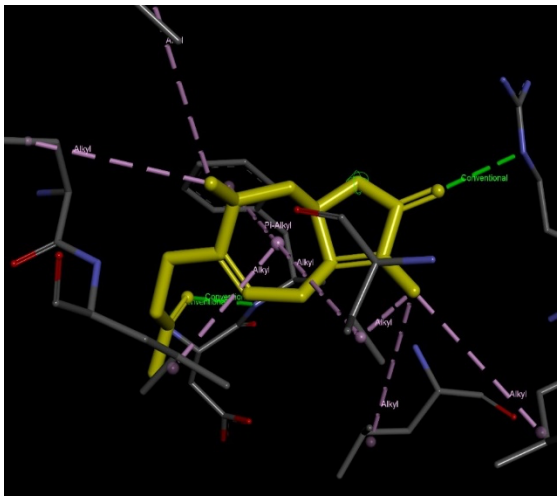

Figure 4. Ligand Interaction between HER2 and Tomentosin

Conclusion

The binding mechanism between the tomentosine ligand and the HER2 receptor is highly complex as it involves multiple and different types of interactions. Each type of interaction contributes to specific steps in the binding process of tomentosine with HER2. Conventional hydrogen bonds are considered a weak force between molecules, but are often of great importance in biological, chemical, and physical processes. Van der Waals and alkyl bonds are weak interactions that increase the stability of binding. Pi-alkyl interactions are another important type of bonding that reinforces the structural organization and binding efficiency of the ligand.

The findings of this study show that the binding between the tomentosine ligand and HER2 is based on a multifaceted network of interactions and reveal that the binding energy is due to the total of these interactions. It can be argued that each of these interactions provides tomentosine with high affinity and binding potential with HER2. Such binding energies and types of

interactions may play an important role in the development of potential therapeutic strategies for the HER2 receptor.

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