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A Study of The Anticancer Effect of 1,8 Cineole: Molecular Docking Analysis

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Abstract: Since cancer is a serious disease that affects many people around the world, scientists focus on studies on the diagnosis and treatment of cancer. Plants have been used for therapeutic purposes for many years. Plants that form the basis of traditional medicine contain therapeutic compounds. These compounds have important properties such as anticancer, anti-inflammatory, analgesic, antimicrobial and antioxidant. Essential oils obtained from various plants are known to have therapeutic effects. Terpenes make up the largest part of the composition of plant essential oils. Terpenes have various beneficial effects such as anti-anxiety, anti-depressant, anti-inflammatory, anti-bacterial, anti-cancer, analgesic and mood-boosting. 1,8 cineole is one of the monoterpene compounds found in essential oils. 1,8 cineole is an important compound with various properties such as antioxidant, anti-inflammatory and anticancer. The molecular docking method is one of the computational modeling methods used in drug development programs. In this study, the interactions of 1,8 cineole, which is known to have anticancer properties, with various receptors prominent in anticancer studies (Estrogen receptor beta (ER-β), Epidermal growth factor receptor (EGFR), Receptor tyrosine-protein kinase erbB-2 (HER2) and Tankyrase 1) were examined with the help of the molecular docking method, the interaction profile was determined and presented in comparison with literature studies. As a result of docking studies, it was predicted that the interaction with Tankyrase-1 would be stronger.

Keywords: Essential oil, Molecular docking, Cancer, Plant

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1. INTRODUCTION

Cancer is one of the deadliest diseases in the world, resulting in the death of thousands of people every year. Scientists have been continuing their work on discovering new drugs to fight cancer for a long time. Scientists continue to research agents obtained from nature as well as chemically synthesized pharmaceutical agents in new drug discoveries (Dehelean et al., 2021).

Plants have been used for therapeutic purposes for a long time. Plants, which form the basis of traditional medicine, contain therapeutic compounds. These compounds have various properties such as anticancer, anti-inflammatory, analgesic, antimicrobial and antioxidant (Hoch et al., 2023). Many essential oils obtained from plants are also known to have medicinal benefits. It has been reported in literature studies that 1,8-cineole, which is prominent in the content of essential oils, has pharmacological effects (Murata et al., 2013). 1,8 cineol (eucalyptol), found in the essential oils of various plants such as eucalyptus, rosemary, thyme, and sage, has various properties such as anti-inflammatory, antioxidant, antimicrobial, analgesic and anticancer (Hoch et al., 2023). The anticancer properties of 1,8 cineole have been exhibited by cytotoxicity studies associated with colon (Murata et al., 2013), lung (Rodenak-Kladniew, Castro, Crespo, Galle, & de Bravo, 2020), ovarian (Abdalla et al., 2020), skin (Sampath et al., 2018) and liver (Rodenak-Kladniew, Castro, Stärkel, Galle, & Crespo, 2020) cancers.

The molecular docking method is used as a predictive tool in drug development studies. With this method, the interactions, and binding affinities of drug candidate molecules with target receptors are determined. A prediction profile can be created by examining the interactions of molecules thought to be effective against the disease for which drug development is targeted and disease-related

macromolecules and can be used to support experimental studies.

In cancer studies, receptors are determined according to the cancer type being studied. For example, Estrogen receptor β is an important receptor in the expression of cancer-related genes and ovarian cancer. In a study on ovarian cancer, it was reported that ER-β activated apoptosis and reduced proliferation and migration (Schüler-Toprak, Moehle, Skrzypczak, Ortmann, & Treeck, 2017; Treeck et al., 2007). EGFR activation is associated with tumor growth, invasion and metastasis (Normanno et al., 2006; Sasaki, Hiroki, & Yamashita, 2013). EGFR is known to be overexpressed in non-small cell lung cancer (Lee, 2006). In clinical studies, it has been reported that EGFR is often overexpressed in advanced stages of colon cancer (de Castro-Carpeño et al., 2008). HER-2 activation is known to play a role in tumor development, and its overexpression has been reported in ovarian (Slamon et al., 1989), lung (Riudavets, Sullivan, Abdayem, & Planchard, 2021), liver (Shi et al., 2019) and colorectal cancer (Ivanova et al., 2022). It is known that tankyrase inhibition also plays a role in the antiproliferative effect by affecting some signals in colorectal cancer (Solberg et al., 2018).

In this study, molecular docking studies of 1,8 cineole, which is known to have anti-cancer properties in the literature, were carried out with ER-β, EGFR, HER2 and Tankyrase 1 receptors used as targets in cancer studies, and its interaction profile and binding affinities were determined. Additionally, the interactions of some drugs used in cancer treatment and 1,8 cineole with target receptors were comparatively examined.

2. MATERIAL AND METHOD

Considering that 1,8 cineole has an anticancer effect, molecular docking studies were carried out to examine the interactions of 1,8 cineole with various cancer targets. These targets were selected as ER-β (PDB ID: 1X7J), EGFR (PDB ID: 1M17), HER2 (PDB ID: 3RCD), human tankyrase 1 (PDB ID: 4W6E). In the preparation step of the study, 1,8 cineole (PubChem ID: 2758) was optimized with DFT/B3LYP/6-311++G(d,p) basis set using Gaussian09 (Frisch et al., 2009) and receptors were downloaded from PDB DataBank (https://www.rcsb.org/). 1,8 Cineole and the selected receptors were prepared for docking analysis via AutoDock Tools 1.5.6. All molecular docking studies were realized using AutoDock Vina (Trott & Olson, 2010). The molecular docking studies were completed successfully, and the visualizations of molecular docking results were realized with the help of Pymol (DeLano, 2002) and Discovery Studio Visualizer 2019 (Studio, 2008).

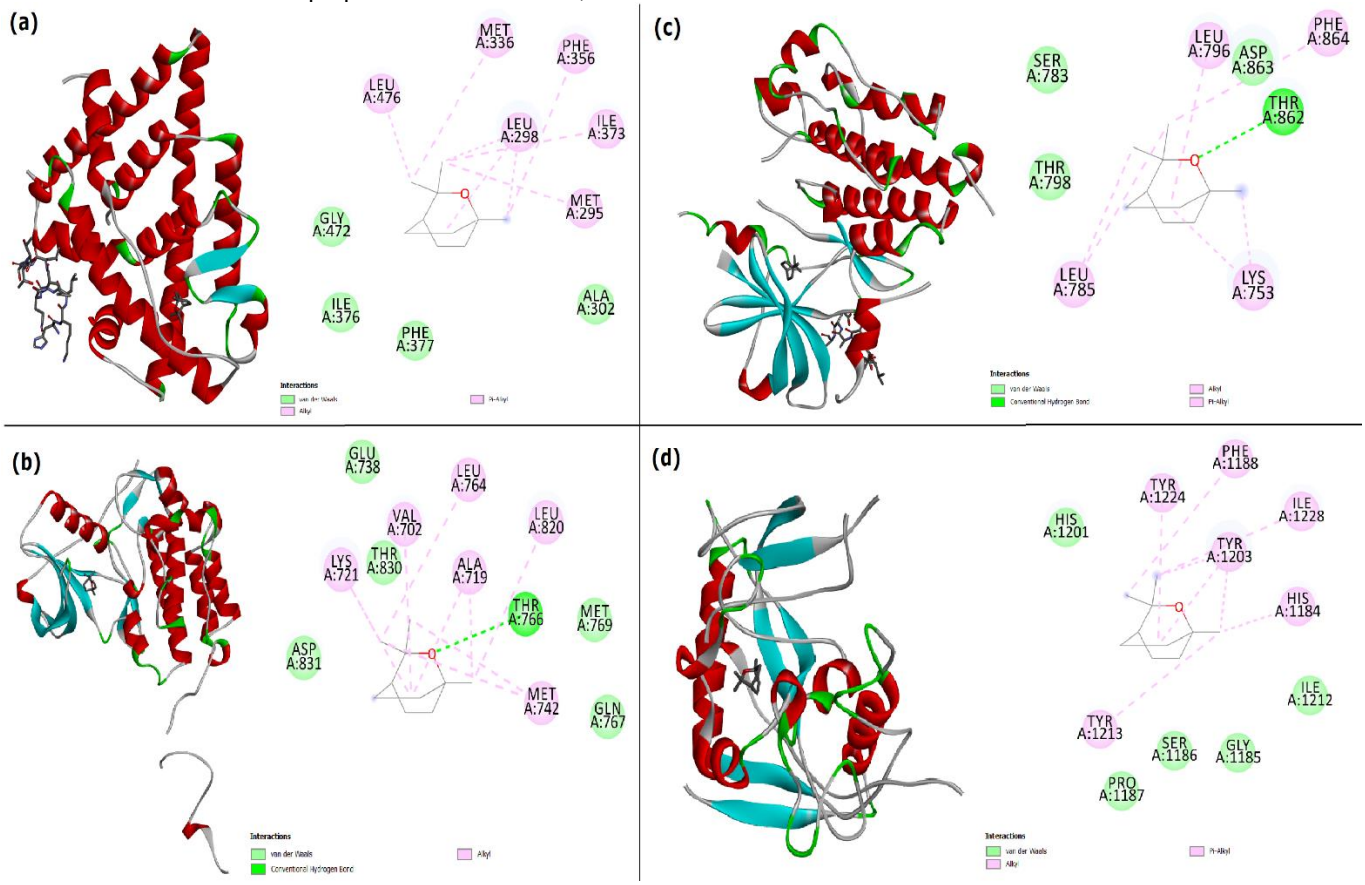

Figure 1. The close interactions of 1,8 Cineole at ERβ (a), EGFR (b), HER2 (c) and TNKS 1 (d) active sites.

Table 1. Results of molecular docking studies of 1,8 Cineole.

Receptor	Interaction residues	Binding Affinity (kcal/mol)
1X7J	**Alkyl:** Leu-476, Met-336, Leu-298, Ile-373, Met-295 **Pi-Alkyl:** Phe-356 **VdW:** Ala-302, Gly-472, Ile-376, Phe-377	-5.6
1M17	**H-Bond:** Thr-766 **Alkyl:** Lys-721, Val-702, Leu-764, Ala-719, Leu-820, Met-742 **VdW:** Glu-738, Thr-830, Asp-831, Met-769, Gln-767	-5.6
3RCD	**H-Bond:** Thr-862 **Alkyl:** Leu-796, Lys-753, Leu-785 **Pi-Alkyl:** Phe-864 **VdW:** Asp-863, Ser-783, Thr-798	-5.4
4W6E	**Alkyl:** Ile-1228 **Pi-Alkyl:** Tyr-1224, Phe-1188, Tyr-1203, His-1184, Tyr-1213 **VdW:** His-1201, Pro-1187, Ser-1186, Gly-1185, Ile-1212	-6.2

3. RESULTS

The first molecular docking study was carried out with ER-β. As a result of the docking study, the binding energy was determined as -5.6 kcal/mol, and the fact that the RMSD values were below 2 Å is an indication that the docking study was successful. In the study, 1,8 Cineole docked to the active site of ER-β made pi-alkyl interaction with the Phe-356 residue and alkyl interaction with the Leu-476, Met-336, Leu-298, Ile-373, Met-295 residues of ER-β (see Figure 1 and Table 1). Additionally, as a result of the docking study, it was determined that 1,8 cineole has van der Waals (VdW) interaction with Ala-302, Gly-472, Ile-376, Phe-377 residues of ER-β. 1,8 Cineole also had pi interactions, alkyl interactions, and VdW interactions with the same residues of ER-β as genistein (reference compound) (Manas, Xu, Unwalla, & Somers, 2004).

In the molecular docking study of 1,8-cineole and EGFR, it was determined that the binding energy was calculated as -5.6 kcal/mol, and RMSD values was below 2 Å. 1,8 Cineole made hydrogen bond, alkyl and VdW interactions in the active site of EGFR. 1,8 Cineole interacted with Thr-766 residue of EGFR and formed hydrogen bond having 3.0 Å. In addition, it was observed that alkyl interactions with Lys-721, Val-702, Leu-764, Ala-719, Leu-820, Met-742 residues and VdW interactions with Glu-738, Thr-830, Asp-831, Met-769, Gln-767 residues (see Figure 1 and Table 1).

In the study conducted with HER2 (PDB ID: 3RCD), the binding affinity was determined as -5.4 kcal/mol, similar to other docking studies. 1,8 Cineole formed hydrogen bond with Thr-862 residue of HER2. Other interactions were determined as alkyl, pi-alkyl and VdW. 1,8 Cineole interacted with Lys-753 (alkyl), Leu-796 (alkyl), Leu-785 (alkyl), Phe-864 (pi-alkyl), Asp-863 (VdW), Ser-783 (VdW), Thr-798 (VdW).

In the docking study performed with Tankyrase-1 (PDB: 4W6E), 1,8 Cineole made alkyl, pi-alkyl and VdW interactions (see Figure 1). Pi-alkyl interactions formed between 1,8 Cineole and Tyr-1224, Phe-1188, His-1184, Tyr-1213 residues of Tankyrase-1. Alkyl interaction occurred between 1,8 Cineole and Ile-1228 residue. In addition, VdW interactions occurred between 1,8 Cineole and His-1201, Pro-1187, Ser-1186, Gly-1185 and Ile-1212 residues. Binding affinity was calculated as -6.2 kcal/mol, and RMSD values gave very good results for docking study.

4. DISCUSSION AND CONCLUSIONS

Molecular docking is a preferred method in drug design. It is a useful and supportive method in new drug discovery studies. In the molecular docking method, the appropriate orientation and binding affinity of the ligand (drug candidate) in the active site of the target receptor is predicted (Korkmaz & Ayaz, 2023). In this study, considering that 1,8 Cineol is in various types of cancer (Abdalla et al., 2020; Murata et al., 2013; Rodenak-Kladniew, Castro, Crespo, et al., 2020), the receptors selected are ERβ, EGFR, HER2 and Tankyrase 1. ER-β has a wide distribution in different body regions (Hsu, Chu, & Kao, 2017; Lazennec, 2006; Siegfried, 2001; Williams, DiLeo, Niv, & Gustafsson, 2016). It has been reported in the literature that estrogen has a special place in cancers such as lung, colon and ovarian (Hsu et al., 2017; Lazennec, 2006; Siegfried, 2001; Williams et al., 2016). EGFR activation is associated with tumor growth, invasion, and metastasis (Normanno et al., 2006; Sasaki et al., 2013). Therefore, it is expressed in many types of cancer (Bethune, Bethune, Ridgway, & Xu, 2010; Glaysher et al., 2013; Rego et al., 2010). Due to these properties, it is among the important targets in anticancer studies. HER2 belongs to the EGFR tyrosine kinase family and is another important receptor chosen as a target in antitumor studies (Iqbal & Iqbal, 2014). HER-2 activation is associated with tumor development. It has been presented in literature studies that HER-2 is overexpressed in various types of cancer (Ahcene Djaballah, Daniel, Milani, Ricagno, & Lonardi, 2022; Riudavets et al., 2021; Slamon et al., 1989). Tankyrases are involved in a number of cellular functions such as telomere homeostasis, Wnt/β-catenin signaling, viral replication. Tankyrases, which play a role in disease-related cellular processes, have become one of the important targets in drug discovery studies (Kamal, Riyaz, Kumar Srivastava, & Rahim, 2014). Tankyrase is one of the prominent targets in different cancer studies. Varying levels of tankyrase expression have been reported in various types of cancer (Mehta & Bhatt, 2021; Verma, Kumar, Chugh, Kumar, & Kumar, 2021).

According to the results of the docking study performed with ERβ, it has been determined that genistein, the reference compound of ER-β (PDB ID: 1X7J), and 1,8 cineole have similar close interactions in the active site of ER-β (Manas et al., 2004). As a result of a successful docking study with EGFR, when the interaction profiles were compared with erlotinib, a cancer drug, it was seen that it has similar interactions (PDB ID: 1M17) (Stamos, Sliwkowski, & Eigenbrot, 2002). In the molecular docking study performed with HER2 (PDB ID: 3RCD), 1,8 cineole has similar interaction profiles as reference compounds (Ishikawa et al., 2011; Prabhavathi et al., 2022). When compared to neratinib, a cancer drug, and TAK-285 (reference compound in the PDB file), it was observed that 1,8 cineole, like TAK-285 (Ishikawa et al., 2011), made hydrogen bonds with Thr-862 and alkyl interactions with Leu-785. Additionally, 1,8 cineole was found to have alkyl interactions with Leu-796 and Lys-753, like both reference compounds. In the molecular docking study performed with Tankyrase-1, 1,8 cineole made similar interactions with similar residues as the reference compound in the PDB (PDB ID: 4W6E) (Johannes et al., 2015). When compared to the docking study performed with caffeic acid, 1,8 cineole was observed to have different types of interactions with similar residues (Neagu, Stefaniu, Albulescu, Pintilie, & Pirvu, 2021).

1,8 cineole is an important compound that has antimicrobial, anti-inflammatory, and anticancer properties and is found in different amounts in various essential oils. In this study, we focused on the anticancer effect of 1,8 cineole, and its interactions with ERβ, EGFR, HER2 and Tankyrase-1, which are prominent targets in cancer research, were examined by molecular docking method. Interaction profiles were compared with reference compounds and similar interaction profiles were obtained.

It has been reported in literature studies that 1,8 cineole has an apoptotic effect on human colon cancer cell lines and is associated with the inactivation of survivin and Akt and the activation of p38 in treatment (Murata et al., 2013). It is also known from literature studies that tankyrase inhibition blocks the Wnt/β-catenin pathway, which is activated in almost all human colorectal cancer, and reverses the resistance to PI3K and Akt inhibitors in colorectal cancer (Arqués et al., 2016). It was determined that the study in which 1,8 cineole had the best binding energy and RMSD value was the molecular docking study performed with Tankyrase 1. Considering the literature studies, this study predicts that 1,8 cineole may have a role in the apoptotic effect on colorectal cancer cells.

With further application of experimental in vitro studies of different cancer types, theoretically targeting different receptors depending on the cancer type and examining the best binding profiles can be guiding in pre-clinical studies.

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Author Contributions
All process steps such as conceptualization, investigation, analysis, visualization, methodology and writing were written by Bilge Bicak. The author has read and agreed to the published version of manuscript.

Conflict of Interest
The authors have no conflicts of interest to declare.

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