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Interaction of Bioactive Compounds from *Mentha arvensis* with HER2 Receptors as Anti-Breast Cancer Drugs

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Abstract

Mentha arvensis is a medicinal plant known to contain bioactive compounds such as flavonoids, terpenoids, and phenolic compounds with potential anticancer activity. This study aims to evaluate the potential of compounds from *Mentha arvensis* as HER2 inhibitors (PDB ID: 5TDN) using an in silico approach. The methods employed include drug-likeness evaluation based on Lipinski's Rule and molecular docking simulations using PyRx software, with interaction visualization performed using Discovery Studio. The docking results showed that catechin and diosmetin exhibited the best affinity values, at –8.5 kcal/mol. These findings support the potential of compounds from *Mentha arvensis* as natural anticancer candidates, particularly for breast cancer therapy, although further experimental validation is still required.

Keywords: breast cancer, HER2, Lipinski, *Mentha arvensis*, molecular docking.

Introduction

More than 2.3 million people worldwide are diagnosed with breast cancer each year, resulting in over 670,000 deaths. The incidence rate is projected to undergo an escalation of approximately 40% over the ensuing quarter-century (Tarantino et al., 2023). Annually, breast cancer remains the leading malignancy worldwide, characterized by millions of incident cases and a substantial mortality toll reaching hundreds of thousands (Wong et al., 2025). Developing nations exhibit an 88% higher incidence of breast cancer compared to developed counterparts, with respective rates of 55.9 and 29.7 per 100,000, and a concomitant mortality rate of 17%. Indonesia is among the countries experiencing a rising burden of this disease. Based on 2022 data, breast cancer dominated cancer cases in the country, with 66,271 new patients identified, accounting for approximately 16.2% of all cancer diagnoses (Saudi et al., 2026).

Cancer can be triggered by various factors, including genetic predisposition, exposure to carcinogens (such as chemicals, radiation, viruses, hormones, and chronic irritation), as well as behavioral or lifestyle factors like smoking, unhealthy diet, alcohol consumption, and lack of physical activity. However, more than 30% of cancer-related deaths are associated with behavior and dietary patterns. These factors include high body mass index, low consumption of fruits and vegetables, insufficient physical activity, smoking habits, and alcohol intake. In particular, smoking is a major contributor, accounting for approximately 70% of deaths worldwide (Pietil et al., 2024).

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Among various plant species, *Mentha arvensis* is a well-known member of the Lamiaceae family and is commonly referred to as corn mint, which is widely cultivated in Europe and Asia (Wei et al., 2023) and has traditionally been valued for its essential oil content and its use in traditional medicine (Nagaraj et al., 2026). Mint is a highly aromatic perennial herb, botanically characterized by branched stems with a square cross-section, and it spreads widely through stolons in the form of rhizomes both below and above the ground (Vining et al., 2020). Currently, this herb is cultivated across thousands of hectares worldwide. Nevertheless, projected land requirements are anticipated to escalate further, particularly in the post-pandemic era, which has catalyzed a substantial surge in the demand for natural compounds characterized by antimicrobial, antiviral, and immunostimulant properties (Tiwari, 2016). In addition to volatile components, the leaves of this plant also contain various bioactive compounds such as phenolic acids, flavonoids, sterols, coumarins, and triterpenoids, which exhibit significant pharmacological potential(Francolino et al., 2025). Hydrodistillation of fresh Japanese mint aerial parts produces an essential oil predominantly composed of menthol (62–78%), with significant secondary constituents including menthone, isomenthone, and limonene. This oil is widely utilized in various industries, including pharmaceuticals, food and confectionery, toothpaste, cosmetics, tobacco product flavoring, beverages, and other related industries (Singh et al., 2023). Additionally, the antioxidant and antimicrobial activities of *Mentha arvensis* suggest its utility as a natural source for developing therapeutic applications (Naseem et al., 2025).

Human epidermal growth factor receptor 2 (HER2), encoded by the HER2 proto-oncogene, is a member of the ErbB family, which consists of four tyrosine kinase receptors. Among this family, HER2 has the strongest kinase activity; overexpression of this receptor triggers strong signaling through HER2 heterodimer formation, thereby increasing cell proliferation (Rubin et al., 2024). The identification of the biological and clinical significance of HER2 expression in breast cancer, both in early and advanced stages, has had a major impact on therapeutic strategies. This has led to the development of targeted pharmacological interventions that have significantly redefined the treatment paradigm for HER2-positive tumors (Tarantino et al., 2023).

Based on data from the Protein Data Bank (www.rcsb.org), the crystal structure of PDB 5TDN provides high-resolution X-ray diffraction data at 1.63 Å, allowing precise atomic-level modeling of a human (Homo sapiens) antibody chain binding to a HER2 epitope in its native, untreated form. This supports accurate docking positions for small molecules, including Mentha arvensis derivatives. The biological dimer arrangement and low R-factor values (Rwork = 0.197 and R-Free = 0.223) confirm the excellent quality of the model, minimizing the complementarity-determining region (CDR) interacting with the HER2 extracellular domain (ECD). As part of the 4D5 lineage on which trastuzumab (Herceptin) is based, this structure represents the binding-ready conformation of HER2, making it an ideal model for virtual screening of target sites for breast cancer therapy.

HER2 overexpression is a driver in approximately 20–30% of breast cancer cases, and the 5TDN structure summarizes clinically validated anti-HER2 interactions. This allows testing of bioactive compounds for competitive or allosteric control mechanisms similar to those of existing inhibitors. The presence of a glycerol ligand and engineered interface modifications highlights the presence of hydrophobic and polar pockets relevant for natural product docking. Thus, predictions of binding affinity for anticancer efficacy can be refined without ligand bias. Compared with other HER2 extracellular domain (ECD) templates such as 1N8Z (2.5 Å resolution binding to Herceptin) or 3PP0 (kinase domain), the high resolution and human origin of 5TDN reinforce its selection as a model for rigorous interaction analysis in studies involving Mentha arvensis-derived compounds (Sohrab & Kamal, 2022)

HER2 (ErbB) is considered a promising target in cancer therapy because tumor cells exhibit a higher dependence on HER2 to maintain survival and support proliferation compared to normal cells (Galogre et al., 2023). Therefore, this study was conducted to evaluate the potential of active compounds from *Mentha arvensis* as candidates for breast cancer anticancer agents using an *in silico* approach. The analysis was carried out using the molecular docking method on the HER2 protein (PDB ID: 5TDN) to assess ligand–protein interactions computationally.

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Method

Material and Equipment.

The tools used for this in silico study included a laptop with Windows 11 specifications. The software used for protein and ligand preparation, as well as molecular docking, was PyRx and Pymol, while the visualization of docking results was performed using Discovery Studio.
The HER2 protein with PDB ID: 5TDN was obtained from the Protein Data Bank (www.rcsb.org). The ligands used were derived from compound data of mint (*Mentha arvensis*) leaves, based on Sravanthi et al. (2025).

Protein Preparation.

The target protein structure in .pdb format obtained from the Protein Data Bank was processed using PyMOL for the cleaning stage (protein preparation). At this stage, water molecules (H_2O) bound to the protein were removed using the "remove water" command in the PyMOL console or graphical interface. The removal of non-essential molecules aims to prevent interference during the docking simulation while ensuring that only the main polypeptide chain is used in the analysis. After the cleaning process, the modified protein file was saved again in .pdb format and then imported into the PyRx software for molecular docking simulation based on AutoDock Vina. The protein file was processed in PyRx using the Make Macromolecule function.

Ligand Preparation.

The active compounds from the *Mentha arvensis* plant were obtained by searching the PubChem database (pubchem.ncbi.nlm.nih.gov) and downloaded in .sdf structure format. They were then imported into the PyRx software, a platform for molecular docking processes based on AutoDock Vina. The compound structures were uploaded through the Import > Load Molecule feature, then converted to .pdbqt format using the Open Babel module integrated within PyRx. Before conversion, each compound underwent energy minimization using the Minimize Structure feature to obtain a more stable molecular conformation that resembles biological conditions. After all ligand structures were prepared, each file was saved in .pdbqt format for docking with AutoDock Vina.

Molecular Docking.

The prepared protein structure was opened in PyRx through the File > Load Molecule menu, then designated as the receptor using the Make Macromolecule feature. The protein was then locked as the target molecule (receptor) in the docking process. Meanwhile, the ligand structures that had been prepared and energy-minimized were imported through the Load Molecule menu in .sdf or .mol2 format, then converted to .pdbqt format using the Open Babel module available within PyRx.

After the ligands and protein were successfully prepared, the next step was to determine the grid box or the active binding area on the protein. Grid box configuration is performed through the Vina Wizard tab by adjusting the center point coordinates and box dimensions based on the location of the intended active site. This location generally refers to specific chains or residues reported in the literature or follows the position of the native ligand. Once the grid position and size parameters are locked, all test ligands are entered into the docking list. The docking simulation phase is then initiated by pressing the Start button located at the bottom of the PyRx window.

Subsequently, AutoDock Vina calculates the binding affinity between the ligand and the receptor, yielding a free energy value (ΔG) expressed in kcal/mol. The output of this docking process comprises energy scores and the optimal conformations (poses) for each evaluated ligand. The spatial orientation and positioning of the ligand relative to the target protein can be monitored directly via the 3D display in PyRx or exported to specialized visualization software, such as Discovery Studio, for more rigorous analysis. These data then serve as the empirical basis for assessing the interaction strength and specificity of *Mentha arvensis*-derived compounds against the HER2 target protein (PDB ID: 5TDN).

Validation of Molecular Docking.

Validation of the molecular docking results in PyRx was performed to assess the stability and

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strength of the ligand-protein interactions within the computational simulation. The fundamental parameter under analysis was the binding free energy (ΔG) calculated by AutoDock Vina, with values expressed in kilocalories per mole (kcal/mol). Principally, a more negative ΔG value reflects a higher ligand affinity for the protein's active site, indicating a thermodynamically superior stability of the ligand-protein complex.

Visualization of Docking Results.

The docking results obtained from PyRx were then exported to Discovery Studio Visualizer. At this stage, the ligand with the best affinity value was visualized in complex with the target protein to observe specific interactions such as hydrogen bonds, hydrophobic bonds, and the ligand's orientation within the active pocket. Additionally, the ligand positions in various docking poses can be compared to evaluate their consistency and stability at the binding site. This analysis allows the identification of important amino acid residues directly involved in the interaction, thereby supporting the molecular biology interpretation of the potential anticancer activity.

Result and Discussion

The *Mentha arvensis* plant is known to contain bioactive compounds such as flavonoids, terpenoids, and phenolic compounds that have potential as pharmacological agents. One of the benefits currently being developed from this plant is its potential as an anticancer agent. Therefore, research was conducted using an in silico approach to analyze the potential of active compounds from *Mentha arvensis* as a candidate for breast cancer medication. In this analysis, compounds isolated from the plant, which have previously been reported to have biological activity, were used, and then molecular docking simulations were performed on the breast cancer target protein, HER2.

The active compounds from *Mentha arvensis* were analyzed based on Lipinski's rule to determine their suitability as anticancer agents. The analysis results are presented in **Table 1**.

Table 1. Lipinski Analysis of *Mentha arvensis* Plant.

Compound	MW	HBA	HBD	Log P	PSA
	<500 g/mol	**<10**	**<5**	**<10**	**<140 º A**
Ferrulic acid	194	4	2	1.49	51
Caffeic acid	180	4	3	1.19	46
Chrysin	254	4	2	2.7	69
Catechin	290	5	5	1.54	73
Diosmetin	300	6	3	2.43	77

In **Table 1**, the Lipinski analysis can be concluded that several compounds in the *Mentha arvensis* plant have characteristics suitable for drugs. Some compounds meet the main criteria, such as relatively low molecular weight, a moderate number of hydrogen bonds, and balanced lipophilic properties (Pantsar & Poso, 2018). This condition indicates that these compounds have the potential for good absorption in the body through the oral route (Lipinski et al., 2001).

In **Table 2**, the interactions between these compounds and the cancer target protein are shown through binding affinity values as well as active residue interactions.

Table 2. Docking Results of *Mentha arvensis* Compounds.

No	Ligand	Binding Affinity	rmsd/ub	rmsd/lb
1	Catechin	-8.5	0	0
2	Diosmetin	-8.5	0	0
3	Chrysin	-8.3	0	0
4	Caffeic acid	-6.7	0	0
5	Ferulic acid	-6.7	0	0

Based on the docking results, all compounds from *Mentha arvensis* showed affinity toward HER2, indicated by negative ΔG values. The compounds with the strongest interactions were Catechin (–8.5

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kcal/mol), followed by Diosmetin (–8.5 kcal/mol). All ligands have negative *binding affinity* values, indicating that all compounds are able to bind spontaneously to the target protein. The lower (more negative) the *binding affinity* value, the greater the affinity and the more stable the ligand–protein complex formed (Nguyen et al., 2020).

Previous studies have demonstrated that several catechin derivatives, including EGCG, EGC, ECG, and EC, are able to interact with the HER2 receptor through hydrogen bonding at key amino acid residues located within the active site. These observations suggest that catechin-related compounds generally exhibit affinity toward HER2 binding regions. Accordingly, the catechin compounds identified from *Mentha arvensis* in the present study may also possess potential inhibitory activity against HER2-mediated breast cancer cell progression (Fakih & Tjahjono, 2020). Besides that, previous studies conducted by reported that ferulic acid could modulate HER2 expression and activate downstream signaling pathways such as AKT and ERK in MCF7 breast cancer cells. These findings support the present docking results, suggesting that ferulic acid has biological relevance toward HER2-associated mechanisms (Chang et al., 2006). According to Lewinska et al. (2016), Diosmin has a strong impact on how MCF-7 cells work at low amounts, and it looks like it could be a good option for anticancer therapy. Meanwhile, research conducted by Liu et al. (2023) shows that a combination of chrysin plus pyrotinib potentiates autophagy in HER2-positive breast cancer cells by inducing ER stress.

Caffeic acid is characterized by the presence of a phenol ring with hydroxyl (OH) groups attached at the C-3 and C-4 positions, alongside an acid-functionalized hydrocarbon chain at C-1. These structural features render caffeic acid highly effective as a metal-reducing agent, though they also make it susceptible to autoxidation and biological degradation. Its interaction with oxidizing free radicals is mediated by the catechol group bonded to an unsaturated carboxylic acid chain. Specifically, caffeic acid is a cinnamic acid derivative whose structure comprises a phenyl ring with hydroxyl orientations at positions 3 and 4. In nature, caffeic acid is predominantly found in the *trans* configuration, although the *cis* isomer can also be encountered. Ultimately, it is this geometric characteristic and structural uniqueness that stimulate the compound's anticancer activities (Alam et al., 2022).

Binding free energy represents the overall contribution of multiple interaction components, including electrostatic interactions, Van der Waals forces, and non-polar desolvation energy, involved in receptor–ligand binding. These energy components can be quantitatively calculated from various conformations obtained from molecular simulation trajectories (Fakih & Tjahjono, 2020).

After obtaining the affinity values from the docking simulation, the next step was to visualize the interactions between the ligand and the protein. This procedure aims to map the characteristics and coordination of the resulting bonds, encompassing hydrogen bonding, hydrophobic interactions, and the ligand's orientation within the HER2 protein's active pocket. Through this visual dissection, the specific amino acid residues driving the binding process can be precisely identified. Such insights refine the understanding of the test compounds' potential as HER2 inhibitors from both structural and mechanistic perspectives.

Protein-ligand interactions are fundamental to a comprehensive understanding of biological protein functions, as proteins facilitate molecular recognition by binding with a diverse range of specific molecules (Du et al., 2016). Molecular interactions observed in docking visualization represent various specific chemical forces involved in the binding between the ligand (small molecule) and the target protein. These interactions constitute an essential basis for understanding the stability of the binding complex and its potential biological activity, particularly in the context of drug development (Ma et al., 2024). The binding interactions that occur at the active amino acid site are used as indicators to predict and function to determine compounds with the highest potential biological activity (Spassov, 2024). Hydrophobic interactions and van der Waals forces contribute positively to strengthening the binding interactions and increasing the stability of the ligand-protein complex (Kumar et al., 2026). Besides that, there are hydrogen bonds, ionic interactions, and other types of interactions (Ma et al., 2024).

Based on **Table 3**, several interactions are highlighted in red, indicating the presence of unfavorable bumps or steric hindrance between the ligand and specific protein residues, such as ARG and GLN. The occurrence of these interactions can potentially decrease the stability and affinity of the ligand toward the protein, making them crucial points for evaluation during the ligand design optimization

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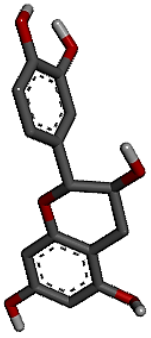
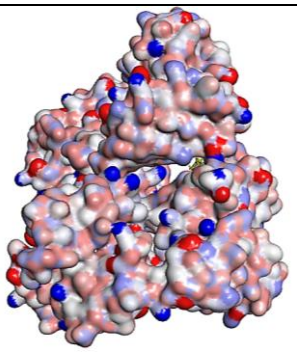
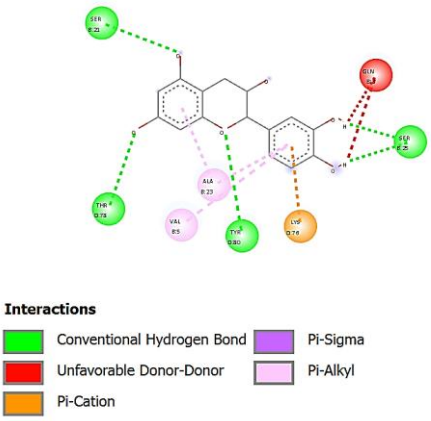
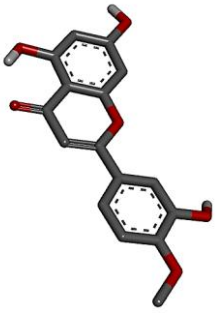
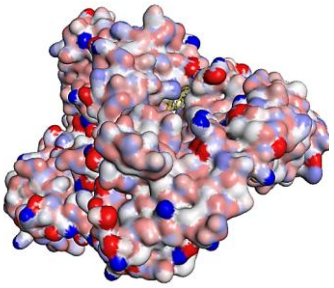
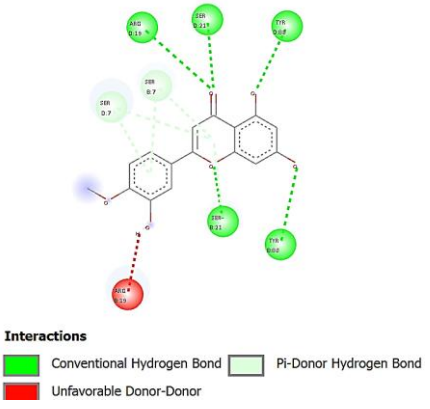
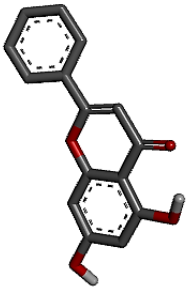
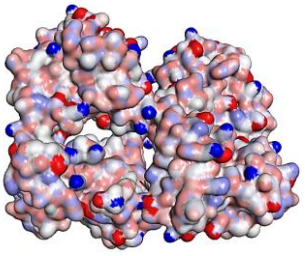
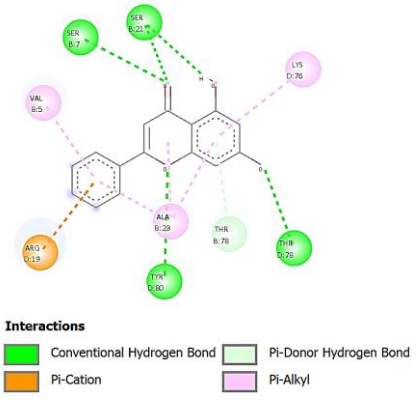
process. On the other hand, alkyl interactions represented by light purple dashed lines were also detected involving hydrophobic residues such as ALA (alanine), LYS (lysine), and VAL (valine). These hydrophobic alkyl interactions play a vital role in maintaining the stability of the ligand within the protein's binding pocket. Overall, the combination of observed hydrogen bonds and hydrophobic interactions further strengthens the stability of the ligand–protein complex, while simultaneously validating the high affinity values obtained from the previous docking simulations.

Table 3. Visualization and Interaction Results of Molecular Docking.

No	Ligand	Visualization of docking results	Amino acid residues directly involved in the interaction
1	Catechin 		
2	Diosmetin 		
3	Chrysin 		

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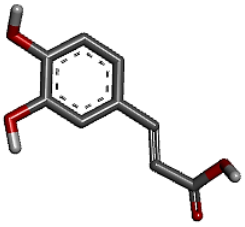
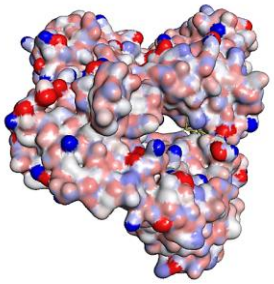
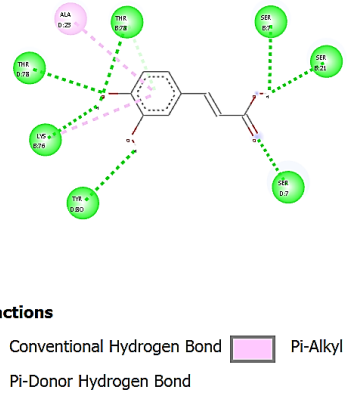
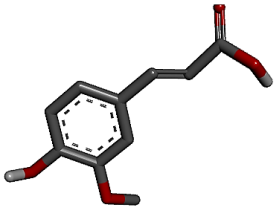
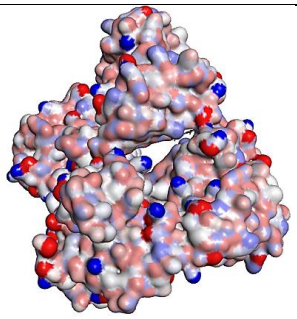
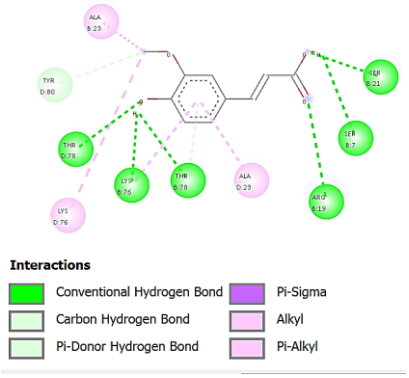
No	Ligand	Visualization of docking results	Amino acid residues directly involved in the interaction
4	Caffeic acid 		
5	Ferulic acid 		

The chemical structures of flavonoids, such as catechin, diosmetin, and chrysin, are significantly more intricate than those of simple phenolic acids like caffeic or ferulic acid. The presence of extensive aromatic rings and an abundance of hydroxyl groups allows flavonoids to establish a more diverse range of interactions with proteins, primarily through hydrogen bonding and hydrophobic pathways. The stability of the resulting ligand–protein complex is highly dependent on both the quantity and the strength of these interactions. Consequently, a profound understanding of the ligand's chemical architecture serves as a critical foundation for developing more potent and effective inhibitor candidates.

Conclusion

This *in silico* study successfully evaluated the anticancer potential of active compounds from *Mentha arvensis* against the HER2 protein (PDB ID: 5TDN). According to Lipinski's analysis, all tested compounds satisfy the criteria for drug-likeness. Nevertheless, these molecules cannot yet be considered entirely ideal for immediate use as anticancer agents. Further optimization of the ligand design is necessary to mitigate unfavorable steric clashes. The docking results highlighted catechin and diosmetin as the compounds with the highest affinity for HER2, supported by stable interactions with key active residues. Collectively, these findings reinforce the potential of *Mentha arvensis* as a promising source of inhibitor candidates that warrant deeper exploration through experimental studies.

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