**Introduction**

Breast cancer is the second leading cause of cancer death in women, with approximately 25% of breast cancers classified as HER-2 positive [1]. Human epidermal growth factor receptor 2 (HER2) is overexpressed in 20–30% of breast cancer tumors [2]. Treatment of breast cancer depends on the size of the lesion, hormone receptivity and histologic markers, presence or absence of metastatic or contralateral disease, and patient age. HER2-targeted therapies are an important advance in breast cancer treatment. Lapatinib, a tyrosine kinase inhibitor that targets HER-2, is a drug used for breast cancer therapy [3]. Signaling through other ErbB/HER RTKs can transactivate HER2 and amplify signal transduction downstream, thus bypassing the inhibitory effect of lapatinib [4].

Another strategy to find treatment for HER-2 overexpression breast cancer is exploiting the natural ingredients to be developed into pharmaceutical products. Baicalin is the most abundant flavonoid glycoside found in *Scutellaria baicalensis* species [5]. Baicalin induces the oxidative degradation of DNA and proteins that lead to the death of MCF-7 cells [6]. Baicalin can inhibit the metastasis of breast cancer by inhibiting the migration and invasion of the breast cancer cell lines MDA-MB-231 and 4T1 [7].

A preliminary test by *in silico* molecular docking of baicalin in inhibiting HER-2 receptor overexpression is required. This method can predict the interaction between the molecule and protein [8]. Therefore, this study aims to study the potential effect of baicalin to inhibit HER-2 activity using the molecular docking method.

**Methods**

The molecular docking study of baicalin and lapatinib was performed as previously reported [9,10]. Briefly, baicalin and lapatinib structures were obtained from [https://pubchem.ncbi.nlm.nih.gov/](https://pubchem.ncbi.nlm.nih.gov/) and optimized using HyperChem 8. The HER-2 protein (PDB ID: 3PP0) containing 03Q native ligand was retrieved from [http://www.rcsb.org](http://www.rcsb.org) and they were separated by Chimera 1.10.1. The grid box size and grid center coordinate for validation of the docking protocol and baicalin and lapatinib docking were refer to Putra et al. [10].

**Results**

The single-point calculation and geometric optimization energies of baicalin compounds were -5208.21 kcal/mol and -6596.2147 kcal/mol, while for lapatinib were -8781.79 kcal/mol and -8860.12
In silico study of baicalin as an inhibitor of HER-2 receptor in breast cancer

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kcal/mol. The 3D structures of optimized baicalin and lapatinib are shown in Figure 1. HER-2 protein preparation involved the separation of protein from 03Q native ligand. The prepared protein and the obtained 03Q native ligand were displayed in Figure 2. The validation of docking process produced ten conformations of 03Q native ligand which the lowest RMSD value was 0.47 Å (Table 1).

Docking of baicalin and lapatinib to HER-2 protein resulted in ten conformations with the lowest binding energy of baicalin and lapatinib were -6.21 kcal/mol and -12.19 kcal/mol (Table 2 and 3). The 03Q native ligand, lapatinib, and baicalin interacted to HER-2 through hydrogen bonding. The 03Q native ligand and lapatinib associated to HER-2 through MET 801 residue, while baicalin through LYS 753 residue (Figure 3).

Discussion

Our results showed that baicalin has the energy binding of -6.21 kcal/mol, while the binding energy of 03Q native ligand and lapatinib were -10.47 kcal/mol and -12.19 kcal/mol, respectively. The negative value of the binding energy indicates the affinity between the test compounds with the target protein. The lower the binding energy, the stronger the interaction formed [11].

Figure 1. The 3D structures of optimized baicalin and lapatinib. (a) single point calculation of baicalin, (b) geometry optimization of baicalin, (c) single point calculation of lapatinib, (d) geometry optimization of lapatinib

Figure 2. The results of protein preparation. (a) HER-2 protein without native ligand, (b) 03Q native ligand
**In vitro** studies on the anti-breast cancer activity of baicalin were assessed in MCF-7 breast cancer cells. The result demonstrated that 20 and 30 µM baicalin reduced cell proliferation in 48 and 72 hours, indicating that this compound inhibits cell proliferation [12]. Baicalin also showed a significant effect on migration and invasion suppression in highly aggressive breast cancer metastases both **in vitro** and **in vivo**, via reversal of the
epithelial-to-mesenchymal transition (EMT) process and downregulation of β-catenin expression [7]. In addition, baicalein inhibits the metastatic phenotypes of nasopharyngeal carcinoma cells by modulating integrin β8 [13]. Baicalein, a baicalin-like compound, has been reported to have anti-breast cancer activity in MCF-7 cells by inhibiting cell proliferation due to cytoskeletal alteration [14]. In silico molecular docking study of quercetin against HER-2 protein yielded a binding energy value of -8.24 kcal/mol [15].

**Conclusion**

Baicalin has a potential as an HER-2 protein inhibitor which benefits to be developed in breast cancer therapy.

**Acknowledgment**

None.

**Declaration of interest**

The authors declare no competing interests

**Author contributions**

KAAW and NKNC conceptualized the study design, KAAW and MAWS investigated the data, KAAW, MAWS, NKNC, and NKDPD wrote original draft, KAAW, MAWS, NKDPD reviewed and edited final version, KAAW looked for the funding, KAAW supervised all experiments. All authors have read the final manuscript.

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### Table 3. The result of molecular docking of lapatinib on HER-2

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Conformations</th>
<th>Binding Energy (kcal/mol)</th>
<th>Amino acid residues</th>
<th>Groups in hydrogen bonds</th>
</tr>
</thead>
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<td>HN-N</td>
</tr>
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<td>MET 801</td>
<td>HN-N</td>
</tr>
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<td></td>
<td>3*</td>
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<td>MET 801</td>
<td>HN-N</td>
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<td>-</td>
</tr>
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<td>6</td>
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**References**


