Screening *in silico* the human epidermal growth factor receptor-2 inhibitory effect of isoflavones by molecular docking method for their potential use in breast cancer

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**Abstract:**

Isoflavones are secondary phenolic metabolites found in most legumes. These compounds have important pharmacological significance such as anti-osteoporosis, anti-aging, and anti-cancer properties. Breast cancer is one of the most common cancers in women worldwide. Human epidermal growth factor receptor-2 (HER2) is an important target in breast cancer treatment. In this study, we evaluated the ability of sixty isoflavones compounds to inhibit the HER2 enzyme for their potential use in breast cancer treatments by the molecular docking method. Molecular docking was done by Autodock vina software. Lipinski 5 rule is used to compare compounds with drug-like and non-drug-like properties. Pharmacokinetic parameters of potential compounds were evaluated using the pkCSM tool. Our results showed that 35 compounds inhibited HER2 stronger than the positive control. Next, we analysed the drug-likeness according to Lipinski's rule of five and predicted pharmacokinetic-toxicological parameters of these 35 compounds. We obtained two compounds, genistein and biochanin A, which could become promising drugs for breast cancer treatment. However, *in vitro* and *in vivo* studies on the inhibition of the HER2 enzyme need to be conducted.

**Keywords:** biochanin A, breast cancer, genistein, HER2, isoflavone, molecular docking.

**Classification number:** 3.3

1. **Introduction**

Cancer is one of the leading causes of death globally, accounting for nearly 10 million deaths in 2020 of which breast cancer accounted for 2.3 million cases [1]. Breast cancer is considered the leading cause of cancer death in women [2]. In Vietnam, according to statistics from the World Health Organization, there were about 21,555 cases of breast cancer in both sexes and all ages (11.8% of cancer cases) reported in 2020 [1].

Human epithelial growth factor (EGF) receptor type 2 (HER2) is one of the EGF receptor family members. HER2 was first discovered in mice in 1984 by Weinberg’s group and was thought to play an important role in the development of breast cancer [3]. HER2 is present at high levels in about 30% of breast cancer cases [4]. HER2 gene overexpression is activated primarily through gene amplification. This leads to the activation of HER2 signalling networks such as MAPK (RAS-RAF-MEK-ERK) and phosphatidylinositol 3-kinase pathways (PI3K) (PI3K-AKT-mTOR) to induce cell proliferation, angiogenesis, and control of tumour growth [5]. Therefore, HER2 is a specific and promising target for breast cancer treatment.

Isoflavones are a subclass of flavonoids with the diphenylpropane structure (C6-C3-C6). Isoflavones are found in many different plant species such as the *Leguminosae* family, especially *Glycine max* L. and *Trifolium pratense* L. [6]. The tumour inhibitor function of isoflavones has been demonstrated in breast cancer cell lines and animal models [7, 8]. Isoflavones also have other pharmacological effects such as protease inhibition, tyrosine kinase inhibition, and anti-angiogenesis [9]. Studies of soy-based diets revealed soy use significantly decreased total cholesterol, LDL cholesterol, and triglyceride levels [10].

Molecular docking is a modelling technique used to study the binding ability and position of a protein to another structure or small molecule. Molecular docking is one of the most popular methods in structure-based drug design because of its high accuracy in predicting the structure of small molecule ligands in suitable target binding sites [11].
2. Materials and methods

2.1. Model docking

Preparation of protein structures: The crystal structure of the enzyme HER2 (ID: 3PP0) was retrieved from the Protein Data Bank RCSB (https://www.rcsb.org/) [12]. The 3PP0 complex contains the co-crystal ligand 2-{2-[4-({5-chloro-6-[3-(trifluoromethyl)phenoxy]pyridin-3-yl}amino)-5Hpyrrolo[3,2-d]pyrimidin-5 yl]ethoxy}ethanol (ID: 03Q).

We removed water molecules and co-crystals ligands from the protein molecule by using Discovery Studio software. Next, we used MGL Autodock Tools 1.5.6 software to add hydrogen atoms, optimise polar hydrogens, and Kollman charges. The active region of the protein was determined in a grid box size of 30x30x30 Å with the grid centre (x,y,z) corresponding to (34, 46, -12) [13]. This protein was saved in PDBQT format to prepare for the docking program.

Preparation of ligands: Based on previous publications, 60 isoflavones have been identified with the ability to inhibit HER2 [14-21]. The structures compounds were downloaded from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/) in SDF format. Then, we converted them to PDB format using Chimera software [22, 23]. Finally, the ligands were optimised by Avogadro software using the conjugate gradients method and converted to PDBQT format using Autodock Tools 1.5.6 [24, 25].

Performance of molecular docking: We began molecular docking enzyme HER2 with isoflavones by using Autodock Tools software. The positive control trastuzumab was downloaded from the PubChem database. Trastuzumab is one of the Food and Drug Administration’s (FDA) approved antineoplastic agents for the treatment of HER2-positive breast cancer [26-28]. The docking scores of trastuzumab were used as the positive control for selecting compounds with HER2 inhibitory effects.

Evaluation of docking results: To evaluate the docking results, the co-crystal ligand, after being separated from the protein, was redocked to the active site of the target. The process was performed successfully if the root mean square deviation (RMSD) value was less than or equal to 1.5 Å [29]. For substances that need docking, their binding ability is assessed through interaction with amino acids and its interaction energy is calculated by the scoring function of Autodock vina. If the chosen compound had a docking score lower than the positive control trastuzumab, then it was evaluated by Lipinski’s rule of five and pharmacokinetic - toxicological (ADMET) parameters.

2.2. Evaluation Lipinski’s rule of five

Lipinski’s rule of five is used to study drug-like and non-drug-like molecules to evaluate a potential molecular to become a therapeutic drug [30]. We used the online tool (http://www.scbio-iitd.res.in/software/drugdesign/lipinski.jsp) to evaluate Lipinski’s rule of five. After selecting the drug-like compounds, we continued to analyse the pharmacokinetic and toxicological parameters to provide the final results.

2.3. Prediction of ADMET by computational analysis

We use the online tool pkCSM (http://biosig.unimelb.edu.au/pkcsm/prediction) to predict the pharmacokinetic and toxicological properties of the compounds as input data SMILES formulas [31]. Predictive results of ADMET parameters including absorption, distribution, metabolism, elimination, and toxicity of potential compounds were analysed.

3. Results

3.1. Evaluation of the docking model

Before screening the compounds, the co-crystal ligand was re-docked to the active site of the target to determine the root mean square deviation (RMSD), which helps to evaluate the suitability of the docking parameters. To evaluate the similarity structural, we determined the RMSD value by Chimera software. We obtained the structural overlap of the co-crystal ligand before and after docking with the RMSD value of 1.076<1.5 Å, which will demonstrate that the results of molecular docking on the target were reliable (Fig. 1). Fig. 2 shows the 2D interaction between the co-crystallised ligand and HER2 protein.

![Fig. 1. Co-crystallised ligand re-dock results of HER2.](image-url)
3.2. Molecular docking of compounds to the target protein

After preparing the ligand, we docked sixty isoflavone compounds to screen for HER2 inhibitory activity. Our results obtained 35 compounds that had negative docking scores (ΔG) smaller than the positive control trastuzumab (ΔG=-9.4 kcal/mol), which are shown in Table 1.

### Table 1. The docking results of the 35 most potent natural and reference compounds.

<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>Docking score with HER2 (kcal/mol)</th>
<th>No.</th>
<th>Name</th>
<th>Docking score with HER2 (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Genistein</td>
<td>-9.5</td>
<td>19</td>
<td>Daidzin-4,7-diglucoside</td>
<td>-10.4</td>
</tr>
<tr>
<td>2</td>
<td>Genistin</td>
<td>-10.4</td>
<td>20</td>
<td>Isoflavone glycoside</td>
<td>-10.3</td>
</tr>
<tr>
<td>3</td>
<td>Daidzin</td>
<td>-10.1</td>
<td>21</td>
<td>Alpinum isoflavone</td>
<td>-10.9</td>
</tr>
<tr>
<td>4</td>
<td>Melonogenistin</td>
<td>-10.0</td>
<td>22</td>
<td>Angustone C</td>
<td>-10.7</td>
</tr>
<tr>
<td>5</td>
<td>Biochanin A</td>
<td>-9.7</td>
<td>23</td>
<td>Isolupalbigenin</td>
<td>-10.1</td>
</tr>
<tr>
<td>6</td>
<td>Puerarin</td>
<td>-9.5</td>
<td>24</td>
<td>Licissoflavone A</td>
<td>-9.9</td>
</tr>
<tr>
<td>7</td>
<td>Pueraria glycoside</td>
<td>-9.7</td>
<td>25</td>
<td>Licissoflavone B</td>
<td>-10.2</td>
</tr>
<tr>
<td>8</td>
<td>Oonin</td>
<td>-10.4</td>
<td>26</td>
<td>Quercetinitrinin</td>
<td>-9.6</td>
</tr>
<tr>
<td>9</td>
<td>6''-O-Acetylgenistin</td>
<td>-10.5</td>
<td>27</td>
<td>Angustone A</td>
<td>-10.5</td>
</tr>
<tr>
<td>10</td>
<td>6''-O-Acetyldaidzin</td>
<td>-10.2</td>
<td>28</td>
<td>Kaunisamine 3</td>
<td>-10.4</td>
</tr>
<tr>
<td>11</td>
<td>Siisustin</td>
<td>-10.5</td>
<td>29</td>
<td>Noshuvarisoflavone</td>
<td>-10.0</td>
</tr>
<tr>
<td>12</td>
<td>Prunetin</td>
<td>-9.7</td>
<td>30</td>
<td>Isosoueroberine</td>
<td>-11.3</td>
</tr>
<tr>
<td>13</td>
<td>Sophoricoside</td>
<td>-10.7</td>
<td>31</td>
<td>Chudalactone</td>
<td>-11.3</td>
</tr>
<tr>
<td>14</td>
<td>Erypogin K</td>
<td>-10.6</td>
<td>32</td>
<td>Methylgenistin</td>
<td>-9.9</td>
</tr>
<tr>
<td>15</td>
<td>Biochanin A 7-O-β-D-glucoside</td>
<td>-9.6</td>
<td>33</td>
<td>6''-O-malonylactone</td>
<td>-10.9</td>
</tr>
<tr>
<td>16</td>
<td>Mirilactone</td>
<td>-9.8</td>
<td>34</td>
<td>Dihydroisooderrinone</td>
<td>-11.3</td>
</tr>
<tr>
<td>17</td>
<td>3'-Methoxypuerarin</td>
<td>-9.6</td>
<td>35</td>
<td>Fisetinoflavone</td>
<td>-10.9</td>
</tr>
<tr>
<td>18</td>
<td>Puerarin 4' -O-glucoside</td>
<td>-10.2</td>
<td>36</td>
<td>Trastuzumab</td>
<td>-9.4</td>
</tr>
</tbody>
</table>

The positive control trastuzumab is the first HER2-targeted therapeutic agent to be approved by the FDA for the treatment of breast cancer and metastatic breast cancer [31, 32]. Trastuzumab binds to HER2 and inhibits HER2-mediated malignant transformation (Fig. 3). Trastuzumab has a negative docking score of -9.4 (kcal/mol) and a hydrogen bond with amino acid GLY732; a π-σ bond with LEU852; and a π-alkyl bond with PHE1004, ALA751, and LEU726 to the active site. Currently, trastuzumab is the most common treatment for breast cancer. Many studies have shown that the combination of trastuzumab with substances such as pertuzumab, vinorelbine, capcitabine, and docetaxel in the treatment of HER2-positive advanced breast cancer gives more effective results than when used alone [33].

### 3.3. Lipinski’s rule of five

Compounds are considered to be “drug-like” when they satisfy more than 2 of the 5 criteria of Lipinski’s rule of five: molecular weight (MW) <500 Da; high lipophilicity (logP does not exceed 5); no more than 5 donors of hydrogen bonding (HBD); no more than 10 acceptors of hydrogen bonds (HBA1); and a molar refractivity (MR) between 40-130. Table 2 shows the results of 20 compounds that satisfied more than 2 criteria of Lipinski’s rule of five. Next, these compounds were further predicted as ADMET.
Table 2. The results of 20 compounds that satisfied the evaluation Lipinski’s rule of five.

<table>
<thead>
<tr>
<th>No.</th>
<th>Name</th>
<th>MW</th>
<th>HBD</th>
<th>HBA1</th>
<th>Log P</th>
<th>MR</th>
<th>Drug-likeness</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Genistein</td>
<td>270.0</td>
<td>3</td>
<td>5</td>
<td>2.42</td>
<td>70.81</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>Daidzin</td>
<td>416.0</td>
<td>5</td>
<td>9</td>
<td>0.187</td>
<td>101.88</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>Biochanin A</td>
<td>284.0</td>
<td>2</td>
<td>5</td>
<td>2.723</td>
<td>75.70</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>Puerarin</td>
<td>416.0</td>
<td>6</td>
<td>9</td>
<td>0.229</td>
<td>101.87</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>Ononin</td>
<td>430.0</td>
<td>4</td>
<td>9</td>
<td>0.4901</td>
<td>106.77</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>6''-O-Acetyldaidzin</td>
<td>458.0</td>
<td>4</td>
<td>10</td>
<td>0.758</td>
<td>111.43</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>Prunetin</td>
<td>284.0</td>
<td>2</td>
<td>5</td>
<td>2.723</td>
<td>75.70</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>Erypoegin K</td>
<td>354.0</td>
<td>3</td>
<td>6</td>
<td>2.788</td>
<td>93.57</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>Alpinum isoflavone</td>
<td>336.0</td>
<td>2</td>
<td>5</td>
<td>3.898</td>
<td>92.89</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>Angustone C</td>
<td>420.0</td>
<td>3</td>
<td>6</td>
<td>5.113</td>
<td>117.69</td>
<td>Yes</td>
</tr>
<tr>
<td>11</td>
<td>Isoluphalgenin</td>
<td>406.0</td>
<td>3</td>
<td>5</td>
<td>5.437</td>
<td>117.084</td>
<td>Yes</td>
</tr>
<tr>
<td>12</td>
<td>Licousoflavone A</td>
<td>354.0</td>
<td>4</td>
<td>6</td>
<td>3.634</td>
<td>95.61</td>
<td>Yes</td>
</tr>
<tr>
<td>13</td>
<td>Licousoflavone B</td>
<td>352.0</td>
<td>3</td>
<td>6</td>
<td>3.6058</td>
<td>94.55</td>
<td>Yes</td>
</tr>
<tr>
<td>14</td>
<td>Angustone A</td>
<td>422.0</td>
<td>4</td>
<td>6</td>
<td>5.143</td>
<td>118.75</td>
<td>Yes</td>
</tr>
<tr>
<td>15</td>
<td>Kmusiatone 3</td>
<td>438.0</td>
<td>4</td>
<td>7</td>
<td>4.3073</td>
<td>119.17</td>
<td>Yes</td>
</tr>
<tr>
<td>16</td>
<td>Neohavaisoflavone</td>
<td>312.0</td>
<td>5</td>
<td>6</td>
<td>-0.0531</td>
<td>77.146</td>
<td>Yes</td>
</tr>
<tr>
<td>17</td>
<td>Isoderrone</td>
<td>336.0</td>
<td>2</td>
<td>5</td>
<td>3.898</td>
<td>92.89</td>
<td>Yes</td>
</tr>
<tr>
<td>18</td>
<td>Chandalone</td>
<td>404.0</td>
<td>2</td>
<td>5</td>
<td>5.4069</td>
<td>116.025</td>
<td>Yes</td>
</tr>
<tr>
<td>19</td>
<td>Dihydroisoderrondiol</td>
<td>370.0</td>
<td>4</td>
<td>7</td>
<td>2.279</td>
<td>94.82</td>
<td>Yes</td>
</tr>
<tr>
<td>20</td>
<td>Ficuisoflavone</td>
<td>354.0</td>
<td>3</td>
<td>6</td>
<td>2.788</td>
<td>93.57</td>
<td>Yes</td>
</tr>
</tbody>
</table>

3.4. Prediction of ADMET profile

The interaction between pharmacokinetics, toxicity, and potency are crucial for effective drugs. The pharmacokinetic profile of a compound defines its ADMET properties. After analysing the twenty above compounds, we obtained two compounds with the best prediction of ADMET and toxicity properties including genistein and biochanin A, which are presented in Table 3.

Table 3. Pharmacokinetic and toxicological prediction results.

<table>
<thead>
<tr>
<th>Properties</th>
<th>Genistein</th>
<th>Biochanin A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption Caco2 (logPapp in 10^6 cm/s)</td>
<td>0.9</td>
<td>0.897</td>
</tr>
<tr>
<td>Intestinal absorption human (% HIA)</td>
<td>93.387</td>
<td>93.028</td>
</tr>
<tr>
<td>Distribution VDs (log V/kg)</td>
<td>0.094</td>
<td>-0.341</td>
</tr>
<tr>
<td>BBB (logBBB)</td>
<td>-0.71</td>
<td>-0.221</td>
</tr>
<tr>
<td>CNS (logPS)</td>
<td>-2.048</td>
<td>-2.115</td>
</tr>
<tr>
<td>Metabolism CYP2D6 inhibitor</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>CYP3A4 inhibitor</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Excretion Total clearance (log ml/min/kg)</td>
<td>0.151</td>
<td>0.247</td>
</tr>
<tr>
<td>Renal OCT2 substrate</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Toxicity AMES</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>HEPG</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Oral rat acute toxicity (LD50)</td>
<td>2.268</td>
<td>1.851</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Skin sensitisation</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

The first property is the absorption process using human intestinal absorption (HIA) and human colon adenocarcinoma-2 cell line (Caco2), which are two important parameters that determine the absorption of a drug. A compound has high Caco2 permeability if it has logPapp >0.9 [34]. Table 3 shows that both compounds have good membrane permeability with genistein at 0.9 and biochanin A at 0.897. All compounds have good intestinal absorption (HIA>80%).

Next is the distribution process. Compounds are considered to be well distributed to tissues if logVDss>0.45 and poorly distributed if logVDss<-0.15 [34]. In Table 3, genistein and biochanin A both have a poor volume of distribution to tissues. In addition, two parameters of permeability across the blood-brain barrier (BBB) and central nervous system (CNS) are also important when evaluating the neurologic safety of the drug. The compound can penetrate the BBB if logBBB>0.3 and the corresponding CNS with values are less than -2 [35, 36]. Calculated results show that both compounds failed to enter the BBB, with little to complete failure to enter the CNS.

Cytochrome P450 enzymes are essential for the metabolism of many compounds in the liver. The two most significant enzymes of cytochrome P450 are CYP3A4 and CYP2D6. Both studied compounds are not inhibitors of CYP2D6. Genistein showed the ability to inhibit CYP3A4. Therefore, the bioavailability of substances metabolized by the CYP3A4 enzyme may be increased if used together with genistein.

Regarding elimination, we predicted total clearance and renal organic cation transporter 2 (OCT2) substrate activity. OCT2 plays an important role in the uptake of organic cations across the basolateral membrane and is considered a major transporter in the active secretion of organic cations in the kidney. Both compounds are not OCT2 substrates. The total clearance values were 0.151 and 0.247 (log ml/min/kg) for genistein and biochanin A, respectively. The toxicity prediction results demonstrated that both compounds are non-mutagenic (AMES), non-hepatotoxic, non-cardiotoxic, and have no skin toxicity.

The interaction between the two compounds with HER2 is shown in 2D by Discovery Studio Visualizer 4.0 in Figs. 4 and 5.
Figure 4 shows that genistein interacts with essential amino acids by π-alkyl bonds with LYS753, VAL734, ALA751, LEU796, and MET774; by π-σ bond with LEU785; and van der Waals with ASP863 and LEU852. Similarly, biochanin A also has π-alkyl or alkyl bonds with LYS753, VAL734, ALA751, LEU852, LEU726, MET774, and LEU796; π-σ bond with LEU785; and van der Waals with ASP863 and GLU770. Both compounds showed similarity in binding to the co-crystallised ligand of the HER2 enzyme crystal. These are also important amino acids in the active region of the HER2 enzyme. The identification of good binding with amino acids at the active site is an important step and targeting this site can inhibit the activity of 3 PP0.

The results of the docking score values showed that the two compounds have good ΔG energy values: genistein with -9.5 kcal/mol and biochanin A with -9.7 kcal/mol. The energy difference between these two isoflavones is consistent because biochanin A is strongly bound to more important amino acids at the active site. Therefore, it can be confirmed that both of these isoflavones compounds can interact well with the HER2 enzyme.

4. Discussion

In this study, we conducted virtual screening of sixty isoflavones compounds downloaded from the PubChem database. From these results we obtained twenty compounds that satisfy the criteria for an oral drug, and two promising compounds that could be developed into drugs due to their good pharmacokinetic parameters as well as low toxicity: genistein and biochanin A.

Genistein (4’,5,7-Trihydroxyisoflavone) is an isoflavone abundantly found in soybeans and other legumes. Other foods that have been shown to contain genistein consist of alfalfa, broccoli, clover sprouts, cauliflower, and sunflower seeds [37]. The compound genistein is believed to be a potent tyrosine kinase inhibitor, cell proliferation inhibition, and differentiates cancer cells [38]. Previous studies have shown that genistein at concentrations ≥1 μM inhibited HER2 protein expression and phosphorylation through an ER-independent mechanism. In the presence of ERα, genistein mimicked E2 and inhibited HER2 protein phosphorylation [39]. Genistein was a potent growth inhibitor in both MCF-7 cells (IC50 values of 10.5 μg/ml) and MDA-468 cells (IC50 values of 6.5 μg/ml) [40]. According to another study, a high soy diet containing up to 45 mg of genistein per day that could help reduce cancer risk [41].

Biochanin (5,7-Dihydroxy-4’-methoxyisoflavone) is a member of the 7-hydroxyisoflavone group substituted by an additional hydroxyl group at the 5 position and a methoxy group at the 4’ position. Biochanin A is a natural isoflavone found in many species of clover (Trifolium pratense), especially red clover, and in many herbal supplements. In addition, it is also present in other crops such as soybeans, alfalfa, peanuts, and chickpeas [42, 43]. It was found that biochanin A selectively targets HER-2-positive SK-BR-3 breast cancer cells without affecting normal breast epithelial cells (Michigan Cancer Foundation [MCF]-10A)
Another reported research has proved that biochanin A displays the best potency towards cancerous breast cells with an IC<sub>50</sub> of 0.32 μM [45]. In HER2-positive breast cancer, biochanin A was shown to inhibit cell survival, signalling pathways, invasive enzyme expression, and activity in SK-BR-3 cancer cells when they were treated with biochanin A (2-100 μM) and incubated for 72 hours at 37°C [44, 46]. Apart from breast cancer, this compound has also been shown to play a potential role in prostate cancer cells, pancreatic cancer cells, and melanoma cancer cells [44]. Therefore, biochanin A is a good candidate for further research and improvement of the properties of this compound.

5. Conclusions

In conclusion, from sixty isoflavone compounds, we found two highly promising natural HER2 inhibitor compounds that satisfy the criteria of Lipinski’s rule of five and ADMET. Genistein and biochanin A, with good pharmacokinetic parameters, low toxicity, low hepatotoxicity, and excreted by the kidneys. However, further in vitro and in vivo studies are needed to evaluate these two potential compounds as breast cancer drugs.

CRediT author statement

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COMPETING INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

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