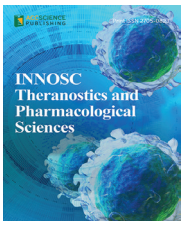
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RESEARCH ARTICLE

Molecular Docking Studies of Glabrene and Human Epidermal Growth Factor Receptor Kinase

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Abstract:

Background: Human epidermal growth factor receptor 2 (*Her2*) gene located in human chromosome17, encodes Her2 tyrosine kinase protein, and is overexpressed in breast cancer cells. *Her2* is activated on phosphorylation of tyrosine by adenosine triphosphate (ATP). Nonetheless, *Her2* excessively partakes in the development and prognosis of specific types of aggressive breast cancers. Therefore, *Her2* inhibition therapy is primary target for the treatment of aggressive breast cancer. At present, lapatinib is one of the Food and Drug Administration approved *Her2* inhibitors used in cancer therapy. In molecular docking process, glabrene with slightly higher binding energy competitively bound to the active receptor site comparable to lapatinib and ATP. Therefore, glabrene could emerge as a potential candidate for restricting *Her2* overexpressed breast cancer.

Objective: The present study aimed to demonstrate the inhibitory activity of glabrene, an isoflavene and xenoestrogen found in liquorice root, along with known *Her2* inhibitor, lapatinib.

Methods: ATP, lapatinib, and glabrene were docked on human *Her2* protein 3D structure which revealed glabrene as a competitive *Her2* inhibitor akin to lapatinib.

Results: The docking results suggested the binding site similarities of ATP, lapatinib, and glabrene. The binding energies of docked ATP, lapatinib, and glabrene complexes with *Her2* were −9.1 kcal/mol, −10.5 kcal/mol, and −11.3 kcal/mol, respectively.

Conclusion: The *in silico* docking simulation of ATP, lapatinib, and glabrene suggested that glabrene is likewise a competitive *Her2* inhibitor.

Keywords: Breast cancer, Human epidermal growth factor receptor 2, Adenosine triphosphate, Lapatinib, Glabrene, *In silico* docking, Molecular dynamics.

1. Background

Human epidermal growth factor receptor 2 (*Her2*) gene belongs to the epidermal growth factor receptor family. *Her2* gene encodes *Her2*, a tyrosine kinase protein. *Her2* is activated by phosphorylation of tyrosine by adenosine triphosphate (ATP). Amplification of *Her2* on cells surface of breast cancer cells leads to the proliferation and growth of cancer. Multiple factors had been associated with

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breast cancer progression including overexpressed estrogen receptor alpha (ERα) and *Her2*. Nevertheless, overexpression of *Her2* on cells surface plays a key role in the signal transduction cascade with uncontrolled activity contributing to proliferation of cancerous cells [1,2]. Besides, *Her2* partakes in the development and prognosis of specific types of aggressive breast cancers. In 1980s, targeting *Her2* was a key focus in the discovery of monoclonal antibodies that hinder the functions in extra cellular domains (ECD) [3]. A common feature of kinase active site includes ATP binding pocket in kinases and on the activation of kinase, the C-helix of kinase swivels around 90^0 to position the glutamate residue. Furthermore, the activation loop extends away from C-helix and exposes the substrate binding site. Small molecule inhibitors demonstrate better binding affinity to the receptor by mimicking the shape and hydrogen bonding interactions of ATP, restricting the receptor activation [4]. Besides, *Her2* ECD, inept for oncogenic function, is often cleaved in tumors suggesting possible restraint of ECD-targeting approaches [5]. Overexpression of *Her2* ensues in about 15–30% of breast cancers and 10–30% of gastric/gastroesophageal cancers and, therefore, is a prognostic and predictive biomarker. Henceforth, *Her2* is a vital biomarker for targeted therapy in aggressive breast cancer patients [6]. However, *Her2* overexpression has also been noticed in other cancers such as ovary, endometrium, bladder, lung, colon, and head and neck. *Her2* targeted therapies have radically changed the outcome of patients with *Her2* positive breast and gastric/gastroesophageal cancers. Conversely, the same treatment outcome for other *Her2* overexpressing cancers was not effective [7].

The World Health Organization affirmed breast cancer as one of the leading malignant cancers in women globally. *Her2* receptor plays a significant function in pathogenesis of a plethora of human cancers regulating cell growth, survival, and differentiation. These processes occur through multiple transduction pathways resulting in cell proliferation and differentiation. *Her2*, a new oncogene is also familiar as *p185* or *ErbB2*. The *Her2* receptor is encoded by *Her2* gene located in human chromosome 17(17q12). *Her2* contains1255 amino acid residues forming a 185 kD *trans*membrane glycoprotein [8]. *Her2* receptor is present as a monomer on the cell surface. *Her2* is present in open confirmation and, hence, is the most accessible dimerization partner with high ligand binding affinity resulting in signaling potency. Furthermore, *Her2*-HER3 heterodimer is the most potent stimulator of downstream pathways (PI3K/Akt and MAKPK/ERK1/2) that are extremely crucial for regulating cell growth and survival [9,10]. At present, lapatinib is the only active *Her2* kinase inhibitor drug approved by Food and Drug Administration (FDA) for *Her2*-positive advanced stage breast cancer patients. As a result, breast cancer treatment depends on the regulation of *Her2*, often determined using dual probe fluorescence *in situ* hybridization.

Despite the fact that there has been a remarkable development in *Her2*-targeted therapies, much of *Her2*-positive patients still die of reverted breast cancer suggesting the prerequisite for alternative therapies. To develop novel potential *Her2* inhibitors, the structure-based high-throughput virtual screening was evaluated for glabrene using OSIRIS property explorer server. The results were as follows: (i) cLogP 3.65; (ii) solubility −4.01; (iii) molecular weight 322.36; (iv) topological polar surface area (TPSA) 58.9; (v) drug likeness −3.09; (vi) H bond acceptor 4; (vii) H bond donor 2, (viii) Nb stereo centers 0; (ix) Nb rotatable bonds 1; and (x) drug-score 0.27. The results from server suggested no noticeable mutagenic, tumorigenic, and irritant toxicity risks for glabrene [11].

Postmenopausal women are increasingly shifting toward the usage of botanicals to reduce menopausal symptoms due to increased risk of traditional breast cancer estrogen-based hormonal therapies. The side effects of such therapies include fatigue, vaginal dryness and discharge, nausea, hot flashes, and joint and muscle pains [12]. Glabrene is a rare natural isoflav-3-ene present in licorice root (*Glycyrrhiza glabra*). *In vivo*, glabrene functioned as a ER suggesting it's potential to impersonate the beneficial activities of estrogen [12]. Furthermore, glabrene bound to human ER, operated as agonist for ER-mediated transcription while activating creatine kinase (a known estrogen responsive gene marker) in estrogen responsive tissues. Glabrene ameliorated estrogenic activity in breast, bone, and vascular cancer tissues. In addition, glabrene

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displayed antimutagenic activity [12,13]. Glabrene with or without estradiol-17β could be novel target for modulation of vascular injury and atherogenesis for the prevention of cardiovascular diseases in postmenopausal women [14]. Glabrene exerted almost identical effects to that of raloxifene on creatine kinase activity suggesting that glabrene is an antagonist to estradiol-17β in these processes, with both agonistic and antagonistic effects [15]. Earlier *in silico* docking study revealed that glabrene was a potential agonist with strong binding energies to ERα and ERβ receptors [16]. Therefore, glabrene has been classified as a phytoestrogen with diversified activities as tyrosine inhibitor that inhibits melanin formation in melanocytes. Hence, glabrene is a prospective cosmetic skin lightning agent [17]. Nevertheless, safety should be foremost consideration for tyrosine inhibitors, especially for the ones in food and cosmetic products due to their regular use in unregulated quantities. The structures of ATP, lapatinib, and glabrene are shown in **Figure 1**.

Glabrene exerted estrogenic effects on breast, vascular, and bone tissues. Furthermore, glabrene functioned as ER agonist in different tissues. *In vivo*, glabrene displayed tissue specific stimulatory effects comparable to estradiol. Glabrene prevented melanin formation by inhibiting tyrosinase [17]. This led us to investigate glabrene effect on *Her2* positive breast cancer using *in silico* docking and molecular dynamic simulation studies. The potential *Her2*-inhibitor observed in our present study could be useful in designing a new *Her2*-inhibitor in postmenopausal women.

2. Methods

2.1. Lipinski's rule of five

The initial stage of drug discovery process requires the assessment of drug-likeness of lead molecules that can help in reducing experimental costs. The best lead candidate should not violate more than one criterion as defined by the Lipinski's "rule of five" (RO5). These rules include molecular weight (no greater than 500 Daltons or g/mol), octanol-water partition coefficient (Log_p of 5 or less), hydrogen bond donors (5 or less), and acceptors (10 or less). The drug likeliness tool software (DruLiTo) is a freely available software package used to establish the physicochemical characteristics of glabrene, lapatinib, and ligand (2-{2-[4-({5-chloro-6-[3-(trifluoromethyl)phenoxy]pyridin-3-yl} amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy} ethanol), while ligand was cocrystallized RCSB PDB ID: 3PP0 crystal structure. Of these, three compounds glabrene complied with majority of Lipinski criteria compared to lapatinib and ligand (**Table 1**) [18].

2.2. Receptor protein preparation

For the present study, the X-ray diffraction crystal structure of *Her2* kinase domain, along with cocrystalized ligand (PDB ID: 3PP0) with 2.25 Å resolution was retrieved from RCSB protein data bank. The coordinates of protein structure contained chain-A and chain-B, cocrystallized water, and ligand responsible for elevated resolution and stability of protein. Hence, water molecules, ligand, and chain-B were removed

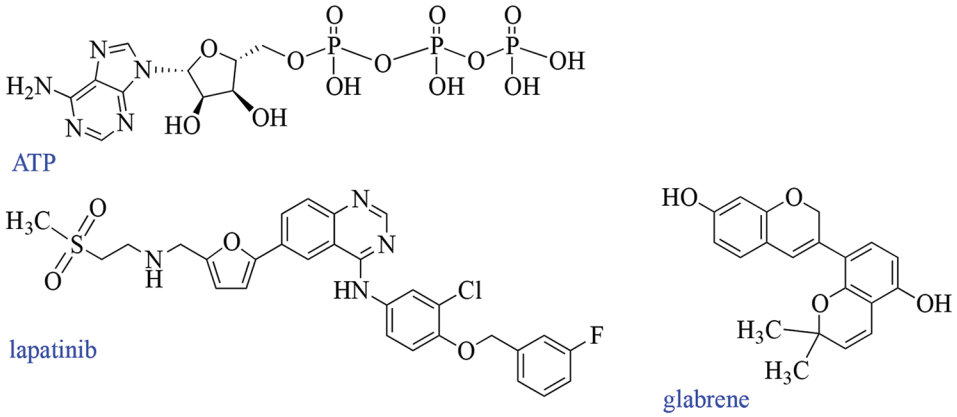


Figure 1. Structures of ATP, lapatinib, and glabrene.

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Table 1. Lipinski rule of five for glabrene, lapatinib, and ligand

Ligand	Mol. Wt (≤500)	Log_p (≤5)	H-Donors (≤5)	H-Acceptors (≤10)
Glabrene	322.36	2.463	0	4
Lapatinib	581.06	1.749	0	8
Ligand	493.90	1.4	0	8

using Discovery Studio software while retaining chain A for docking study. The missing bond orders, charges, bonds, and hybridization states of the protein were allocated with the help of Molegro Virtual Docker (MVD) [19].

2.3. Protein validation

The quality of *Her2 (*3PP0) protein was validated with Ramachandran plot (Ramachandran plot, Ramachandran map, and Ramachandran diagram) (Ramachandran Plot Server, Zlab. University of Massachusetts Medical School). The 248 (99.200%) residues in favored region, 2 (0.800%) residues in allowed region, and 0 (0.000%) residues in outlier region, while the parameters of *Her2* chain A are stable and suitable for superior quality docking purpose (**Figure 2**).

2.4. Ligands and target preparations

The two dimensional structures of lapatinib (Pubchem CID: 208908) and glabrene (Pubchem CID: 480774) were generated with the help of ChemDraw 20.0 and then, converted to 3D structure using Chem3D 20.0 software. The ligands molecular geometry optimization was achieved with energy minimization applying molecular mechanics (MM2) force field and saved in PDB format (Chem3D 20.0 software). Furthermore, the target preparation, optimization, and energy minimization (Charmm19 force field) attained using Discovery Studio 2021 client software.

2.5. Docking between *Her2* and ligands

Glabrene and lapatinib simulated interactions with *Her2 (*3PP0) were established using AutoDock Vina (Molecular Graphics Lab, La Jolla, CA, USA) [20]. A potential binding cavity selected for this docking study was identified on *Her2* receptor (3PP0 chain A) with a volume of 133.12 Å using

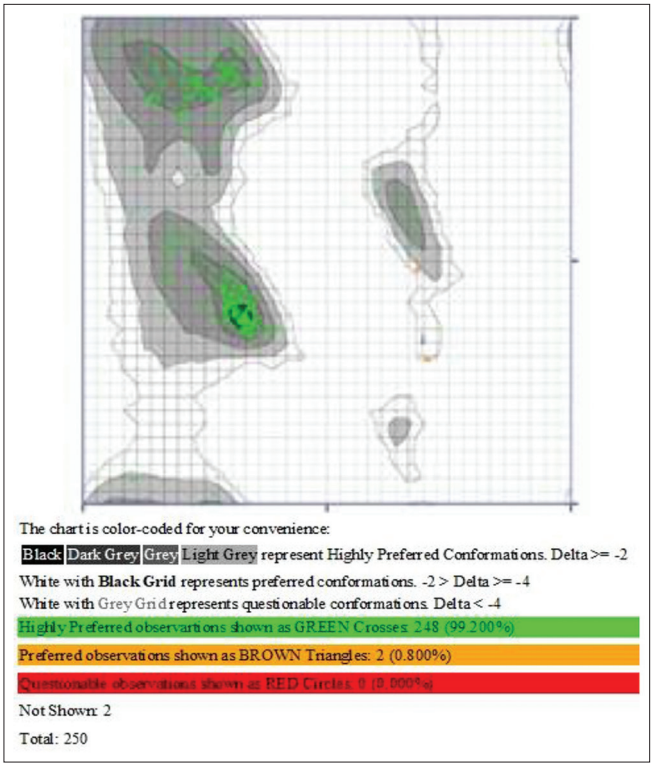


Figure 2. Ramachandran plot of *Her2*.

Molegro Virtual Docking 2011. 4.3.0 (MVD) and Ligscout 4.4.8 softwares (**Figure 3**). The PyRx integrated AutoDock Vina software prepared the target in a rigid conformation, while the ligands were allowed to be adaptable to the target. The software determined the lowest binding energies using varied confirmations of each ligand [21].

The docked results of fourteen naturally occurring isoflav-3-enes; 2-metoxy judaicin, 2'-O-methylsepiol, dimethoxytrihydroxyisoflavene, erypoegin A, erypoegin B, glabrene, haiginin A, haiginin B, haiginin C, haiginin D, judaicin, judaicin-malonyl-glucoside, neoraufladene, and sepiol are shown in **Figure 4**.

The docked binding energies of these compounds with *Her2* kinase suggested that glabrene with lowest binding energy is ideal candidate for further explorations (**Table 2**).

The docked complexes of ligand, ATP, lapatinib, and glabrene to *Her2* are shown in **Figure 5**.

2.6. Protein-ligand unbinding simulation

Protein-ligand interactions transpiring away from the active site at the time of ligand binding and unbinding could determine molecular selectivity and activity. Molecular Motion Algorithms

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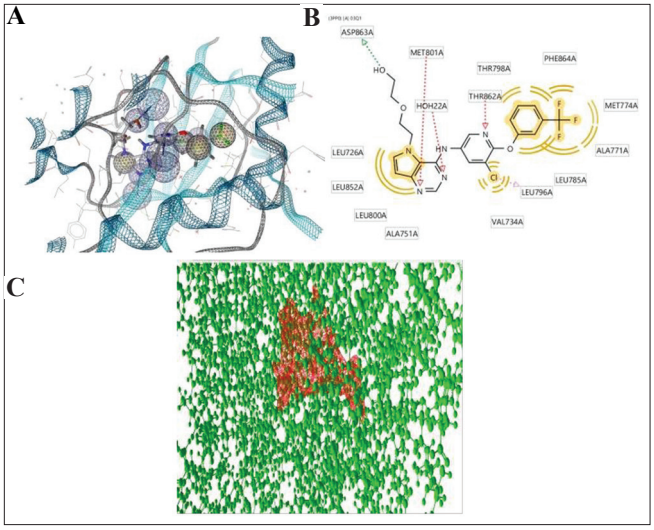


Figure 3. (A) Ligand in *Her2* Cavity. (B) Ligand interactions with amino acids in *Her2* cavity and (C) *Her2* active-site cavity volume (in red).

Table 2. Binding energies of isoflav-3-enes

Sample No.	Name	Binding Energy (Kcal/mol)
1	2'-*O*-methylsepiol	−8.8
2	2-methoxy judaicin	−9.3
3	Dimethoxytrihydroxyisoflavene	−9.2
4	Erypoegin A	−9.1
5	Erypoegin B	−10.2
6	Glabrene	−11.3
7	Haiginin A	−8.9
8	Haiginin B	−8.8
9	Haiginin C	−9.3
10	Haiginin D	−9.0
11	Judaicin	−10.0
12	Judaicin-malonyl-glucoside	−10.1
13	Neoraufladene	−9.2
14	Sepiol	−9.2

(MoMA)-LigPath is a web server to calculate MoMA. The server simulates ligand unbinding from the binding site of target to the surface. Furthermore, the server studies flexibility of protein side-chains and ligands including statistical restrictions. This method generates mechanistic data of ligand pathway from surface of protein to the binding site and/or from binding site to the surface. MoMA-LigPath offers molecular interface graphics, guiding the ligand from surface of protein to binding site. Meanwhile, MoMA-LigPath sorts selected residues that are away from binding site and play an essential role in ligand binding or in driving the ligand to binding site. The ligand unbinding from receptor pathways generated by MoMA-LigPath are a primary approximation, providing valuable information about protein ligand interactions that prompted the selection of docked molecular complexes of 3PP0/glabrene and 3PP0/lapatinib for unbinding simulations with MoMA-LigPath application (**Figure 6**) [22,23].

2.7. Molecular dynamics simulation study

Internal coordinates normal mode analysis (iMOD) server instinctively recreates the combined functional motions of biological macromolecules. iMOD server facilitates the exploration of such functions, simultaneously generating feasible transition pathways between two homologous structures, even with larger molecules. The specific internal coordination ameliorates the efficacy of normal mode analysis while extending its application and simultaneously maintaining stereochemistry. Vibrational analysis, motion animations including morphing trajectories can be conducted at different resolutions almost interactively. In this context, iMOD provides progressive visualization capabilities for clarifying collective motions and improved affine-model-based arrow representation of domain dynamics. The resultant all-heavy-atoms confirmations are applicable for more advanced modeling flexibility. The binding effects of ATP, lapatinib, and glabrene on *Her2* kinase were assessed based on conformational stability of protein/ligand complex interactions by performing normal mode analysis (NMA) using iMOD server [24]. In this process, multiple properties such as deformability and eigenvalues of protein/ligand interactions, variance, covariance, and elastic factors taken into consideration [25,26].

3. Results and discussion

3.1. *In silico* docking study

Lapatinib, used in the treatment of *Her2* overexpressed breast cancer, displayed side effects including dermatologic adversities and cardiac toxicities [27,28]. The objective of this study is to initiate the discovery of potential lead molecules

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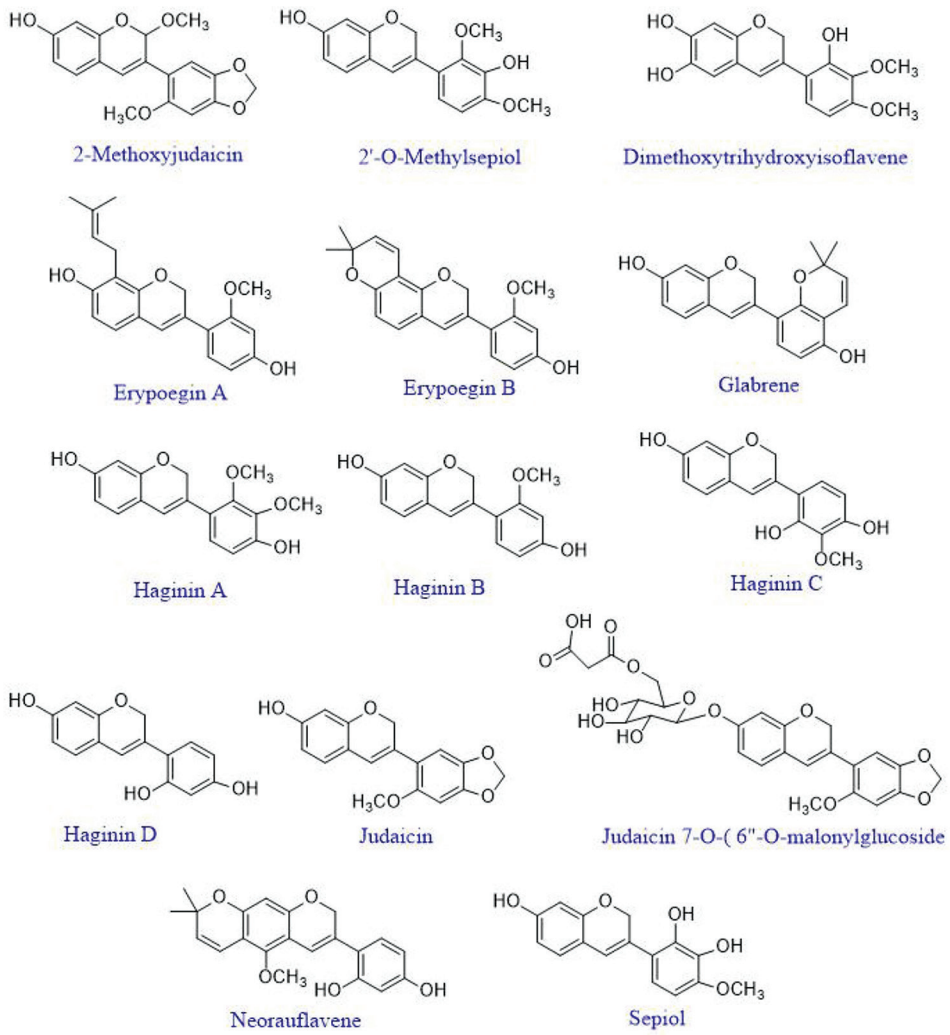


Figure 4. Isoflav-3-enes: 2-metoxy judaicin, 2'-O-methylsepiol, dimethoxytrihydroxyisoflavene, erypoegin A, erypoegin B, glabrene, haginin A, haginin B, haginin C, haginin D, judaicin, judaicin-malonyl-glucoside, neoraufladene, and sepiol.

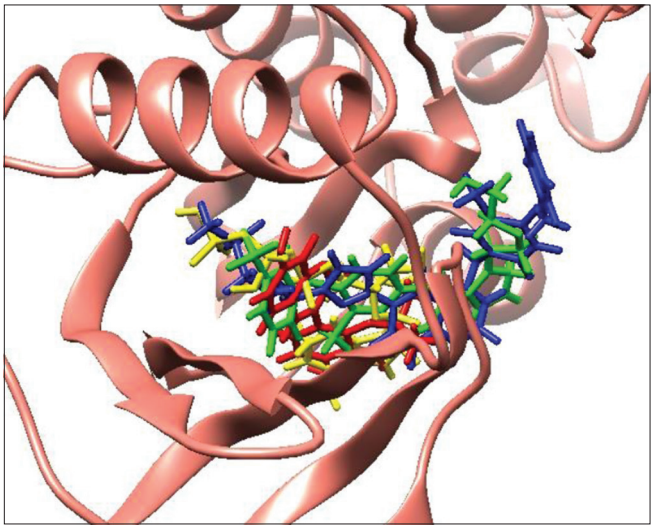


Figure 5. The docked complexes of ligand (yellow), ATP (green), lapatinib (blue), and glabrene (red) to *Her2* (hot pink).

that display effective inhibitory activity of over expressed *Her2* kinase in breast cancer cells in postmenopausal women. The active binding site of *Her2 (*3PP0) was identified through the observation of ligand binding interactions with *Her2* in *Her2*/ ligand complex X-ray crystallographic structure retrieved from Protein Data Bank. Through docking study, the hit molecule, glabrene was thoroughly evaluated for its binding ability and behavior in protein active site. The resultant best pose complex from docking was subjected to molecular dynamics simulation analysis to further establish its efficacy in breast cancer therapies. The data suggested that the hit molecule behaved almost in accordance with FDA approved drug and lapatinib (*Her2* inhibitor). Besides, ring generator (Rg) and potential energies suggested compact

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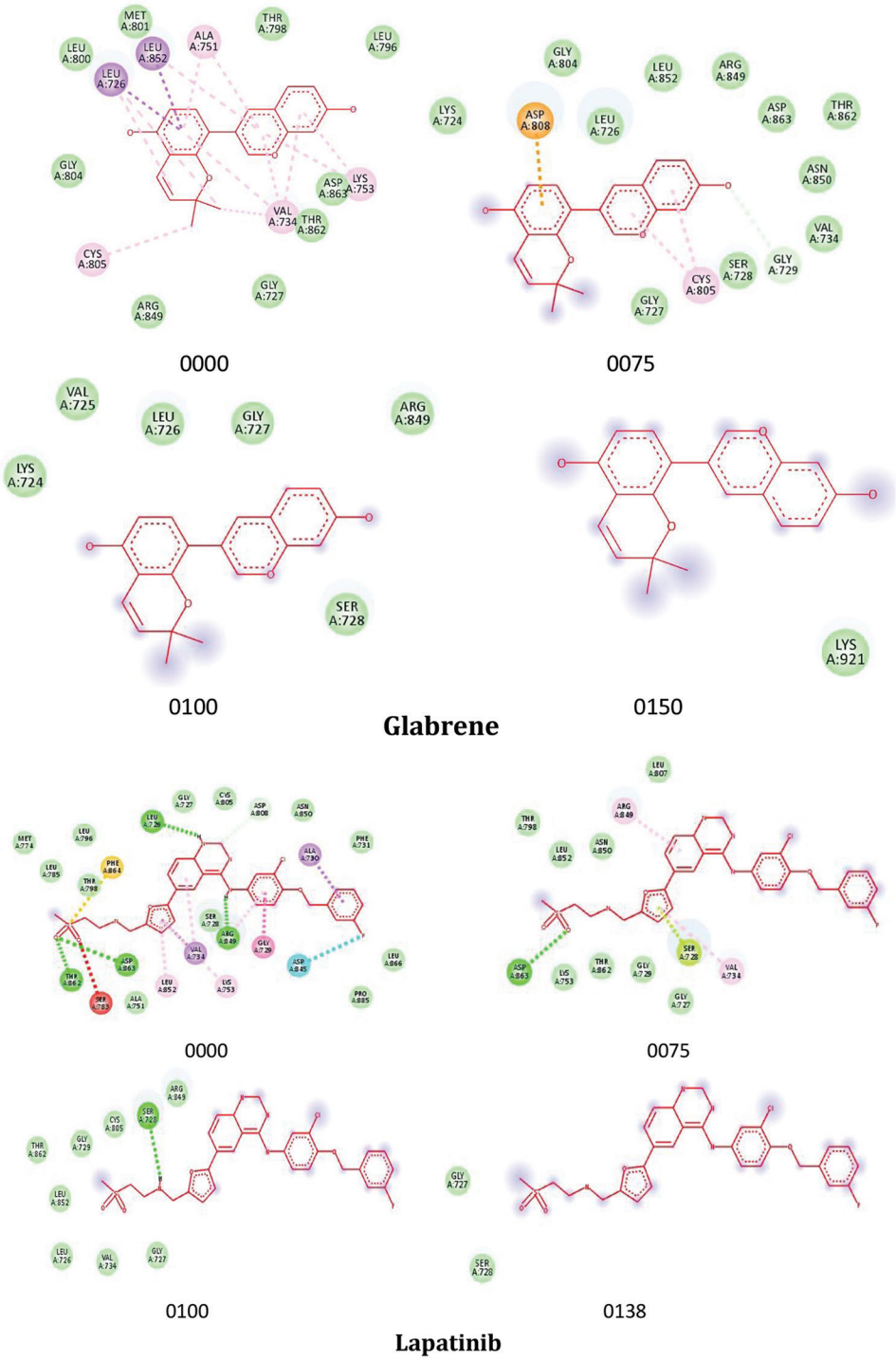


Figure 6. The unbinding simulations of glabrene and lapatinib from *Her2* binding site to protein surface.

and consistent protein-hit complexes throughout the simulation process. The residues Met 801 and Asp 863 located in *Her2* cavity constructed polar interactions with glabrene surrounded by hydrophobic contacts. The binding patterns and alignments of glabrene and lapatinib to *Her2* were almost similar suggesting that glabrene could emerge as an efficient inhibitor of *Her2*.

Glabrene formed hydrogen bonds (darker green) with Met 801 and Asp 863; alkyl and pi-alkyl interactions (light purple) with, Val 734, Ala 751, Lys 753, and Cys 805; and Pi-Sigma interactions (dark purple) with Leu 726 and Leu 852, while Vander Waals interactions (light green) with Gly 727, Ser 728, Gly 729, Ile 752, Leu 785, Leu 796, Thr 798, Gln 799, Leu 800, Arg 849, and Thr 862 amino acid residues of *Her2*.

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Nonetheless, lapatinib formed hydrogen bonds (darker green) with Ser 783, Arg 849, Thr 862, and Asp 863; alkyl and pi-alkyl interactions (light purple) with Lys 753, Cys 805, Leu 852, and Pe 864; Pi-Sigma interactions (dark purple) with Ala 730 and Val 734; and Pi-Sulpur interaction (attractive orange) with Phe 864, while Van der Waals forces with Leu 726, Gly 727, Phe 731, Ala 751, Met 774, Leu 785, Leu 796, Pro 805, Asp 808, Asp 845, Aln 850, Leu 866, and Lys 883 amino acid residues of *Her2* (**Figure 7**). However, lapatinib displayed unfavorable acceptor with Ser 783.

Glabrene displayed slightly higher binding energy (combined value of hydrogen bonds and Van der Waals) −11.3 kcal/mol with *Her2* compared to lapatinib −10.5 kcal/mol and ATP −9.1 kcal/mol suggesting glabrene that is a competitive binder to *Her2* active site comparable to lapatinib and ATP (**Figure 7**). In addition, glabrene formed hydrogen bonds with Met 801 and Asp 863 of *Her2* with bond lengths of 2.08 Å and 2.18 Å, respectively. On the contrary, lapatinib formed hydrogen bonds with Leu 726, ARG 849, Thr 862, and Asp863 with bond lengths of 3.31 Å, 5.72 Å, 2.48 Å, and 3.10 Å, respectively (the bond lengths are measured as described in Discovery Studio manual). Glabrene with a small molecular weight of 322.36 g/mol and shorter interaction distances of hydrogen bonds appears to be a competitive inhibitor comparable to lapatinib with molecular weight 581.06 g/mol and with longer interaction distances of hydrogen bonds. Glabrene displayed higher binding energy of −11.3kcal/mol, while the binding energy of lapatinib was −10.5 kcal/mol [29]. Besides, glabrene molecular weight is within Lipinski's rule of five criteria for molecular weight (<500 g/mol.) in contrast with lapatinib [18].

3.2. Protein-ligand unbinding simulation

MoMA LigPath identifies selected residues, despite being away from the binding site could yet play a key role in ligand binding or in driving the ligand to the binding site. MoMA LigPath of glabrene yielded data of different molecular interactions related to decreasing distance from binding site. In docking study, glabrene displayed greater negative binding energy with *Her2* than lapatinib. This binding energy as well as combined

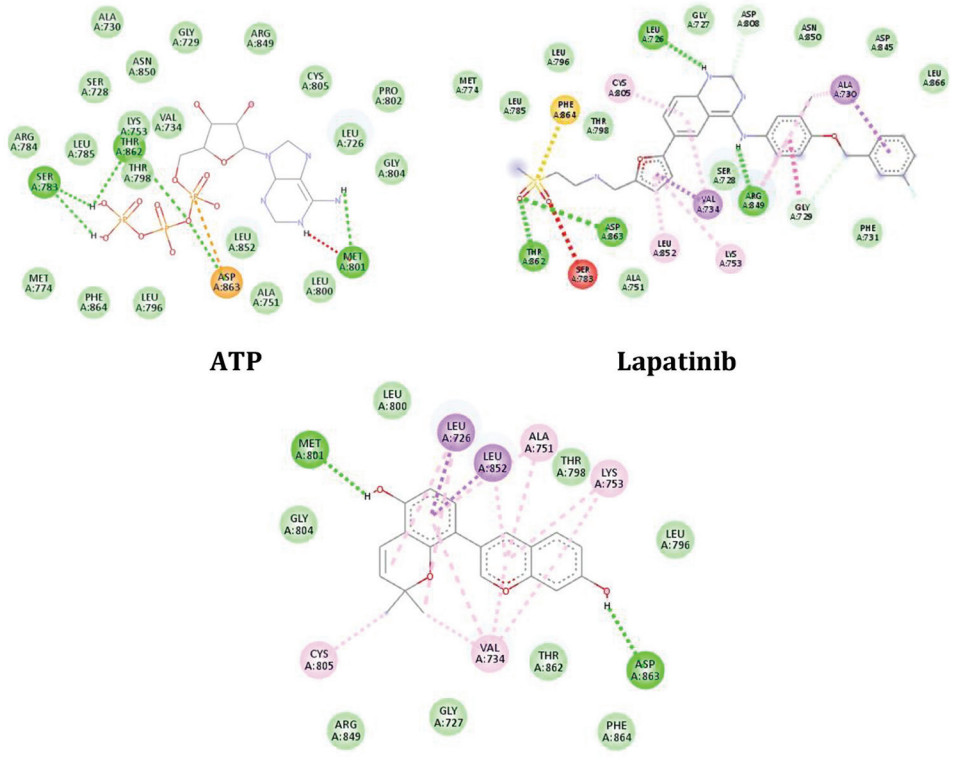


Figure 7. Interactions of ATP, lapatinib, and glabrene with *Her2*.

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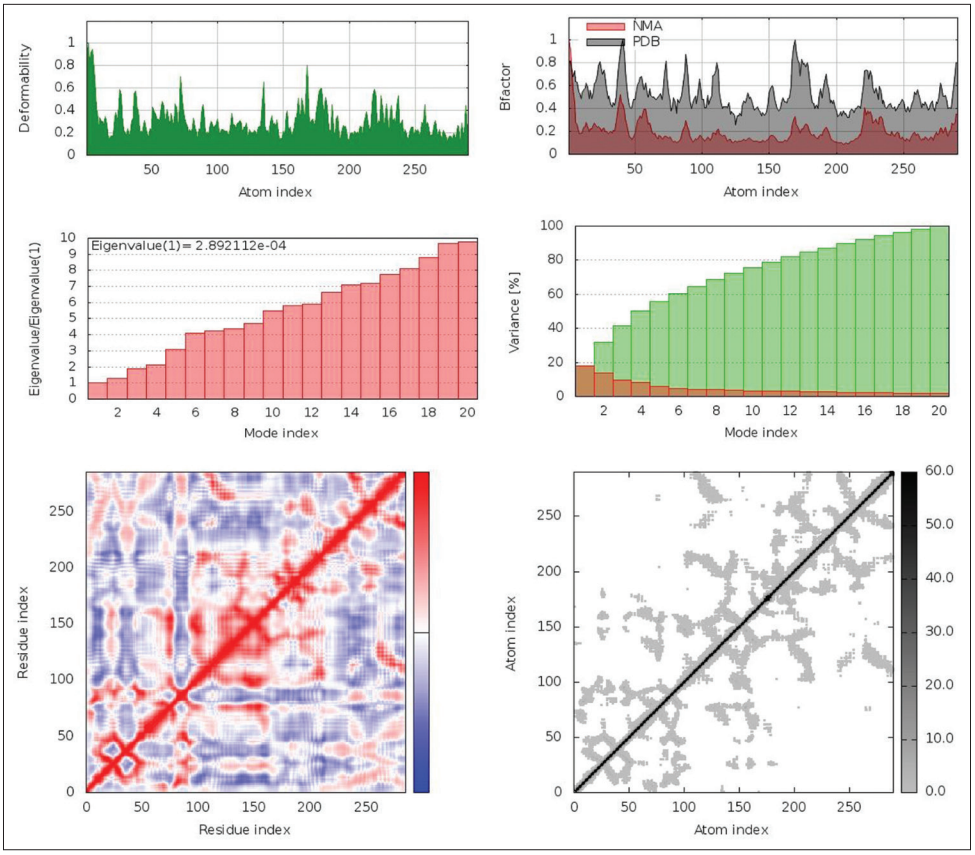


Figure 8. ATP and *Her2* kinase complex: deformability, Bfactor, Eigenvalue, Variance, Residue Index, and Atom Index.

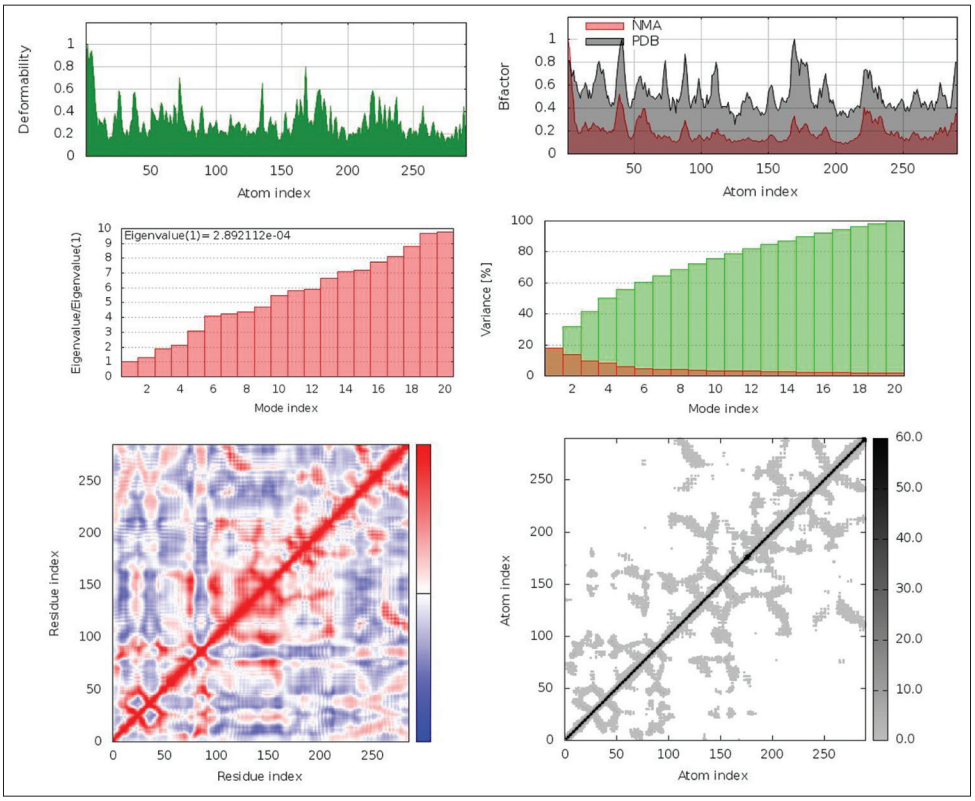


Figure 9. Glabrene and *Her2* kinase complex: deformability, Bfactor, Eigenvalue, Variance, Residue Index, and Atom Index.

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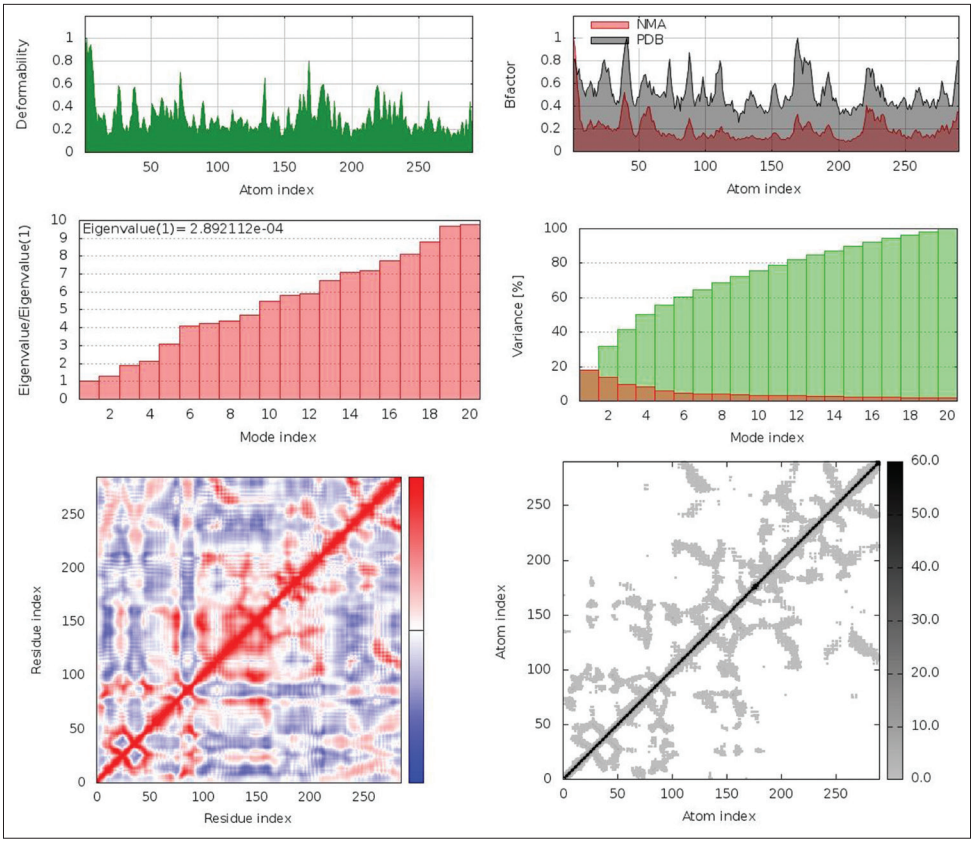


Figure 10. Lapatinib and *Her2* kinase complex: deformability, Bfactor, Eigenvalue, Variance, Residue Index, and Atom Index.

binding interactions could be retaining glabrene in the cavity for a reasonably longer duration. The MoMA simulation results vindicated the efficacy of glabrene comparable to lapatinib, as shown in **Figure 6** [30].

3.3. Dynamic simulation study

Internal coordinate normal mode analysis server (IMODS) data suggested that a higher covariance matrix indicated a better correlation of protein ligand complex residues. A good correlation between residues indicated in red color, while the lack of correlation indicated white color and anti-correlation represented in blue color. The analysis for comparing ATP, glabrene, and lapatinib suggested that glabrene displayed equally good correlation comparable to lapatinib and ATP. The energies required for *Her2* complexes with glabrene, lapatinib, and ATP are almost identical. The binding interactions of ATP, glabrene, and lapatinib induced almost identical changes in *Her2* receptor. These statistics generated by external iMODS server suggest that glabrene with lesser side effects could be a potential replacement for lapatinib. Since, glabrene displayed almost similar interactions with *Her2* receptor comparable to lapatinib and ATP, the graphics of *Her2* receptor appear to be similar.

Deformability (A), Bfactor (B), Eigenvalue (C), Variance (D), Residue Index (E), and Atom Index (F) effects of *Her2* (**Figures 8**–**10**).

4. Conclusion

Globally, breast cancer is the second foremost cancer type after lung cancer. Computational approaches have been utilized for discovery and development of new drugs as multi-targeted inhibitors in diseases caused by overexpressed proteins. Glabrene, apart from showing antitumor activity, also acted as skin lightening agent by preventing the formation of melanin. The present study focused on targeting *Her2* kinase, responsible for uncontrolled tumor cell growth.

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Molecular docking of *Her2* with glabrene revealed that glabrene formed complex with *Her2* with binding energy of −11.3 kcal/mol. Glabrene exhibited slightly higher affinity toward tyrosine kinase domain of *Her2* comparable to ATP and FDA approved drug lapatinib. Therefore, glabrene appears to be a promising lead candidate for the treatment of *Her2* overexpressed breast cancer in postmenopausal women. Consequently, *in vitro* and *in vivo* evaluation of glabrene as a novel *Her2* inhibitor is recommended.

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Conflict of interest

The authors declare that they do not have any conflicts of interest of any kind for this study.

Author contributions

R.G. designed, completed experiments, and prepared the manuscript. N.K.K., R.G., A.V., and N.M. participated in technical discussion, created, and arranged the graphics and edited the manuscript. A.V., N.M., P.K.R., and A.T participated in technical discussions.

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