

In silico Evaluation of Selected Compounds from *Bergenia ciliata* (Haw.) Sternb against Molecular Targets of Breast Cancer

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ABSTRACT

Background: A daunting public health issue that mainly affects women is breast cancer. Resistance to drugs applied in the treatment of this cancer as well as their side effects have made it necessary to look for new therapeutic agents. **Objectives:** The study is aimed at identification of multi-targeted inhibitors of molecular targets associated with breast cancer. **Methods:** We investigated fifteen compounds from *Bergenia ciliata* (haw.) Sternb against four major molecular targets of breast cancer viz; estrogen receptor- α (ER- α), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2/ERBB2) and epidermal growth factor receptor (EGFR) by docking simulation. Properties describing ADME/T aspects of the potential compounds were also investigated by *in silico* approach. **Results:** Among the fifteen compounds investigated, stigmaterol, β -sitosterol, paashaanolactone and afzelechin exhibited more or comparable binding affinity values with the different targets compared to that of native ligands and therefore may be developed as leads for multi-targeted therapy against breast cancer. **Conclusion:** Considering the molecular docking results and ADME/T analysis, it can be suggested that these compounds can be subjected to further structural modification and *in vivo* analysis for evaluating the potential of their candidacy as new drugs in the field of treatment and management of breast cancer.

Key words: *Bergenia ciliata*, Breast cancer, *In silico*, Molecular docking, ADME.

INTRODUCTION

Breast cancer with approximately 1.5 million worldwide diagnosis each year is the second responsible reason for death in women among different types of cancers.¹ It has been estimated that the incidence of breast cancer in women will be about 3.2 million annually by the year 2050.² Diagnosis and mortality rate are much higher in postmenopausal women than in premenopausal women. In 2018, 1.4 million postmenopausal and 645000 premenopausal women were diagnosed with breast cancer globally.³ Incidence is highest in women from high and high-middle income countries whereas mortality rates are higher in women from low-middle and low income countries.⁴ Increased incidence in higher income countries may be due to

lifestyle factors and lower mortality can be attributed to better treatment facilities.⁵ Metastasis of breast cancer is associated with 90% of the observed mortality.⁶ The survival of patients with metastatic breast cancer ranges from 8.0 to 36.0 months.⁷ Risks factors associated with breast cancer can be both modifiable and non-modifiable. Family history, benign breast cancer disease, high mammographic density, age and sex are among the non-modifiable factors.⁸ The major modifiable risk factors involve weight, alcohol consumption, hormone replacement therapy and hormonal contraceptives.⁹ Breast cancer is often classified into subgroups by varied level of expression of estrogen receptor (ER), progesterone receptor (PR) and human

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epidermal growth factor receptor 2 (HER2/ ERBB2) in cancer cells. Luminal A subtype is marked by abnormal cells that are ER and PR positive but negative for HER2.¹⁰ ER+ tumor with higher expression of HER2 is classified as luminal B (HER2+) and with normal level expression of HER2 is classified as luminal B (HER2-).¹¹ Basal like breast cancer/triple negative breast cancer is indicated by absence of expression of ER, PR and also HER2 with poor prognosis.¹² Current major treatment options for breast cancer comprise surgical intervention, radiotherapy, chemotherapy, hormonal therapy and targeted therapy depending on type, stage, menopausal status and many other factors.¹³ Patients diagnosed with luminal A type are treated primarily with oral endocrine therapy such as ER modulator and aromatase inhibitors.¹⁴ Tamoxifen which is a selective ER modulator exerts its antiestrogen effect by competitively inhibiting binding of estrogen to ER whereas letrozole, anastrozole and other aromatase inhibitors reduce the production of estrogen.¹⁵ Anti-HER2 therapy with trastuzumab, pertuzumab, lapatinib and others alone or in combination are extremely useful in treating HER2+ cancer.¹⁶ Systemic treatment regimen for basal like breast cancer is not specific and different molecular targets such as epidermal growth factor receptor (EGFR), poly ADP-ribose polymerase (PARP), androgen receptor (AR) and various pathways are being investigated.¹⁷ In spite of unprecedented development in breast cancer treatment strategies, the problem of resistance to therapeutic agents used in all subtypes is still to be solved and more therapeutic options need to be searched for luminal B and aggressive triple negative type breast cancers.¹⁸

Plants are used as a source of medicine from ancient to present time. They have proven to be a great source of anticancer drugs.¹⁹ Vinca alkaloids, taxols, podophyllotoxins, camptothecin along with their semi-synthetic or synthetic derivatives are notable anticancer agents from plant origin. The plant in our current study, *Bergenia ciliata* (haw.) Sternb of Saxifragaceae family is a perennial herb that grows mainly in different temperate and cold parts of East and Southeast Asia.²⁰ It contains numerous classes of compounds including phenols, sterols, flavonoids, glycosides, terpenoids and saponins.²¹ The most commonly used part of this herb is its rhizomes followed by leaves.²² Rhizome of *Bergenia ciliata* contains bergenin -a glycoside as main constituent and rhizomes are also found to contain a novel lactone called paashanolactone.²³ Aerial part of this plant also contains bergenin along with other glycosides and flavonoids.²⁴ Antiulcerogenic, anticancer, antimicrobial, antioxidant, antidiabetic and anti-tussive

effects have been investigated for this plant.²⁵⁻²⁸ Silver nanoparticles prepared from aqueous extract of *Bergenia ciliata* rhizomes have shown anticancer potential via inhibition of protein kinase activity.²⁹ Brine shrimp bioassay using rhizome extract showed pronounced cytotoxic activity at low doses.³⁰ Both methanolic and aqueous extracts of *Bergenia ciliata* exhibited potent concentration dependent cytotoxicity on MDA-MB-435S cell line which is a human breast carcinoma cell line.³¹ However, there is no extensive data and *in silico* study of its compounds of this plant against breast cancer. Therefore, in the present study, we investigated some selected compounds from *Bergenia ciliata* against four molecular targets related to breast cancer i.e. ER- α (estrogen receptor- α), PR (progesterone receptor), HER2 (human epidermal growth factor receptor 2) and EGFR (epidermal growth factor receptor) to get preliminary idea about breast cancer protective effect of this multipotent plant.

MATERIALS AND METHODS

Molecular docking simulation

Three dimensional crystal structures of major molecular targets of breast cancer i.e. ER- α (PDB code: 3ERT, R-value free: 0.262, resolution: 1.90 Å),³² PR (PDB code: 4OAR, R-value free: 0.234, resolution: 2.41 Å),³³ HER2 (PDB code: 3RCD, R-value free: 0.294, resolution: 3.21 Å),³⁴ and EGFR (PDB code: 2J6M, resolution: 3.10 Å, R-value free: 0.249)³⁵ were acquired from Research Collaboratory for Structural Bioinformatics Protein Data Bank (<https://www.rcsb.org/>). Complexed ligands and water molecules were eliminated and hydrogens were added to the structures. A total of fifteen compounds from *Bergenia ciliata* illustrated in Figure 1 were docked against the proteins. Molecular structures of the compounds were obtained from the PubChem database. Energy minimization of the compounds were performed applying mmff 94 force field in Open Babel (version 2.4.0).³⁶ Molecular docking simulation was carried out in AutoDock Vina (version 1.1.2).³⁷ Docking procedure was validated by re-docking the native ligands in the binding pockets of corresponding proteins. Active sites of ER- α , PR, HER2 and EGFR were selected analyzing binding interaction of tamoxifen, ulipristal acetate, TAK-285 and AEE788, respectively. Grids used for docking were placed on the active sites of the proteins. The grid co-ordinates (X, Y, Z) for docking against ER- α , PR, HER2 and EGFR were (26.48, -1.06, 26.92), (11.85, 27.09, 14.34), (14.56, -2.26, 25.13) and (-51.70, -0.54, -19.26), respectively. The dimension of grids were 25.00, 25.00,

25.00 angstrom. Interaction of the compounds with the targets were analyzed with Discovery Studio Client 2019.

***In silico* ADME/T prediction**

Molecular properties i.e. molecular weight, hydrogen bond donors and acceptors, lipophilicity, molar refractivity as described in Lipinski's rule of five were determined using SwissADME.³⁸ The ADME and toxicological attributes of the compounds were predicted from online server admetSAR (<http://lmmd.ecust.edu.cn/admetSAR2/>).

RESULTS AND DISCUSSION

Molecular docking simulation

Molecular docking of fifteen compounds from *Bergenia ciliata* were performed against four major molecular targets of breast cancer viz; ER- α , PR, HER2 and EGFR. Binding affinities of each compound and corresponding native ligands with the target proteins are shown in Table 1. Among the fifteen compounds investigated, stigmasterol, β -sitosterol, paashaanolactone and afzelechin were found to have higher binding affinities

towards ER- α , PR, HER2 and EGFR than other compounds. The binding pattern of these compounds with the proteins are shown in Table 2 and Table 3. Stigmasterol exhibited greater binding affinity of -9.4 and -8.8 kcal/mol towards PR and EGFR, respectively, when compared to -9.2 and -8.5 kcal/mol of respective native ligands. Although β -sitosterol, paashaanolactone and afzelechin did not exhibit higher binding affinity than native ligands of the proteins but their binding affinities are considerable.

ER- α is expressed over normal levels in 50% of all breast cancers and it is implicated in both the commencement and progression of the cancer.³⁹ Tamoxifen is the most widely applied anti-estrogen therapy but it poses increased risk of uterine cancer, pulmonary embolism and stroke.⁴⁰ Therefore, bioactive compounds from nature can be a great source for anti-estrogen therapy. β -sitosterol and stigmasterol have shown potential activity against ER- α in several *in silico* and *in vitro* studies.⁴¹ In this study, both the phytosterols have also exhibited noticeable binding affinity and interacted with the ligand binding domain of ER- α . β -sitosterol interacted with the receptor through hydrophobic and Van der Waals interaction without forming any hydrogen bonding with the amino acid residues of the active site. This interaction of β -sitosterol is similar to that of tamoxifen which also interacts with ER- α with only hydrophobic and Van der Waals interaction and unlike the agonist estradiol that interacts through hydrogen bonding with Arg394A and His524A residues.⁴² Stigmasterol had greater binding affinity towards ER- α than β -sitosterol with a binding affinity of -9.4 kcal/mol which is comparable to -9.7 kcal/mol of tamoxifen. It also exhibited only hydrophobic and Van der Waals interaction with the receptor active site. Afzelechin which is a tetrahydroxy flavan, formed hydrogen bonding with Gly521A residue and showed hydrophobic interaction with Leu346A, Ala350A, Leu387A, Leu391A, Met421A and Leu525A residues. It possesses chemical structure similar to that of kaempferol which is reported to have the ability to modulate ER- α expression.⁴³ Therefore, further *in vitro* study can be accomplished to get idea about its pharmacological action. Paashaanolactone formed hydrogen bonds with Leu346A and Thr347A residues of ER- α within its active site with considerable binding affinity. It also interacted with hydrophobic amino acid residues Leu346A and Leu525A. The binding patterns of afzelechin and paashaanolactone are illustrated in Figure 2.

PR can modify the behavior of ER- α and its expression is used as biomarker for breast cancer.⁴⁴ Investigation

Table 1: Binding affinities of compounds from *Bergenia ciliata* and native ligands towards molecular targets of breast cancer.

Compounds	ER- α	PR	HER2	EGFR
Native ligands	-9.7	-9.2	-10.7	-8.5
Afzelechin	-8.8	-8.3	-8.3	-8.2
Methyl nonanoate	-5.2	-5.3	-4.8	-4.4
β -asarone	-5.9	-6.1	-5.9	-5.3
Bergenin	-6.5	-6.5	-6.5	-7.3
Methyl cinnamate	-6.2	-6.3	-5.8	-5.4
Damascenone	-6.6	-7.0	-6.7	-6.2
Gallicin	-8.4	-7.7	-7.2	-7.6
Isobutyrophenone	-6.2	-6.5	-6.1	-5.5
Isovaleric acid	-4.5	-4.6	-4.5	-4.0
Limonene	-5.9	-6.6	-5.8	-5.3
Parasorbic acid	-5.2	-5.2	-5.2	-4.3
Paashaanolactone	-8.7	-8.9	-8.7	-8.0
β -sitosterol	-8.7	-8.4	-9.2	-8.3
Stigmasterol	-9.4	-9.4	-10	-8.8
Terpinen-4-ol	-6	-6.6	-5.5	-5.6

Native ligands for ER- α , PR, HER2 and EGFR are tamoxifen (PubChem CID: 2733526), ulipristal acetate (PubChem CID: 130904), TAK-285 (PubChem CID: 11620908) and AEE788 (PubChem CID: 10297043) respectively. Binding affinities are expressed in kcal/mol.

Table 2: Binding interactions of compounds from *Bergenia ciliata* with amino acid residues of ER- α and PR.

Protein	Compounds	Hydrogen bond (distance in Å)	Hydrophobic interactions	Van Der Waals interactions
ER- α	Afzelechin	Gly521 (3.67, 3.91)	Leu346, Ala350, Leu387, Leu391, Met421, Leu525	Met343, Leu349, Glu353, Leu384, Met388, Arg394, Phe404, Glu419, Gly420, Ile424, His524
	β -sitosterol	-	Met343, Leu346, Leu349, Ala350, Trp383, Leu384, Leu387, Met388, Leu391, Leu525	Thr347, Asp351, Arg394, Phe404, Ile424, Met528
	Paashaanolactone	Leu346 (4.60), Thr347 (3.93)	Leu346, Leu525	Met343, Leu349, Ala350, Asp351, Glu353, Trp383, Leu384, Leu387, Met388, Leu391, Arg394, Phe404, Met 528
	Stigmasterol	-	Leu346, Ala350, Leu354, Trp383, Leu384, Leu387, Leu525, Leu536, Leu539	Met343, Thr347, Asp351, Met388, Leu391, Phe404, Met421, Leu428, Met528
PR	Afzelechin	Ile699 (3.63)	Pro696, Val698, Val729, Trp732, Leu758	Leu721, Gln725, Ser728, Gly762, Phe778, Ala779, Pro780,
	β -sitosterol	-	Leu718, Leu721, Trp755, Met759, Val760, Leu763, Phe778, Met801, Cys891, Leu2350B	Asn719, Gly722, Glu723, Gln725, Arg766, Met756
	Paashaanolactone	Gln725 (3.52), Leu758 (5.83), Arg766 (4.24, 5.14, 5.63) Lys822 (4.24)	Ile699, Pro696, Leu721, Ala779	Glu695, Asp697, Val698, Ser728, Val729, Trp732, Met759, Gly762, Leu763, Trp765, Phe778, Phe818
	Stigmasterol	-	Leu715, Leu718, Phe778, Trp755, Met759, Phe794, Leu797, Met801, Ile896, Cys891	Asn719, Gly722, Glu723, Leu726, Met756, Tyr890, Leu892, Asn893, Gln897, Thr894, Leu2350B

Table 3: Binding interactions of compounds from *Bergenia ciliata* with amino acid residues of HER2 and EGFR.

Protein	Ligands	Hydrogen bond (distance in Å)	Hydrophobic interactions	Van Der Waals interactions
HER2	Afzelechin	Ala751 (4.07), Lys753 (4.81), Thr862 (3.37)	Leu726, Val734, Leu852	Ile752, Leu785, Val797, Thr798, Gly804, Cys805, Asp863, Phe1004
	β -sitosterol	-	Phe731, Val734, Ala751, Lys753, Leu755, Leu785, Leu796, Leu852	Leu726, Met774, Thr798, Cys805, Thr862, Asp863, Gly865
	Paashaanolactone	Asn850 (4.08), Thr862 (5.02), Asp863 (3.84), Ser783 (4.90)	Val734, Ala751, Leu785, Leu852, Phe864	Lys753, Leu796, Thr798, Cys805
	Stigmasterol	Thr862 (4.47), Asp863 (4.08)	Leu726, Val734, Ala751, Lys753, Leu800, Cys805, Leu852, Phe1004	Gly727, Ser783, Leu785, Leu796, Thr798, Met801, Gly804, Asp808
EGFR	Afzelechin	-	Leu718, Val726, Ala743, Lys745, Thr790, Leu844	Gly719, Glu762, Met766, Leu777, Leu788, Gln791, Leu792, Met793, Pro794, Gly796, Thr854, Asp855
	β -sitosterol	-	Leu718, Val726, Ala743, Lys745, Met766, Leu788, Leu844	Gly719, Ile744, Glu762, Thr790, Leu792, Met793, Pro794, Gly796, Cys797, Thr854
	Paashaanolactone	Lys745 (4.55), Met793 (4.02), Pro794 (5.21)	Val726, Met766, Leu788	Leu718, Phe723, Ala743, Glu762, Thr790, Gln791, Leu792, Phe795, Gly796, Leu844, Thr854, Asp855
	Stigmasterol	Glu762 (6.71)	Leu718, Val726, Ala743, Lys745, Leu792, Met793, Cys797, Leu844	Gly719, Phe723, Met766, Thr790, Pro794, Gly796, Thr854, Asp855

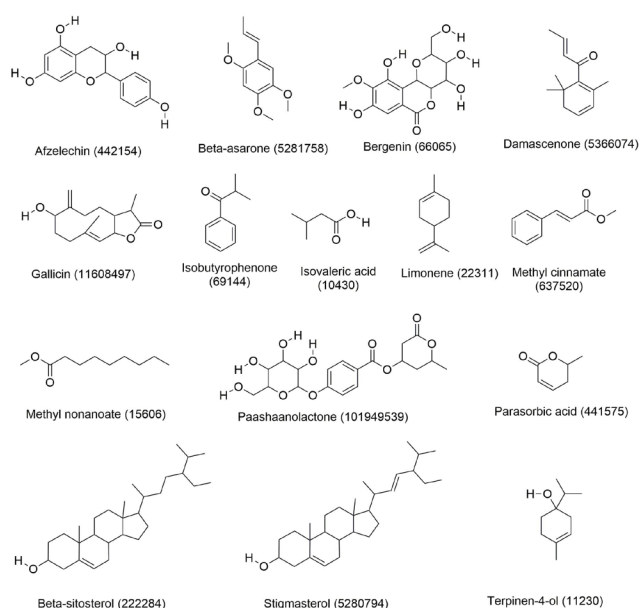


Figure 1: Chemical structure of the compounds from *Bergenia ciliata* with their PubChem ID number that were selected for *in silico* analysis.

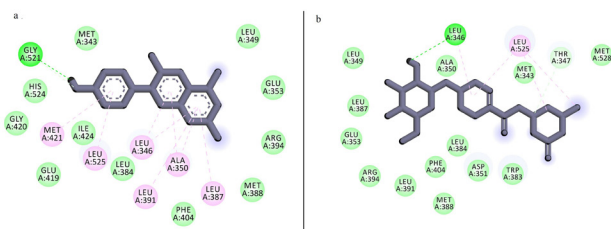


Figure 2: Interaction of (a) afzelechin and (b) paashaanolactone with estrogen receptor- α (ER- α). Green (with dashed line): hydrogen bond; pink (with dashed line): hydrophobic; light shaded green: Van der Waals; cyan (with dashed line): carbon-hydrogen interaction.

of synthetic and natural progesterone antagonists is rising as data from different *in vitro* and animal model studies have shown optimistic results.⁴⁵ Stigmasterol exhibited binding affinity of -9.4 kcal/mol which is higher than -9.2 kcal/mol of reference ligand ulipristal acetate towards PR. It showed hydrophobic interaction with Leu715A, Leu718A, Phe778A, Trp755A, Met759A, Phe794A, Leu797A, Met801A, Ile896A and Cys891A residue of PR. Paashaanolactone also had comparable binding affinity to that of ulipristal acetate exhibiting five hydrogen bond interaction with three residues of PR i.e. Gly725A, Leu758A and Arg766A. It is noteworthy that apigenin which is a reported PR modulator flavonoid also forms hydrogen bond with Gly725A and Arg766A residues.⁴⁶ The binding patterns of stigmasterol and paashaanolactone are illustrated in Figure 3.

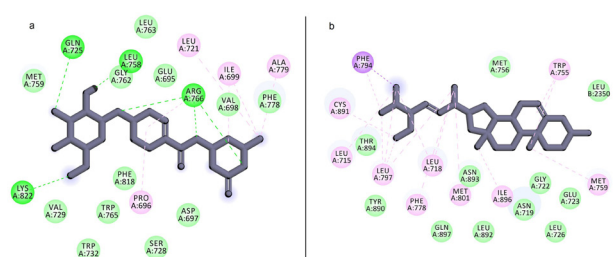


Figure 3: Interaction of (a) paashaanolactone and (b) stigmasterol with progesterone receptor (PR). Green (with dashed line): hydrogen bond; pink (with dashed line): hydrophobic; light shaded green: Van der Waals interaction.

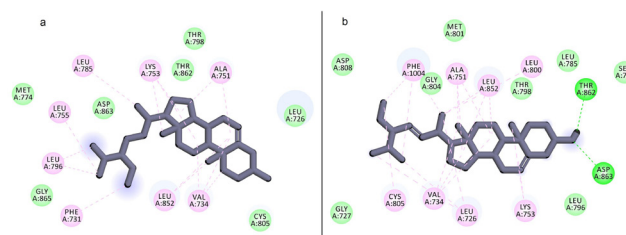


Figure 4: Interaction of (a) β -sitosterol and (b) stigmasterol with human epidermal growth factor receptor 2 (HER2). Green (with dashed line): hydrogen bond; pink (with dashed line): hydrophobic; light shaded green: Van der Waals interaction.

HER2 is implicated in the signaling of cancer cells facilitating the proliferation of malignant cells,⁴⁷ and overexpression of EGFR is often observed in the aggressive triple negative breast cancer.⁴⁸ Small molecule kinase inhibitors of HER2 alone or targeting both HER2 and EGFR have been implicated in breast cancer treatment. The phytosterols i.e. stigmasterol and β -sitosterol interacted efficiently with HER2 as shown in Figure 4. Stigmasterol had binding affinity of -10.0 kcal/mol which is close to the binding affinity of reference ligand TAK-285 (-10.7 kcal) and it formed hydrogen bonds with Thr862A and Asp863A residue of kinase domain of receptor. Although paashaanolactone had lower binding affinity towards HER2 compared to stigmasterol and β -sitosterol, it formed four hydrogen bonds with Ser783A, Asn850A, Thr862A and Asp863A residue of kinase domain of HER2. Analysis of binding interaction of lapatinib which is a potent HER2 kinase inhibitor, suggests that amino acid residues in the range of 700 to 900 are essential for kinase activity of HER2.⁴⁹ Since both stigmasterol and paashaanolactone interacted with the amino acids in this region with considerable binding affinity, the compounds may cause reduction of kinase activity of HER2. Afzelechin, β -sitosterol, paashaanolactone and stigmasterol had considerable binding affinity towards EGFR. The range of amino acids that interacted with the four compounds

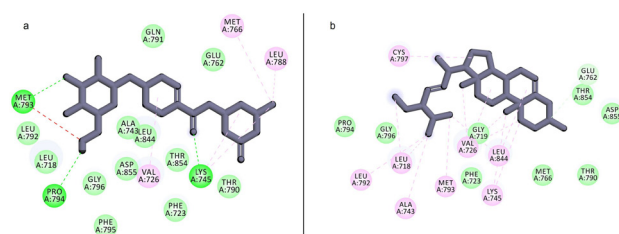


Figure 5: Interaction of (a) paashaanolactone and (b) stigmasterol with epidermal growth factor receptor 2 (EGFR). Green (with dashed line): hydrogen bond; pink (with dashed line): hydrophobic; light shaded green: Van der Waals interaction, cyan (with dashed line): carbon- hydrogen; red (with dashed line): unfavorable acceptor-acceptor interaction.

has similarity with that of EGFR inhibitors like erlotinib and AEE788.⁵⁰ Therefore, these compounds may inhibit kinase activity of EGFR. Stigmasterol had greater affinity of -8.8 kcal/mol towards EGFR than the corresponding native ligand AEE788 and interacted with Glu762A residue through formation of hydrogen bond. Paashaanolactone formed three hydrogen bonds with Lys745A, Met793A and Pro794A residue in EGFR kinase domain. Binding interactions of stigmasterol and paashaanolactone are illustrated in Figure 5.

Since these four compounds i.e. stigmasterol, β -sitosterol, paashaanolactone and afzelechin had considerable affinity towards the targets, they may be considered as credible leads for potential multi-targeted therapy for breast cancer. Therefore, further structural modifications along with biological assays can be performed in search of new drugs.

***In silico* ADME/T prediction**

Physicochemical properties that are associated with the pharmacokinetic or the ADME/T properties of the compounds with considerable binding affinities with breast cancer targets found in molecular docking are presented in Table 4. Lipinski's rule of five states that molecular properties of candidate compounds are required to be within certain ranges for better pharmacokinetics when used through oral route. The conditions of this rule for compounds are molecular weight <500, octanol-water partition ratio (LogP) <5, total number of hydrogen bond donor ≤ 5 , total number of hydrogen bond acceptor ≤ 10 , molar refractivity between 40-130.⁵¹ High molecular weight compounds are less likely to cross membrane bilayer. The compounds whose lipophilicity values are less than 5, are more than 90% likely to have good oral bioavailability.⁵² Molar refractivity is related to molecular weight and has influence on diffusion coefficient.⁵³ High number of hydrogen bond donors

and acceptors increases the interaction of the compound with hydrogen bonding solvents and thereby decreasing permeation through membrane bilayer.⁵² Afzelechin and paashaanolactone fulfilled all the aspects of Lipinski's rule of five. Therefore, these compounds are predicted to have good pharmacokinetic properties related to oral bioavailability. However, the phytosterols β -sitosterol and stigmasterol had one violation as these two compounds had higher lipophilicity value compared to the optimal range. As a result, these two phytosterols are supposed to bind with cell membrane strongly and have decreased bioavailability. To reduce the lipophilicity of these compounds, further structural modifications along with biopharmaceutical studies are required.

Pharmacokinetic and toxicological properties of the potent four compounds i.e. afzelechin, β -sitosterol, paashaanolactone and stigmasterol were predicted by *in silico* approach. Human intestinal absorption and human intestinal colon carcinoma cell (caco-2) permeation values can give idea about intestinal absorption of a compound.⁵⁴ Human intestinal absorption was found to be high for all compounds except paashaanolactone which also had low caco-2 permeability. Caco-2 permeability was low for afzelechin although its human intestinal absorption value was high. β -sitosterol and stigmasterol were found to be blood brain barrier permeant while afzelechin and paashaanolactone were not. CYP450 enzymes are involved in metabolism of drugs. None of the four compounds inhibited CYP2C19, CYP2C9, CYP2D6 and CYP3A4. Afzelechin was identified as substrate for CYP1A2 whereas β -sitosterol, paashaanolactone and stigmasterol were identified as substrates for CYP3A4. β -sitosterol and stigmasterol were shown to be substrate for P-glycoprotein which is a transmembrane protein and is associated with efflux of xenobiotics from cells. Therefore, β -sitosterol and stigmasterol may be extruded out of the cell by P-glycoprotein. The compounds also had no inhibitory effect on P-glycoprotein. All the compounds were found to be non-carcinogenic.

CONCLUSION

Fifteen compounds from *Bergenia ciliata* were screened for activity against breast cancer by molecular docking against ER- α , PR, HER2 and EGFR. Among them stigmasterol, β -sitosterol, paashaanolactone and afzelechin showed efficient binding with the targets eliciting high affinity. These active compounds were selected for ADME/T prediction by *in silico* approach. Molecular docking investigation and calculation of

Table 4: Physicochemical, ADME and toxicological properties of compounds from *Bergenia ciliata*.

Physicochemical and ADMET properties	Afzelechin	β -sitosterol	Paashanolactone	Stigmasterol
Molecular weight	274.27	414.71	412.39	412.69
Hydrogen bond acceptor	5	1	10	1
Hydrogen bond donor	4	1	4	1
Molar refractivity	72.31	133.23	95.07	132.75
LogP	0.79	6.73	-0.62	6.62
Human intestinal absorption	+0.991	+0.993	-0.539	+0.991
Caco-2 permeability	-0.808	+0.539	-0.798	+0.546
Blood brain barrier	-0.278	+0.925	-0.625	+0.925
CYP1A2 inhibition	No	No	No	No
CYP2C19 inhibition	No	No	No	No
CYP2C9 inhibition	No	No	No	No
CYP2C9 substrate	No	No	No	No
CYP2D6 inhibition	No	No	No	No
CYP2D6 substrate	Yes	No	No	No
CYP3A4 inhibition	No	No	No	No
CYP3A4 substrate	No	Yes	Yes	Yes
P-glycoprotein inhibitor	No	No	No	No
P-glycoprotein substrate	No	Yes	No	Yes
Carcinogenicity	No	No	No	No

ADME/T attributes revealed that these compounds may be considered as lead for further structural modifications, *in vitro* and *in vivo* studies in the quest for developing new multi-targeted drugs for treating breast cancer.

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CONFLICT OF INTEREST

The authors declare no conflict of interests.

ABBREVIATIONS

ER- α : Estrogen receptor- α ; **PR**: Progesterone receptor; **HER2/ ERBB2**: Human epidermal growth factor receptor 2/ Erb-B2 receptor tyrosine kinase 2; **EGFR**:

Epidermal growth factor receptor; **TAK-285**: N-[2-[4-[3-chloro-4-[3-(trifluoromethyl)phenoxy]anilino]pyrrolo[3,2-d]pyrimidin-5-yl]ethyl]-3-hydroxy-3-methylbutanamide; **AEE788**: 6-[4-[(4-ethylpiperazin-1-yl)methyl]phenyl]-N-[(1R)-1-phenylethyl]-7H-pyrrolo[2,3-d]pyrimidin-4-amine; **ADME/T**: Absorption, distribution, metabolism, excretion and toxicity; **CYP1A2**: Cytochrome P450 family 1 subfamily A member 2; **CYP2C19**: Cytochrome P450 family 2 subfamily C member 19; **CYP2C9**: Cytochrome P450 family 2 subfamily C member 9; **CYP2D6**: Cytochrome P450 family 2 subfamily D member 6 **CYP3A4**: Cytochrome P450 family 3 subfamily A member 4.

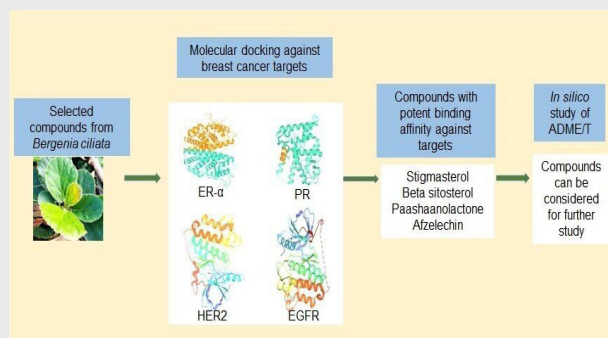
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PICTORIAL ABSTRACT



SUMMARY

Bergenia ciliata is a medicinal plant with reported biological activities including anticancer property. A total of fifteen compounds from *Bergenia ciliata* were screened against some molecular targets of breast cancer. Molecular docking of the compounds against estrogen receptor- α , progesterone receptor, human epidermal growth factor receptor 2 and epidermal growth factor receptor were carried out. Stigmasterol, β -sitosterol, paashaanolactone and afzelechin showed efficient and better binding affinity towards these molecular targets than other compounds. ADME/T properties of these active compounds were also predicted. Further structural modification of these compounds along with biological studies may lead to development of multi-targeted drugs against vicious breast cancer.

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