ORIGINAL RESEARCH

Identification, ADMET evaluation and molecular docking analysis of Phytosterols from Banaba (*Lagerstroemia speciosa* (*L.*)*Pers*) seed extract against breast cancer

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Abstract

Lagerstroemia speciosa (L.) Pers., (Lythraceae), commonly called Banaba, is a native plant of Southeast Asia and is widely used in the treatment of diabetics, obesity, kidney diseases, and other inflammatory disorders. *L. speciosa* consists of several phytoconstituents like glycosides, flavones, corosolic acid, ellagic acids, triterpenes, tannins, which are reported to be present in leaves, stem, flowers, fruit, bark, and roots. This paper presents an investigation on the binding interaction of phytosterols derivatives identified from the ethanolic extract of *Lagerstroemia speciosa* seeds against breast cancer target protein. The ethanolic extracts *Lagerstroemia speciosa* seeds were analyzed via GC–MS for the identification of their chemical constituent. In silico methods are adopted to predict ADME parameters, pharmacokinetic properties, drug-likeliness, and acute toxicity of the identified phytosterols molecules. Molecular docking analysis of the phytosterols was performed against three breast cancer targets. A total of 29 compounds were identified from the extract by GC–MS analysis, among which four phytosterols derivatives namely cholesterol margarate, 7-dehydrodiosgenin, Stigmastan-3,5-diene, and γ-sitosterol have been considered for the present study. These phytosterols are identified as non-toxic, non-carcinogenic, and non-mutagenic. Molecular docking studies reveal the extent of molecular interaction with breast cancer targets. The outcomes of the investigation suggest that the phytosterols obtained from the ethanolic seed extract of *Lagerstroemia speciosa* could act as a promising candidate against breast cancer.

Graphic abstract

Phytosterols from *Lagerstroemia speciosa* seed extract against breast cancer : Extraction, ADMET and Molecular Docking analysis

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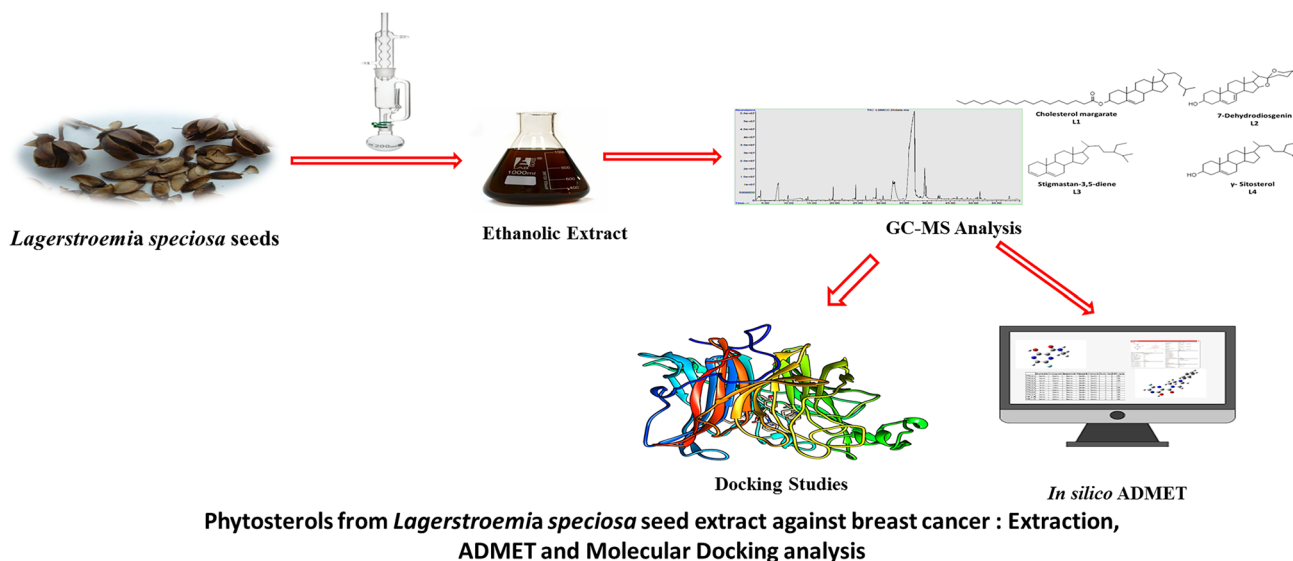
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Introduction

Lagerstroemia speciose plant, a primary native of tropical Southeast Asia, is popular for its values in Ayurvedic and folklore medicines (Thakur and Devaraj 2020; Agarwal et al. 2018). It is widely used in the treatment of diabetics, obesity, kidney diseases, and other inflammatory disorders (Sharmin et al. 2018). The *Lagerstroemia speciosa* plant, commonly called Banaba, extracts from various parts of the plant have been studied for the rich mélange of phytochemicals it had retained in it (Mousa et al. 2019). These phytochemical compositions differ with respect to the part of the plant and the solvent of extraction (Sirikhansaeng et al. 2017). The therapeutic effects of *Lagerstroemia speciosa* are often related to the presence of phytochemicals such as corosolic acid, lagerstroemin, and ellagitannins (Andrade et al. 2020). The most commonly isolated phytochemicals are of the leaf extracts of *Lagerstroemia speciosa*, which are investigated for their anti-diabetic, anti-obesity, antimicrobial and anti-inflammatory activities (Amresh et al. 2018). The *Lagerstroemia speciosa* seeds have been previously studied for the estimation of total phenolic content, keto-fatty acids, and their antioxidant activity (Junaid et al. 2013; Jehan et al. 1990). The phytochemical profile of the seed extract has not been well explored. The extracts are rich in organic compounds such as long-chain fatty acids, hydrocarbons, esters, vitamins, and phytosterols which are responsible for their superior medicinal significance.

Phytosterols are phytochemicals with similarity in structure and biological activity to that of cholesterol. Over the years, more than 200 phytosterols have been isolated and characterized from seeds and nuts of various plants (López-García et al. 2019). Phytosterols are known for their protection against chronic ailments like cardiovascular diseases, diabetics, and cancer (Ms et al. 2018). They have been reported to alleviate cancers of breast, prostate, lung, liver, stomach, and ovary. Phytosterols have been shown to inhibit breast cancer and recuperate the altered lipid levels caused by cancer. Breast cancer drug targets the function of receptors such as ERα (estrogen receptor alpha), PR (progesterone receptor), EGFR (epidermal growth factor receptor) etc. ERα plays an vital role in breast cancer initiation and propagation, while over expression of PR is widely observed in breast cancer cells. EGFR has been reported to play an important role in triple negative breast cancer (Acharya et al. 2019). Recently, *Lagerstroemia speciosa* leaf extract was studied for cytotoxicity activity against breast cancer cell lines-MCF-7 (Saraswathi and Santhakumar 2017).

Inspired by the importance of *Lagerstroemia speciosa* and its potential role against breast cancer, we investigate the interaction of phytosterols obtained from the unexplored ethanolic seed extract of *Lagerstroemia speciosa* with breast cancer targets using in silico approaches. The phytochemical constitution of the extract is determined by GC–MS analysis and the identified phytosterols are computed to predict their ADMET, pharmacokinetic properties, and drug-likeness properties. Further to understand the interaction of the phytosterols against breast cancer targets, molecular docking analysis was carried out. This present work signifies the broadening of applications of phytosterols against various cancer targets.

Methods and materials

Collection of plant material

The *Lagerstroemia speciosa* plant seeds were collected from Madras Christian College Campus, Chennai, India, and the plant seed specimen were identified and authenticated at the Department of Plant Biology and Plant Biotechnology, Madras Christian College, Chennai, India. *Lagerstroemia speciosa* (L.) Pers. is an accepted name contained in the plant list database (http://theplantlist.org; accession date 05/09/2020). The seeds were washed thoroughly with distilled water to remove dust and dried in shade for a few days. The dry seeds were later ground into a fine powder.

Preparation of plant seed extract

5 g powdered seeds were extracted in 50 mL ethanol using a soxhlet apparatus. The obtained extracts were filtered and stored in amber bottles under refrigeration to avoid any possible degradation.

GC–MS analysis

The chemical composition of the ethanolic extracts of *Lagerstroemia speciosa* seeds was analyzed using GC–MS, on Agilent technologies (GC-7890B: MS-5977A MSD) using Column HP-5MS (5% phenyl methyl siloxane) 30 m × 205 μm × 250 μm. Helium was used as a carrier gas with a constant flow of 1.0 ml/min with 1 μl injection volume. An injector temperature was maintained at 250 °C. The oven temperature program used was maintained a temperature of 40 °C for 2 min, the heating is increased up to 270 °C at 5 °C/min and maintaining the temperature constant at 270 °C for 15 min. The mass spectrometer scan parameters included electron impact ionization voltage of 70 eV, a mass range of 40–700 m/z. The chemical constituents were

characterized by comparing their mass spectra with those of the NIST library Version-2011.

Molecular docking

3D structures of the phytosterols studied were drawn using draw by PubChem Sketcher V2.4 (https://pubchem.ncbi.nlm.nih.gov/edit3/index.html) in mol file format and later converted into the.pdb format using Open Babel GUI software (Oboyle et al. 2011). The X-ray crystal structure of the three molecular targets estrogen receptor alpha (PDB ID: 3ERT), progesterone receptor (PDB ID: 4OAR), and EGFR (epidermal growth factor receptor (PDB ID: 2JRM), were retrieved as a PDB file from the Protein Data Bank for docking (Acharya et al. 2019). A grid box with the sizes 60, 60, and 60 along the X-, Y-, and Z-axes respectively were set during docking. The docking analysis was carried out using AutoDockVina software (Forli et al. 2012). The 3D docked protein–ligand complex poses were visualized using PyMol-molecular visualization software program (DeLano 2002). The 2D view of protein-inhibitor interactions was generated using Ligplot software (Wallace et al. 1995).

Pharmacokinetics and drug-likeness

The ADME (Adsorption, Distribution, Metabolism, Excretion) and drug-likeness and properties of the phytosterols were evaluated by SWISSADME and admetSAR webservers (Daina et al. 2017; Cheng et al. 2012). To understand the drug likeliness properties of the phytosterols Lipinski's "rule of 5" and the number of free rotatable bonds were evaluated. According to the rule of 5, if a molecule follows 2 or more of the following rules such as lipophilicity (expressed as Log P) must be less than 5, the number of hydrogen bond acceptors should be less than 10, molecular weight must be less than 500 Dalton, the number of hydrogen donors should be less than 5, is said to be a drug-like molecule (Lipinski 2004). Insilco prediction of LD_{50} values and the class of toxicity were obtained from admetSAR results. Some of the toxicity parameters like mutagenicity, tumorigenicity, etc. were computed using OSIRIS Property Explorer (Sander 2001).

Results and discussion

GC–MS profiling of phytochemicals from Lagerstroemia speciosa

The ethanolic extracts of the *Lagerstroemia speciosa* seeds were analyzed for the chemical constituents using gas chromatography and Mass spectrometry (GC–MS). The characterization of the ethanolic extract through GC–MS revealed the presence of twenty-nine (29) compounds

accounting for total components present in it. The phytochemical compounds identified with their respective molecular masses, relative percentage, and retention time have been tabulated in Table 1, From the GC–MS, it is evident that *Lagerstroemia speciosa* seed is a rich combination of organic compounds ranging from long-chain fatty acids, alcohols, esters, hydrocarbons, and phytosterols. Four phytosterols derivatives were identified in the ethanolic seed extract which are Cholesterol margarate(L1), 7-Dehydrodiosgenin (L2), Stigmastan-3,5-diene (L3), and γ-Sitosterol (L4). It must be noted that L2 is a derivative of diosgenin and it is one among the highly studied phytosterols for its utility as an anti-breast cancer agent (Shi et al. 2018). Similarly, L3 and L4 are derivatives of phytosterols stigmasterol and β-sitosterol respectively,

Table 1 Major constituents of ethanolic extracts of the *Lagerstroemia speciosa* as determined by GC–MS

Peak #	Compounds	Retention time	Percentage of total
1	3-Methyl-5-furandione	7.703	5.87
2	3-Methylenedihydro-2,5-furan-dione	9.954	1.05
3	Naphthalene	13.787	0.15
4	Dodecane	14.218	0.21
5	Octan-2-yl 3-chlorobenzoate	18.846	0.20
6	cis-3-Tetradecene	19.44	0.08
7	Tetradecane	19.671	0.94
8	1-Dodecanol	21.58	0.15
9	Dodecanoic acid	23.964	0.57
10	1-Hexadecanol	24.366	0.10
11	Hexadecane	24.566	1.14
12	Dodecyl acrylate	26.691	0.28
13	Tetradecanoic acid	28.347	0.29
14	Octadecane	28.964	0.75
15	*n*-Hexadecanoic acid	32.582	5.04
16	*cis*-9,*cis*-12-Octadecadienoic acid	37.269	69.91
17	*cis*-13,16-Docasadienoic acid	39.468	6.08
18	Eicosanoic acid	39.78	1.05
19	Docosanoic acid	42.729	0.36
20	Tricosanoic acid	44.2	0.13
21	Tetracosanoic acid	45.641	0.12
22	Squalene	46.451	0.19
23	Cholesterol margarate	47.513	0.12
24	Stigmastan-3,5-diene	48.643	0.23
25	γ-Tocopherol	50.5	0.12
26	7-Dehydrodiosgenin	50.886	0.33
27	Stigmastan-3,5-diene	51.391	0.86
28	α-Tocopherol	52.416	0.10
29	γ-Sitosterol	57.758	0.71

which are known for their activity against breast cancer (Kangsamaksin et al. 2017; Ju et al. 2004).

The drug likeness, ADMET analysis, and molecular docking analysis against three breast cancer target proteins were done for the four phytosterols L1, L2, L3, and L4 for the evaluation of their efficacy as anti-cancer agents (Fig. 1).

Drug likeliness

The selected four phytosterols are evaluated for their drug likeliness properties with the help of the Lipinski rule of five filters. This analysis helps to distinguish between drug-like and non-drug-like molecules. From Table 2, it can be noted that out of four molecules, only one compound violates Lipinski's rule of five with two violations (L1, MW > 500 and LogP = 9.01). The molecular mass of L1, L2, L3, and L4 are 641.1, 400.64, 396.69 and 414.71 g/mol respectively. L1 and L3 violate the LogP values by acquiring a value greater than 5. For instance, the Log P values of L1, L2, L3 and L4 are 9.01, 4.75, 5.11, and 4.79, respectively. L1 and L3 violate the LogP values by being assigned a value greater than 5 which indicates its hydrophobic nature. The high LogP value of L1 is because of the long alkyl chain and for L3, it is because of the absence of polar groups, whereas in L2 and L4 the presence of hydrophilic hydroxyl groups supports the low LogP value. It must be noted that at times in the case of naturals products Lipophilicity does not directly relate to its physicochemical profile violating the rule of five. (Lipinski 2016) The number of hydrogen bond acceptors for L1, L2, L3 and L4 are 2, 2, 0, and 1, respectively. Hydrogen bond donors of L1, L2, L3, and L4 are 0, 0, 0, and 1, respectively. The number of rotatable bonds of the

**Table 2** Drug likeliness properties of phytosterols from ethanolic extracts of the *Lagerstroemia speciosa*

	L1	L2	L3	L4
Molecular weight (g/mol)	641.1	400.64	414.71	396.69
Num. of heavy atoms	46	29	30	29
Num. of rotatable bonds	22	0	6	6
Num. of H bond acceptor	2	2	1	0
Num. of H bond donor	0	0	1	0
Log $P_{o/w}$	9.0	4.7	4.79	5.11
Num. of violations	2	1	1	1

four molecules varies from 0 to 22, indicating the flexibility of some molecules compared to others.

ADMET analysis

To understand the pharmacokinetic properties of the molecules, ADMET analysis was carried out. Solubility expressed as Log S is an important parameter of a drug-like molecule at its value ideally vary from − 0.5 to − 5.5.(Joshi et al. 2020) The solubility of all molecules, except L2 (− 6.9) falls in the above-mentioned range indicating the less/insoluble nature of L2. The maximum solubility is shown by L4 (− 4.7) and the least solubility for L2 (− 6.9). The drug once administered orally gets absorbed in the intestine to reach the specific targets. All molecules have shown a positive result with respect to human intestinal absorption (HIA). The parameters such as blood–brain barrier (BBB) and colorectal carcinoma (Caco-2) have been studied to access the permeability of the membrane (Singh et al. 2020). The BBB and Caco-2 values for all molecules show positive values hence it can cross the barriers with ease. The studied molecules are found to be non-inhibitors of Renal Organic Cation Transporter (ROCT) and also shown to be a substrate

Fig. 1 Chemical Structures of the phytosterols studied

Cholesterol margarate
L1

7-Dehydrodiosgenin
L2

Stigmastan-3,5-diene
L3

γ- Sitosterol
L4
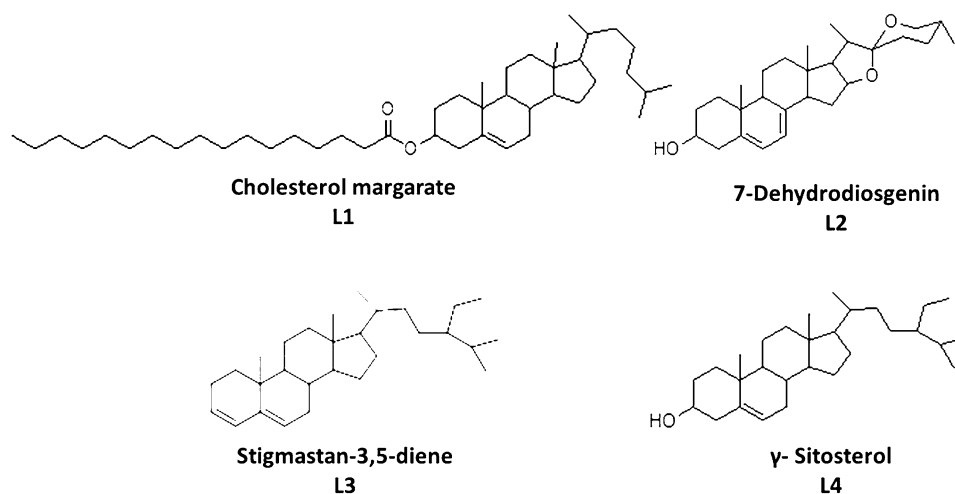
and inhibitor of P-glycoprotein signifying the distribution ability of the drugs (Joshi et al. 2020). Due to the role of cytochrome P450 (CYP450) in Phase I drug metabolism, it is considered as the main parameter to examine ADME of the drugs (Paramashivam et al. 2015). From Table 3 it can be seen that all molecules are shown to be non-substrates and non-inhibitors of CYP450. None of the molecules were found to show toxicity risks such as carcinogenic, mutagenic, etc. All molecules were AMES negative, i.e., non-toxic. The results of LD50 values and other toxicity risks are listed in Table 4.

Bio-molecular interaction studies

Molecular docking analysis was carried out to evaluate the possibility to use these molecules against Breast Cancer. Docking was performed over/on the four phytosterols

(L1–L4) identified from the ethanolic extract of *lagerstroemia speciosa* seeds on the binding pocket of breast cancer target proteins (PDB IDs: 3ERT; 4OAR; 2JRM). All four molecules were docked against the three target proteins and listed in Table 5. All molecules possess a binding score of more than − 7.0 with the three proteins, except L1. For instance, the binding score of L1 with 4OAR is − 6.9 whereas with 2JRM is − 6.2. L1 showed a binding score of − 7.5 when bound to the protein 3ERT with hydrophobic interactions with residues such as Met343, Ala350, Asp351, Thr347, Leu525, Leu346, Leu384, Trp383, Val534, Leu536, Met522, Tyr526, Val533, Lys529, and Glu523. It is interesting to note that in all three cases, L2, a derivative of a potent anti-breast cancer agent diosgenin shows the maximum binding score. The binding score of L2 with 3ERT, 4OAR, and 2JRM are − 8.9, − 8.9, and − 10.0 respectively. L2 shows a Hydrogen bonding

Table 3 ADME profile prediction of the phytosterols from *Lagerstroemia speciosa*

	L1	L2	L3	L4
Log S	− 5.42	− 6.9	− 5.71	− 4.7
Solubility class	Insoluble	Poorly soluble	Poorly Soluble	Poorly soluble
Absorption				
BBB	BBB + (0.9676)	BBB + (0.9391)	BBB + (0.9841)	BBB + (0.9743)
HIA	HIA + (1.0)	HIA + (0.9961)	HIA + (1.00)	HIA + (1.00)
Caco-2	caco2 + (0.7337)	caco2 + (0.5872)	caco2 + (0.6658)	caco2 + (0.7953)
Distribution				
p-glyco substrate	Substrate	Substrate	Substrate	Substrate
p-glyco Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor
ROCT	Non-Inh	Non-Inh	Non-Inh	Non-Inh
Metabolism				
2C9 SUB	Non-sub	Non-sub	Non-sub	Non-sub
C2DR SUB	Non-sub	Non-sub	Non-sub	Non-sub
3A4 SUB	Substrate	Substrate	Substrate	Substrate
1A2 INH	Non-Inh	Non-Inh	Non-Inh	Non-Inh
2C9 INH	Non-Inh	Non-Inh	Non-Inh	Non-Inh
2DR INH	Non-Inh	Non-Inh	Non-Inh	Non-Inh
2C19 INH	Non-Inh	Non-inh	Non-Inh	Non-Inh
3A4 INH	Non-Inh	Non-Inh	Non-Inh	Non-Inh

Table 4 In silico toxicity predictions of the phytosterols from Lagerstroemia speciosa

	L1	L2	L3	L4
H ERG inhibitor	Weak inhibitor	Weak inhibitor	Weak inhibitor	Weak inhibitor
AMES toxicity	Non toxic	Non toxic	Non toxic	Non toxic
Carcinogens	Non carcinogens	Non carcinogens	Non carcinogens	Non carcinogens
Rate acute toxicity	2.0248	1.7459	1.688	2.6561
Toxicity risks				
Mutagenic	None	None	None	None
Tumorigenic	None	None	None	None
Irritant	None	None	None	None
Reproductive effective	None	None	None	None

Table 5 Binding affinity (in Kcal/mol) and binding interaction of phytosterols with three breast cancer molecular targets (PDB ID: 3ERT, 4OAR, 2JRM)

Ligands	3ERT		4OAR		2JRM	
	Residue	Binding affinity	Residue	Binding affinity	Residue	Binding affinity
L1	Met343, Ala350, Asp351, Thr347, Leu525, Leu346, Leu384, Trp383, Val534, Leu536, Met522, Tyr526, Val533, Lys529, Glu523	−7.5	Glu723, Leu726, Trp755, Met759, Gly722, Met756, Leu718, Cys891, Met801, Leu887, Leu887, Thr894, Leu797, Asn719	−6.9	Arg841, Cys797, Asp800, Gly796, Leu718, Phe795, Pro794,Val726, Leu844, Ala 743, Thr790, Thr854, Asp855, Phe723	−6.2
L2	Asp351(2.80), Ala350, Thr347, Leu525, Trp383, Tyr526, Leu536	−8.9	Met759(3,20), Leu763, Val760, Gln725, Phe778, Gly722, Leu718, Cys891, Trp755,Asn719, Met756	−8.9	Leu788, Met766, Thr854, Asp855, Leu844, Arg841,Thr790, Val726, Ala743, Lys745	−10.0
L3	Lys529, Tyr526, Leu539, Leu536, Trp383, Ala350, Asp351,Leu354, Val534, Leu525, Met522	−7.6	Thr894, Leu797, Leu715,Phe794, Leu718, Leu721, Phe778, Gln725, Met759, Gly722, Val760,Trp755, Met756, Asn719	−8.1	Arg841,Asp855,Gly796, Cys797, Leu844, Ala743, Met793,Lys745, Thr790, Val726, Thr854, Asn842,Phe723	−8.3
L4	Lys529, Trp383, Ala350, Leu 346, Leu384, Met343, Asp 351, Leu 525, Thr347, Met528, Cys530	−8.2	Glu723, Trp755, Cys891, Leu718, Phe778, Arg766,Val760, Met759, Leu763,Gln725, Leu721, Gly722, Asn719	−8.3	Asp800(2.99), Cys797, Gly719, Leu718, Val726, Leu844, Ala743, Leu788, Thr790, Lys745, Thr854, Asp855, Glu762	−8.4

interaction with 3ERT (Asp351) and 4OAR (Met759) with a bond length of 2.80 and 3.20 Å respectively. Though L2 has maximum interaction with 2JRM compared to all cases, no hydrogen bonding interactions are possessed. L4 bound to 2JRM is found to show a hydrogen bond with the amino acid residue Asp800 (2.99 Å). All hydrogen bonding falls under the mostly electrostatic type of interactions according to Jeffery (Jeffrey 1997). The number of residues taking part in hydrophobic interactions varies from 6 to 15. For instance, L1 bound to 3ERT is shown to have hydrophobic interactions with amino acid residues, Met343, Ala350, Asp351, Thr347, Leu525, Leu346, Leu384, Tr383, Val534, Leu536, Met522, Tyr526, Val533, Lys529, and Glu523. It must be noted that the ligand–protein complexes with the highest binding score show the least number of hydrophobic interactions. The three-dimensional and two-dimensional conformations of the ligand having the highest binding score (L2) with all the three proteins studied are shown in Fig. 2.

Conclusion

In the present study, chemical constituents from ethanolic seed extract of the *Lagerstroemia speciosa* have been determined by GC–MS analysis. The four phytosterols(L1-L4) identified from the extract was predicted using in silico approaches for their inhibiting activities against breast cancer. One of the phytosterols studied violates the "rule of five" which is common in natural products. All molecules are shown to have positive BBB and Caco-2 values indicating their permeability through membranes. The phytosterols are found to no toxic risks such as carcinogenicity, mutagenicity and with a negative AMES value displaying its non-toxic nature. The molecular docking analysis revealed the high binding nature of the selected phytosterols with the three breast cancer targets studied. L2, a derivative of diosgenin, showed the highest inhibitory effect against all the three proteins as evident from its binding scores. The results support that phytosterols obtained from the ethanolic seed extract of *Lagerstroemia speciosa* could act as potential therapeutics against breast cancer. The current predictions over these phytosterol derivatives will be needed to further investigate in vivo and in vitro conditions to identify the optimum therapeutic efficacy and least toxicity.

Fig. 2 The 3D and 2D diagrams representing the binding pose and protein–ligand interaction respectively of L2 with molecular targets. **a** 3ERT, **b** 4OAR and **c** 2JRM
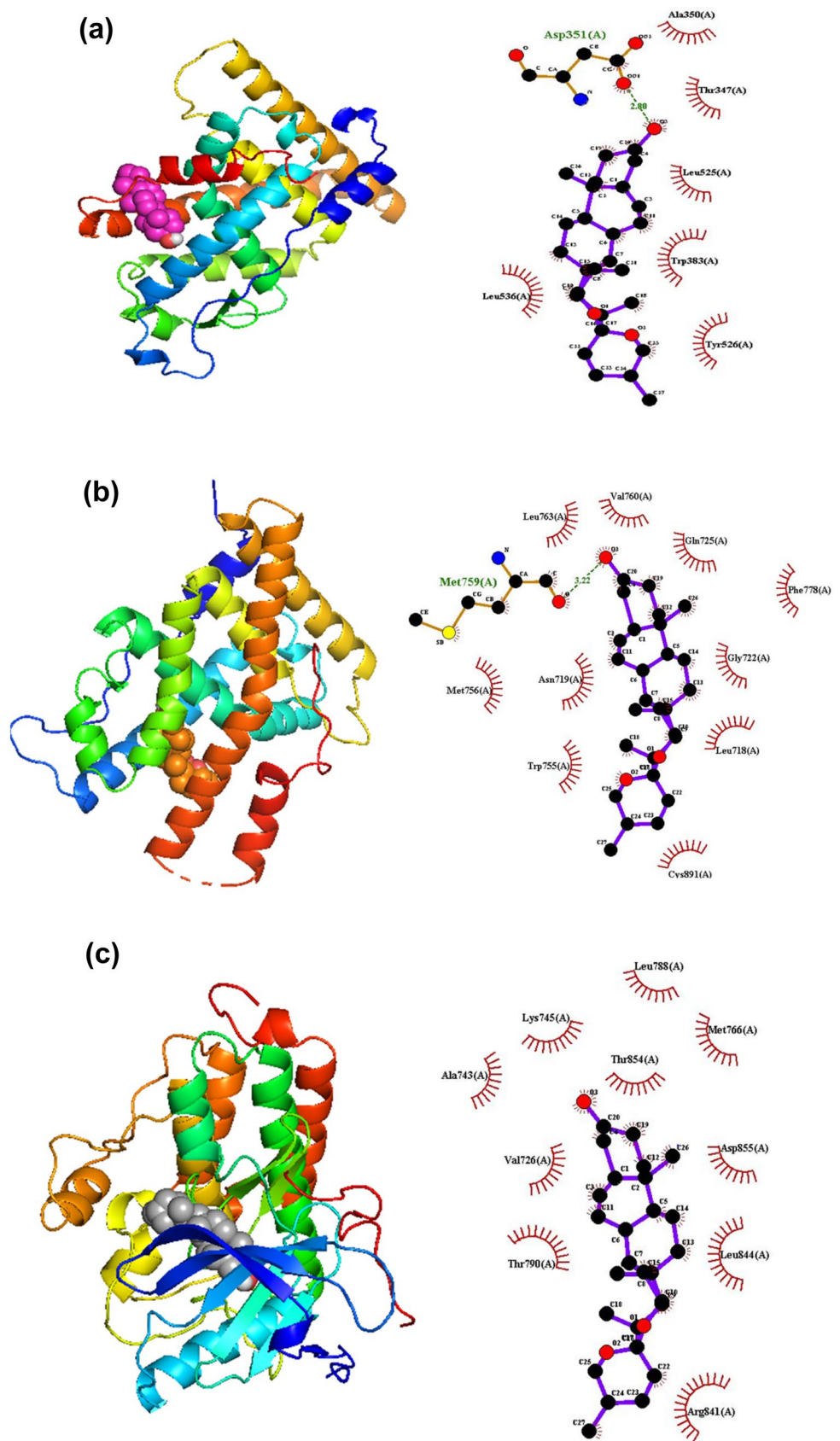
Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

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