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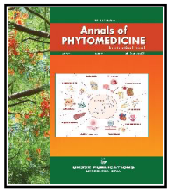

Original Article : Open Access

Computational and experimental pharmacology mediated assessment of bioactives from *Laportea interrupta* (L.) Chew. leaf extract against luminal A breast cancer

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Abstract

Breast cancer is a heterogeneous malignancy characterized by diverse pathological and molecular profiles, which are assessed and predicted using a variety of immunohistochemical (IHC) markers including estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki67. The diagnostic and prognostic evaluation of breast cancer is further nuanced by factors such as tumour size, histological grade, and lymph node involvement. Notably, ER-positive or luminal tumors, which constitute over two-thirds of breast cancer cases, exhibit considerable heterogeneity in their histological features, gene expression patterns, and mutational landscapes, resulting in a broad spectrum of clinical outcomes and therapeutic responses. In this context, the study explored the therapeutic potential of the ethnomedicinal plant *Laportea interrupta* (L.) Chew. in treating luminal A breast cancer. This plant, known for its antibacterial, thrombolytic, antioxidant, membrane-stabilizing, cytoprotective, and nephroprotective properties, was subjected to *in vitro* cytotoxicity assays and systems biology analyses. Gas chromatography-mass spectrometry (GC-MS) analysed the ethanolic leaf extract to identify key bioactive compounds. Among the identified compounds, 2-[4-methyl-6-(2,6,6-trimethylcyclohex-1-enyl)hexa-1,3,5-trienyl]cyclohex-1-en-1-carboxaldehyde exhibited notable binding affinities, with docking scores of -6.611 kcal/mol, -4.744 kcal/mol, and -3.950 kcal/mol for PR (PDB ID: 4OAR), ERα (PDB ID: 3ERT), and epidermal growth factor receptor (EGFR, PDB ID: 2J6M), respectively. *In vitro* assays demonstrated that the ethanolic extract had IC_{50} values of 80.53 ± 0.428 µg/ml against MCF-7 cells and 107.51 ± 0.558 µg/ml against T-47D cells, both of which are luminal A subtypes. For comparison, doxorubicin exhibited IC_{50} values of 26.07 ± 15.70 µg/ml for MCF-7 cells and 35.74 ± 0.65 µg/ml for T-47D cells. Although, the ethanolic extract's cytotoxic efficacy was lower than that of doxorubicin, it demonstrates notable potential as an alternative therapeutic agent for luminal A breast cancer. Further, *in vivo* studies are warranted to substantiate its efficacy and safety profile. Future research should aim at comprehensive *in vivo* evaluations and the development of strategies to enhance therapeutic efficacy and overcome drug resistance in challenging cancer subtypes.

1. Introduction

Breast cancer is a prevalent malignancy and a significant public health issue globally (Arnold *et al*., 2022). It is a leading cause of cancer-related mortality among women (Akram *et al*., 2017). Despite advancements in treatment over the past two decades, it remains a challenging condition. In 2020, the International Agency for Research on Cancer (IARC) reported that breast cancer cases and deaths exceeded those of lung cancer (Qi *et al*., 2024). Incidence rates are notably high in sub-Saharan Africa (5.6% to 30.6%) compared to North America (0.0% to 6.0%). The proportion of distant metastatic cases has decreased from around 35.8% in the early 2000s to 3.2% to 11.6% since 2015, though some stabilization or slight increases have been noted. Higher diagnosis rates are linked to older age and lower socioeconomic status, with younger individuals at 2.0% to 15.7% and older groups at 4.1% to 33.9% (Fuentes *et al*., 2024). Breast cancer includes various subtypes, such as triple-negative breast cancer (TNBC), luminal A, luminal B, and HER2-positive breast cancer (Alharbi *et al*., 2022). Luminal A is the most common subtype, making up over 70% of cases (Alharbi *et al*., 2022). Effective management of luminal A breast cancer is a primary goal in research and treatment (Bertucci *et al*., 2009). Key treatment targets include estrogen receptor alpha (ERα), progesterone receptor (PR), and epidermal growth factor receptor (EGFR). EGFR, a receptor tyrosine kinase, is activated by ligands like EGF and is associated with various cancers, making it a vital target for therapies (Thomas *et al*., 2023).

The estrogen receptor (ER) mediates estrogen's effects and influences treatment strategies, while PR indicates hormone sensitivity in breast cancer (Acharya *et al*., 2019). ERα is crucial in breast cancer development, and PR expression is often elevated in cancer cells. In TNBC, EGFR overexpression is linked to poor prognosis and

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aggressive tumor behavior, prompting exploration of EGFR-targeted therapies (Acharya *et al*., 2019). Throughout history, medicinal plants have been a rich reservoir of medicines, possessing naturally occurring molecules with various biological effects (Salmeron-Manzano *et al*., 2020). Herbal medicine is commonly perceived as being safer and more economically advantageous in comparison to synthetic medications (Dewi *et al*., 2022). *L. interrupta* has been traditionally utilized for its therapeutic properties, including the treatment of coughs, asthma, and muscular pain. Its historical use highlights its significance in herbal medicine as a remedy for respiratory and musculoskeletal ailments. The latest research has broadened the range of its potential use against illnesses like spermatorrhoea, amenorrhoea, prostate diseases, premenstrual syndrome, osteoporosis, and hormonal imbalances (Deepa *et al*., 2014; de Guzman *et al*., 2015). Studies also suggest the plant's potential as an antioxidant, antibacterial, thrombolytic, membrane-stabilizing, cytoprotective, and nephroprotective characteristics (Krishna *et al*., 2014; Safitri *et al*., 2019; Shetty and Khandige, 2021). This study attempts to gauge the effectiveness of the bioactive compounds found in the ethanolic leaf extract of *L. interrupta* to inhibit the growth of breast cancer cells. To identify possible targets for therapeutic intervention, advanced *in silico* molecular docking methods were employed, addressing the current gap in detailed understanding of the molecular mechanisms and cell line-specific effects of *L. interrupta*. The accuracy of these computational predictions was validated through *in vitro* experiments on MCF-7 and T-47D cell lines, representative of the luminal A subtype of breast cancer. The study focuses on exploring the potential of *L. interrupta* as a novel therapeutic option for luminal A breast cancer, aiming to enhance the understanding of its impact and efficacy in this specific cancer subtype (Arif *et al*., 2022; Phurailatpam *et al*., 2022; Shrilakshmi *et al*., 2022; Verma *et al*., 2022).

2. Materials and Methods

2.1 Botanical specimen collection, authentication, and preparation of extract

L. interrupta was collected from Kasaragod, Kerala (12° 302 N, 75° 02 E) and authenticated by Botanist, Dr. Biju P, Government College Kasaragod (Herbarium No: 21PH103R/02). Air-dried leaves were powdered and macerated in ethanol for seven days with intermittent stirring. The extract was then filtered, distilled, and concentrated using a rotary vacuum evaporator to a viscous syrup. It was freeze-dried to a powder and stored in a desiccator in a sealed container (Bindu *et al.,* 2023).

The % yield of the extract was determined using the given equation:

The extract's percentage yield = (Weight of the extract/Weight of the powdered medication) ×100

2.2 Identification of phytoconstituents from the ethanolic leaf extract of *L. interrupta* using GC-MS analysis

The study was undertaken in the School of Biosciences, MG University, Kerala, utilizing a Shimadzu, the QP 2010 series refers to a specific type of gas chromatography-mass spectrometry (GC-MS) machinery. The instrumentation comprised a VF-5ms fused quartz capillary columns of thirty meters in length, 0.25 mm in diameter, and had a film thickness of 0.25 micrometres. The electron ionization was conducted at an energy level of 70 electron volts (eV), using helium gas with a purity of 99.99% as the carrier gas, flowing at a rate of 1.51 ml per min. The temperature of the mass transfer line was kept at 200°C. The oven temperature was set to grow gradually from 70°C to 220°C at an average pace of 10°C each min. The temperature was initially maintained at 220°C and subsequently increased to 300°C. The sample of study was injected into the system without splitting, utilizing a 2 µl solution of ethanol. The mass spectra were obtained by recording data within the atomic mass unit (amu) range of 50 to 600, using a split ratio of 1:40. The entire analysis was concluded in 35 min. The chemical constituents were determined by comparing the acquired spectra with those in the National Institute of Standards and Technology (NIST) repository. This procedure facilitated the determination of components in the extract (Sunitha *et al*., 2023; Kandeepan *et al*., 2022; Tonisi *et al*., 2020).

2.2.1 The Rule of Five by Lipinski

Compounds were assessed for drug-likeness using Lipinski's criteria, evaluating molecular mass, hydrogen bond donors and acceptors, and lipophilicity. Molsoft tools were employed to calculate molecular weight, hydrogen bond donors (HbD), acceptors (HbA), partition coefficient (QpLogP(o/w)), and polar surface area (PSA). These metrics help determine the physicochemical properties, effectiveness, and safety of potential drugs, aiming to identify molecules with favourable drug-like characteristics for pharmaceutical development (Saghiri *et al*., 2023; Madiwalar *et al*., 2022).

ADMET properties were evaluated using QikProp, which analyzes absorption, distribution, metabolism, excretion, and toxicity. It assesses key attributes such as blood-brain barrier permeability, metabolic stability, and oral bioavailability, helping identify compounds with favourable profiles for safe and effective drug development (Sun *et al*., 2016).

2.3 Molecular docking of bioactives

To conduct molecular docking investigations using the bioactive compounds of *L. interrupta*, we obtained the X-ray crystal structures of the epidermal growth factor receptor (EGFR, PDB ID: 2J6M), progesterone receptor (PR, PDB ID: 4OAR) and estrogen receptor alpha (ERα, PDB ID: 3ERT) from the Protein Data Bank (RCSB; https://www.rcsb.org/) (Abdulrahman *et al*., 2020; Tzekaki *et al*., 2021; Yasman *et al*., 2020). The structures were optimized using the Protein Preparation Wizard module within Schrödinger Suite 2019-2, which facilitated comprehensive preparation of the protein models. This process entailed optimising the structure, adding hydrogen atoms, and eliminating superfluous water molecules to improve the precision and dependability of subsequent docking simulations (Arthur *et al*., 2018; Khanal *et al*., 2024).

2.3.1 Ligand synthesis

LigPrep module from Schrödinger Suite 2019-2 was employed to produce the three-dimensional configurations of the ligands. This process refined the conformations of the ligands to improve the precision of the protein-ligand docking simulations (Hussain *et al*., 2023).

2.3.2 The process of creating a grid

Docking simulations were performed using predefined parameters, focusing on receptor-ligand interactions. The receptor cavity was

modelled to accommodate various ligand conformations, and docking was assessed based on Glide scores (G-scores). A grid was created around the receptor to ensure comprehensive coverage of the active site. After initial docking, selected ligand positions were re-evaluated for improved analysis. Results were meticulously reviewed to ensure accuracy and reliability (Hussain *et al*., 2023).

2.3.3 Ligand-protein docking

Ligand-protein docking predicts the binding orientation and affinity of a ligand with a protein, forecasting how a small molecule interacts with a target protein or nucleic acid and evaluating the interaction strength. This study investigated the binding of phytochemicals from *L. interrupta* to three key receptors: progesterone receptor (PR, PDB ID: 4OAR), estrogen receptor alpha (ERα, PDB ID: 3ERT), and epidermal growth factor receptor (EGFR, PDB ID: 2J6M). Molecular docking simulations were used to evaluate binding affinities and potential effects on these receptors. ERα and PR are crucial for hormone signalling, while EGFR is vital for cell growth. The goal is to elucidate these interactions and explore novel therapeutic strategies targeting these receptors with *L. interrupta* derived bioactive chemicals (Shukla *et al*., 2012; Bhattacharya *et al.*, 2024; Patil *et al.*, 2022).

2.4 *In vitro* studies

2.4.1 Procurement of cells and chemicals

MCF-7 and T-47D cell lines, which are indicative of the luminal A breast cancer subtype, were acquired from the National Centre for Cell Science (NCCS), Pune. Media and supplements for cell culture were procured from HI Media Laboratories, LLC. which included DMEM (Dulbecco's Modified Eagle Medium; CAS No: 219A), RPMI-1640 (CAS No: 162S), foetal bovine serum (FBS, CAS No.: RM10938), and trypsin (CAS No.: TCL-007). Lyophilized doxorubicin was procured from shop (ADRIB; ADC2206DRB), and antibiotic-antimycotic solution (Catalogue No. 15240062) was obtained from Gibco™.

2.4.2 Evaluation of cellular toxicity in MCF-7 and T-47D cells

T-47D cells were cultured in RPMI media and MCF-7 cells in DMEM, both supplemented with 10% fetal bovine serum, 1% penicillin-streptomycin, and 1% nonessential amino acids, in T25 and T75 flasks under standardized conditions (37°C, 5% CO^{-}, 95% humidity). Cell viability was assessed post-trypsinization using a cell counter and trypan blue exclusion staining. Subsequently, cells were seeded in 96-well plates for the MTT assay. The test compounds were dissolved in 0.1% dimethyl sulfoxide (DMSO). The extract was prepared at 10 mg/ml and doxorubicin at 1 mg/ml, with both subsequently diluted in culture media to achieve final concentrations of 5, 10, 25, 50, 100, and 250 µg/ml. Cells were treated with these concentrations for 24 h. Experiments were conducted in triplicate to ensure the reproducibility and reliability of the results (Al-Malki *et al*., 2020; Pal *et al*., 2019; Santhanam *et al*., 2022; Dhru *et al*.,2022).

The cytotoxicity was assessed in comparison to doxorubicin, and the percentage of cytotoxicity was determined using the following formula:

Percentage cytotoxicity = (Absorbance of control – Absorbance of test)/Absorbance of control × 100

3. Results

3.1 Percentage yield

The extract's mass was quantified to determine the percentage yield. The reaction yielded 6.5 grams of product, corresponding to a percent yield of 65%. The ethanolic extract was characterized by a pleasant aroma, a rich green colour, and a slightly viscous consistency.

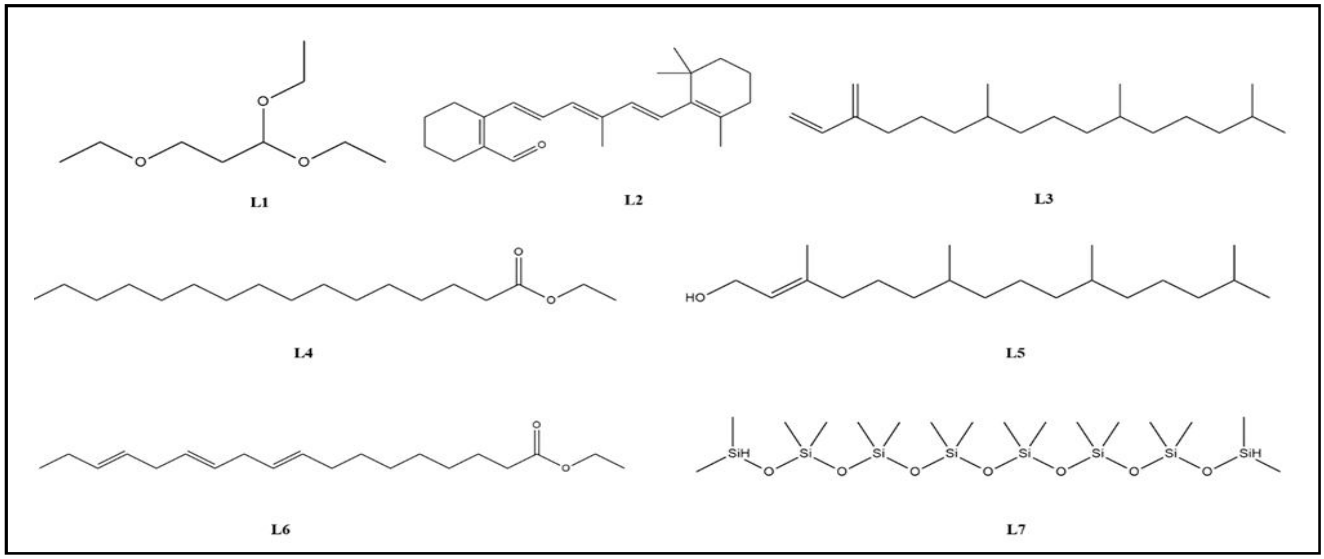

Figure 1: Structures of phytoconstituent ligands L1. Propane, 1,1,3-triethoxy- 9, mol. weight: 176.25 g/mol, mol. formula: $C_9H_{20}O_3$; L2. 2-[4-methyl-6-(2,6,6-trimethylcyclohex-1-enyl) hexa-1,3,5-trienyl] cyclohex-1-en-1-carboxaldehyde mol. weight: 324.5 g/mol, mol. formula: $C_{23}H_{32}O$; L3. Neophytadiene, mol. weight: 278.5 g/mol, mol. formula: $C_{20}H_{38}$; L4. Hexadecanoic acid, ethyl ester, mol. weight: 284.5 g/mol, mol. formula: $C_{18}H_{36}O_2$; L5. Phytol, mol. weight: 296.5 g/mol, mol. formula: $C_{20}H_{40}O$; L6. 9,12,15-Octadecatrienoic acid, ethyl ester, (Z,Z,Z), mol. weight: 306.5 g/mol, mol. formula: $C_{20}H_{34}O_2$ and L7. Octasiloxane,1,1,3,3,5,5,7,7,9,9,11,11,13,13,15,15-hexadecamethyl, mol. weight: 579.2 g/mol, mol. formula: $C_{16}H_{50}O_7Si_8$.

3.2 Analysis with gas chromatography and mass spectrometry (GC-MS)

The compounds identified through GC-MS analysis exhibit a diverse array of biological and chemical properties. 1,1,3-triethoxypropane, an acetal, is notably present in spirits and contributes to the complex aroma profile of alcoholic beverages ((Williams and Strauss *et al*., 1975; Heide *et al*., 1981). The intricate structure of 2-[4-methyl-6-(2,6,6-trimethylcyclohex-1-enyl) hexa-1,3,5-trienyl] cyclohex-1-en-1-carboxaldehyde underscores its significance in organic chemistry due to its complex substituents (Qadir *et al*., 2022). Neophytadiene (NPT), a diterpene, has a diverse array of biological properties, including anxiolytic, sedative, and antidepressant-like effects (Gonzalez-Rivera *et al*., 2023), anti-inflammatory (Bhardwaj *et al*., 2020), cytotoxic (Selmy *et al*., 2023), hepatoprotective (Sahoo *et al*., 2023) as well as antidiabetic properties (Tahya and Karnelasatri *et al*., 2021). The ethyl ester of palmitic acid, ethyl palmitate, exhibits a variety of bioactivities, including antiviral, antimicrobial (Díaz *et al*., 2023), anti-inflammatory (Saeed *et al*., 2012)., antioxidant, antibacterial, antifungal (Ngazizah *et al*., 2017), and acaricidal effects (Bu *et al*., (2012)). It also exhibits anti-chikungunya virus (CHIKV) activity (Sagna *et al*., 2023). Phytol, another diterpene, is recognized for its anticancer (Lakshmi *et al*., 2016), antimicrobial, anticandidal (Lima *et al*., 2020), anti-nociceptive (Santos *et al*., 2013), anticonvulsant (Costa *et al*., 2012) and anxiolytic-like properties (Costa *et al*., 2014) and is being explored for its potential in treating Alzheimer's disease) (Sathya *et al*., 2020). Ethyl linolenate, a long-chain fatty acid ester, has antibacterial and anti-inflammatory activities (Chen *et al*., 2016). Lastly, octasiloxane, a lactone, has been investigated for its unique properties (Khan *et al*., 2021). These findings collectively illustrate the rich variety of chemical and biological functions of the compounds detected in the GC-MS analysis. Plant phytoconstituent ligands ' structures were determined using GC-MS analysis, as depicted in Figure 1.

3.3 Lipinski's Rule of Five compliance analysis

Oral absorption is influenced by drug-likeness properties, primarily the number of free rotatable bonds. All bioactive bio-actives adhere to Lipinski's Rule of Five, with up to two violations being acceptable for oral activity. As detailed in Table 1, the *in silico* prediction of physicochemical properties confirmed that all bio-actives comply with this rule, indicating favourable drug-likeness.

Table 1: Lipinski's Rule of Five and drug-likeness scores for bioactive compounds

Phytoconstituents	MW	Log p	Donor HB	Accept HB	Rule of Five	Drug likeness score
Acceptable range	≤500	>5	≤5	≤10	≤5	≤2
L1	176.255	1.77	0	3	0	-1.28
L2	324.505	6.69	0	1	1	0.18
L3	278.520	8.48	0	0	1	-1.22
L4	284.481	7.84	0	2	1	-1.09
L5	296.535	7.72	1	1	1	-0.87
L6	306.487	7.08	0	2	1	-0.76
L7	579.251	7.24	2	7	2	-1.46
Doxorubicin*	543.17	1.28	7	12	3	0.97

* Standard drug; The table presents key properties of the compounds; including: MW (Molecular Weight), Log P (lipophilicity), Donor HB (estimated number of hydrogen bond donors), and Accept HB (estimated number of hydrogen bond acceptors).

Table 2: Pharmacokinetic properties of bioactive phytoconstituents by Qikprop

Phyto-constituents	% HOA	QPlogS	QPPCaco	#Metab	QplogBB	QPPMDCK	QPlogKhsa	SASA	FOSA	FISA
Acceptable range	>80%: High, low <25%:	-6.5 to 0.5	<25: Poor> 500: great	1 to 8	-3 to 1.2	<25: Poor, >500: great	-1.5 to 1.5	300 to 1000	0.0 to 750	7.0 to 330
L1	100.000	-1.459	9906.03	1	-1.168	5899.293	-0.848	485.350	485.350	0.000
L2	100.000	-6.947	2101.61	5	-0.642	1104.059	1.345	690.210	572.813	71.006
L3	100.000	-10.818	9906.03	1	1.490	5899.293	1.692	706.102	648.038	0.000
L4	100.000	-7.150	3171.36	1	-0.961	1722.413	1.157	761.032	708.869	52.162
L5	100.000	-6.278	4770.41	3	-0.626	2677.868	1.176	706.641	664.314	33.464
L6	100.000	-8.436	3424.38	5	-0.897	1871.417	1.447	820.326	724.502	48.647
L7	100.000	-11.796	8177.00	0	-0.376	4794.645	3.431	1013.15	1004.371	8.785
Doxorubicin*	0	-2.344	4.281	9	-2.606	1.507	-0.554	770.496	344.425	291.18

*Standard drug; The table summarizes the pharmacokinetic properties of the compounds, including: % HOA (per cent human oral absorption), QPlogBB (predicted brain/blood partition coefficient), QPPCaco (predicted apparent caco-2 cell permeability in nm/sec), SASA (solvent accessible surface area), FOSA (hydrophobic component of SASA), FISA (hydrophilic component of SASA), and QPlogS (logarithm of the partition coefficient between n-octanol and water).

3.4 ADMET prediction using QikProp

ADMET predictions using QikProp assessed the pharmacokinetic properties of bioactive phytoconstituents, including their ability to cross the blood-brain barrier (BBB). Table 2 summarizes key factors like solvent-accessible surface area (SASA), tissue penetration, metabolic pathways, and bioavailability. The compounds showed good human oral absorption, aqueous solubility, and intestinal permeability, essential for drug delivery. They also met the BBB permeability criteria, as confirmed by the MDCK model. All compounds had high binding affinity to human serum albumin, with FISA, FOSA, and SASA values within acceptable ranges, indicating low hydrophilicity on heteroatoms.

3.5 Molecular docking

Molecular docking analysis was performed using the Schrodinger Suit software to investigate the interactions between seven ligands (L1 to L7) and three proteins: 3ERT (ERα), 4OAR (PR), and 2J6M (EGFR). The binding free energies displayed a spectrum of values ranging from -6.611 to -0.801 kcal/mol (Figure 3) for ERα, -4.744 to 0.527 kcal/mol for PR (Figure 4), and -3.335 to 2.14 kcal/mol (Figure 5) for EGFR. The docking analysis of ligands with ERα revealed that the phytoconstituent 2-[4-methyl-6-(2,6,6-trimethylcyclohex-1-enyl)hexa-1,3,5-trienyl]cyclohex-1-en-1-carboxaldehyde achieved the most favourable docking score of -6.611 kcal/mol. The chemical 9,12,15-octadecatrienoic acid, ethyl ester, (Z, Z, Z)- achieved a score of -5.114 kcal/mol, which was the second highest score. Phytol obtained a docking score of -4.300 kcal/mol, which was the third-highest score. The docking results for PR indicate that 2-[4-methyl-6-(2,6,6-trimethylcyclohex-1-enyl)hexa-1,3,5-trienyl]cyclohex-1-en-1-carboxaldehyde achieved the highest binding affinity of -3.335 kcal/mol. The subsequent compound was 9,12,15-octadecatrienoic acid, ethyl ester, (Z, Z, Z)-, which had a score of -3.621 kcal/mol. The chemical with the third highest score of -3.147 kcal/mol was octasiloxane,1,1,3,3,5,5,7,7,9,9,11,11,13,13,15,15-hexadecamethyl. The docking studies of ligands with 2J6M (EGFR) suggest that ligand 2-[4-methyl-6-(2,6,6-trimethylcyclohex-1-enyl)hexa-1,3,5-trienyl]cyclohex-1-en-1-carboxaldehyde obtained the highest docking score of -3.950 kcal/mol, followed by octasiloxane, 1,1,3,3,5,5,7,7,9,9,11,11,13,13,15,15-hexadecamethyl- with a score of -3.904 kcal/mol, and propane, 1,1,3-triethoxy- with the third highest score of -2.701 kcal/mol.

The phytoconstituent ligands demonstrate significant binding affinity with estrogen receptor alpha (ERα). Notably, the compound L2 (2-[4-methyl-6-(2,6,6-trimethylcyclohex-1-enyl) hexa-1,3,5-trienyl] cyclohex-1-en-1-carboxaldehyde) exhibits the highest docking score, engaging in hydrophobic interactions with 17 amino acids, forming a hydrogen bond with ARG56, and establishing polar interactions with THR347 (Figure 3). In parallel, these ligands show substantial interactions with the progesterone receptor (PR). The compound L2, again with the highest docking score, interacts hydrophobically with 20 amino acids, forms a hydrogen bond with CYS530, and engages in polar interactions with THR347 (Figure 4). Conversely, the phytoconstituent ligands exhibit minimal interactions with the epidermal growth factor receptor (EGFR). The compound L2, which also has the highest docking score in this context, shows hydrophobic interactions with nine amino acids and forms polar interactions with ASN842 and THR854 (Figure 5).

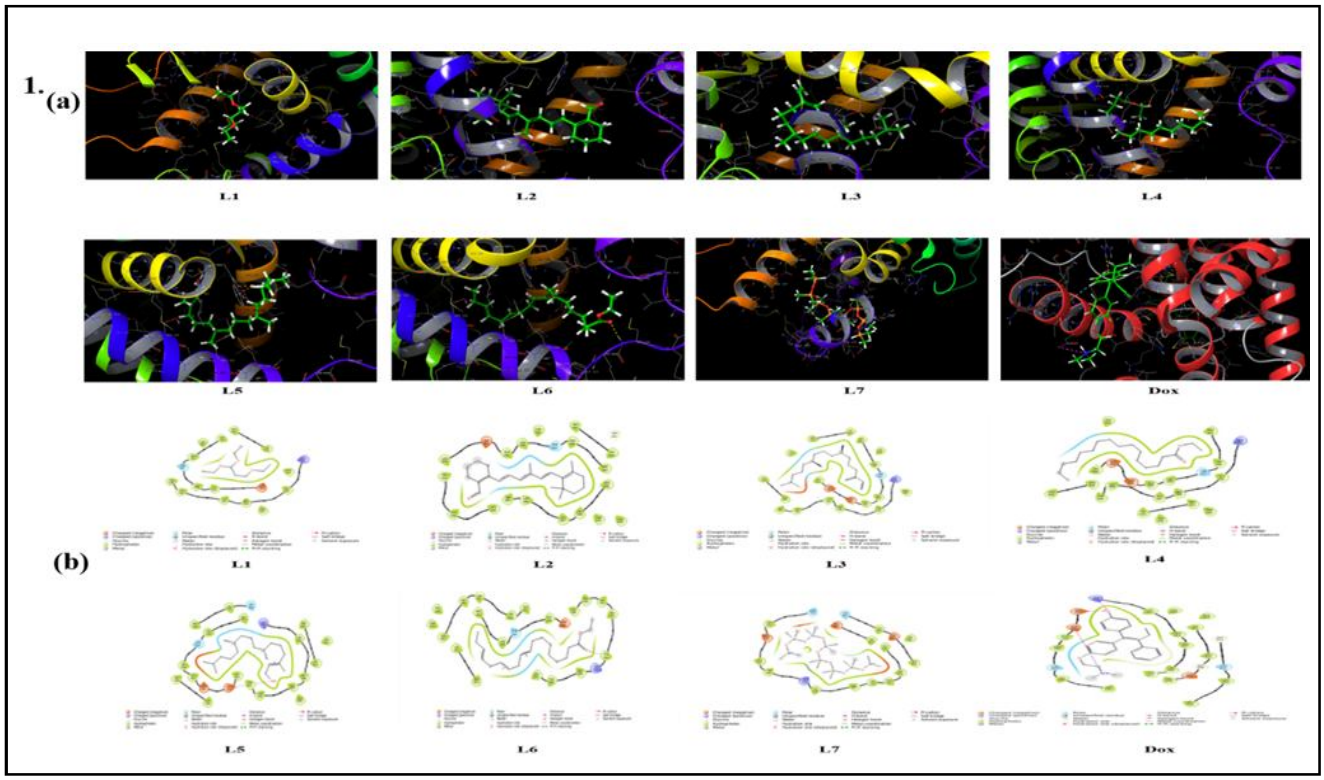

Figure 3: Molecular docking visualizations of phytoconstituent ligands including the standard drug doxorubicin, in 3D (a) and 2D (b) formats with the estrogen receptor alpha.

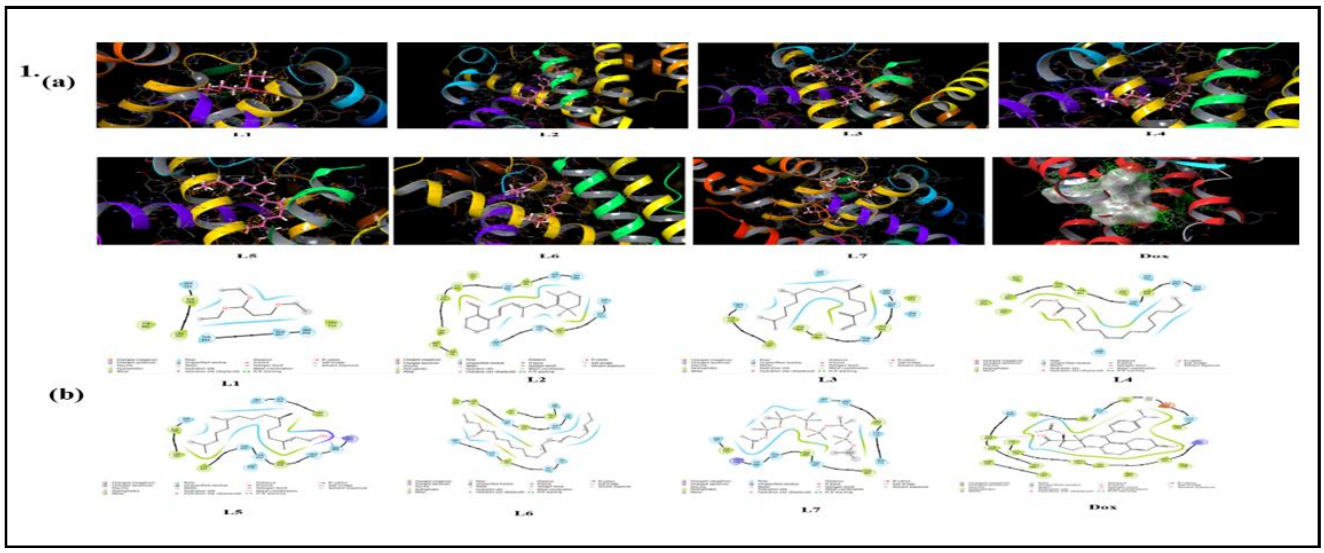

Figure 4: Molecular docking visualizations of phytoconstituent ligands, including the standard drug doxorubicin, in 3D (a) and 2D (b) formats with the progesterone receptor (PR), PDB ID: 4OAR).

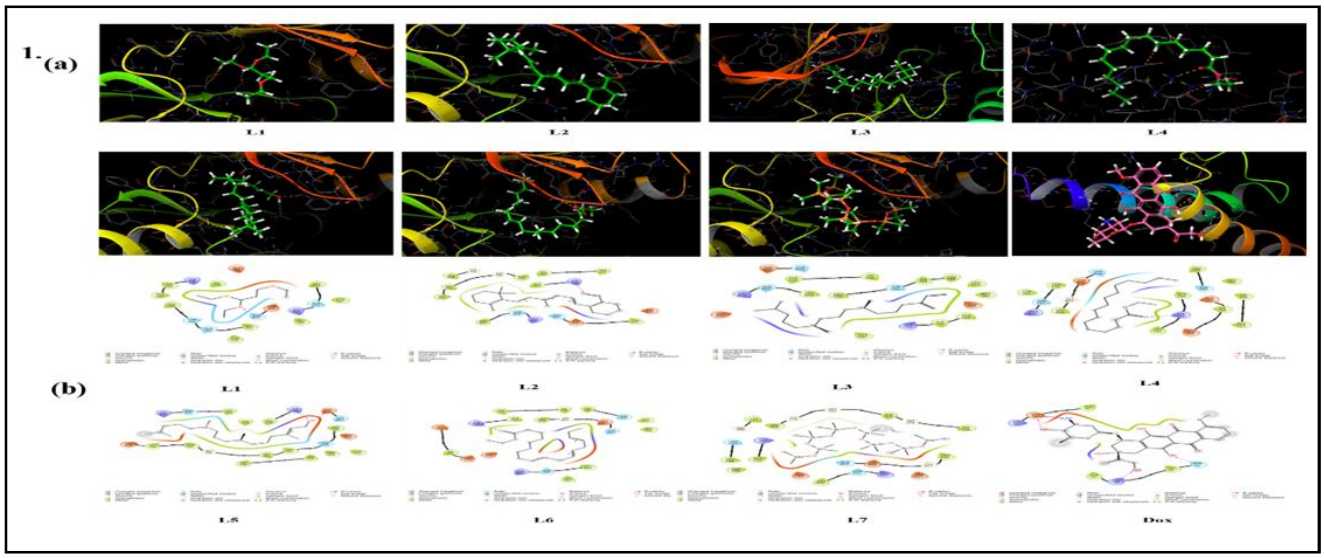

Figure 5: Molecular docking visualizations of phytoconstituent ligands, including the standard drug doxorubicin, in 3D (a) and 2D (b) formats with the epidermal growth factor receptor (EGFR), PDB ID: 2J6M.

3.4 *In vitro* studies

3.4.1 Cytotoxicity assessment by MTT assay

The MTT assay was applied to assess the cytotoxic effects on the breast cancer cell lines T-47D and MCF-7. The cytotoxicity was assessed by determining the proportion of cells that thrive following its treatment with the extract and doxorubicin, based on their respective IC_{50} values. Both the extract and doxorubicin demonstrated significant cytotoxicity in both cell types MCF-7 and T-47D cells. Morphological variations observed under phase contrast microscopy. Treated cells displayed notable alterations in morphology, whereas control cells maintained a uniform and intact appearance, characterized by consistent cell surface and shape, after a 24 h incubation period.

3.4.1.1 MCF-7 cell lines

The cytotoxic effects of *L. interrupta* extract on MCF-7 breast cancer cells were assessed, revealing a substantial decrease in cell viability. The extract demonstrated an IC_{50} value of 80.53 ± 0.428 µg/ml after 24 h of treatment, indicating that it effectively reduces cellular proliferation by 50% at this concentration. The standard chemotherapeutic agent doxorubicin displayed a significantly lower IC_{50} of 26.07 ± 15.70 µg/ml under identical experimental conditions. This suggests that doxorubicin is considerably more potent than *L. interrupta* in the MCF-7 cell line, highlighting the extract's potential as an antiproliferative agent, albeit less effective than the established drug.

3.4.1.2 T-47D cell lines

In the T-47D breast cancer cell line, *L. interrupta* extract showed an IC_{50} value of 107.51 ± 0.558 µg/ml after 24 h of treatment. This indicates that a greater concentration of the extract is required to

attain a 50% reduction in cell viability compared to doxorubicin. The standard drug, doxorubicin, demonstrated an IC_{50} of 35.74 ± 0.65 µg/ml. Despite the higher IC_{50} value for the extract, it still shows promising potential for cytotoxic activity, suggesting that it could be a valuable component in therapeutic strategies, though it is less potent than doxorubicin.

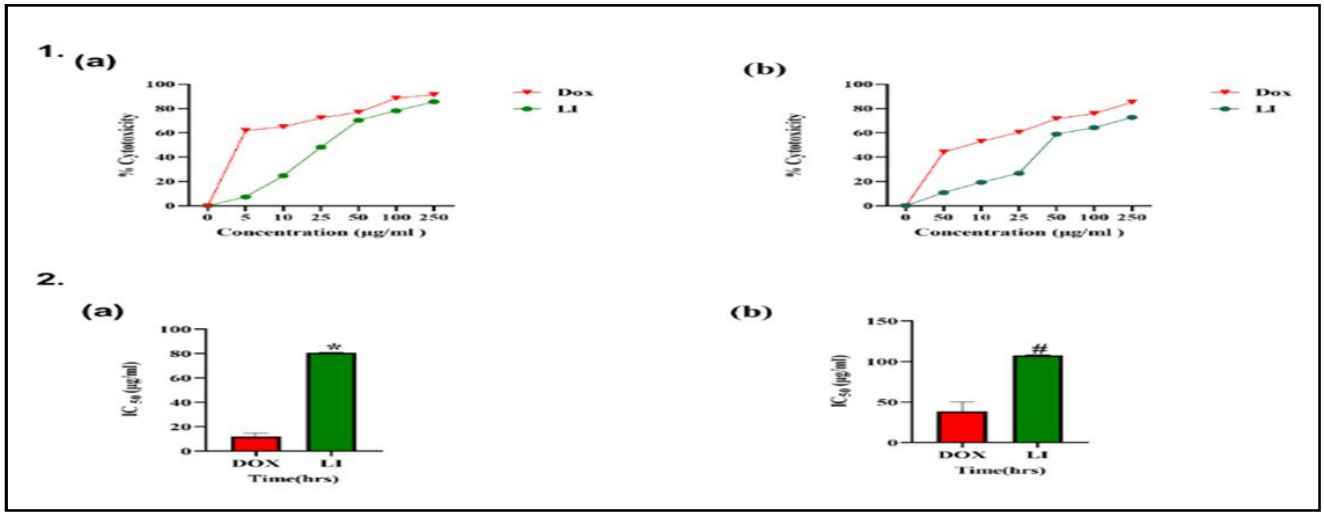

Figure 6: 1. Cytotoxicity of *L. interrupta* extract and doxorubicin as assessed by the MTT assay on (a) MCF-7 cells and (b) T-47D cell lines. 2. Values of IC_{50} for *L. interrupta* extract and doxorubicin on (a) MCF-7 and (b) T-47D cell lines. The results are given as the mean ± standard deviation (SD) for n = 3 attempts. *p<0.0001, #p<0.005.

4. Discussion

Breast cancer (BC) is a major factor influencing both the incidence and mortality rates of cancer among women globally (Akram *et al*., 2017). The condition is distinguished by its wide range of molecular subtypes and different prognoses, principally categorized according to the state of hormone receptors and levels of HER2 expression. The primary subtypes are triple-negative, HER2 positive, luminal A, and luminal B. Luminal A breast cancer is identified by the presence of estrogen receptor alpha (ERα) and progesterone receptor (PR), with typically moderate HER2 expression. This subtype generally has a lower histological grade and a more favourable prognosis compared to other types. Luminal A cancers often respond well to hormonal therapies targeting estrogen signalling pathways, making them a key focus for therapeutic strategies (Alharbi *et al*., 2022). However, resistance to hormonal treatments can occur, highlighting the need for ongoing research to develop more effective therapies. Understanding the unique characteristics of Luminal A breast cancer is essential for advancing treatment approaches and improving patient outcomes (Bertucci *et al*., 2009). Plant-based medicines have garnered significant attention in recent years due to their potential therapeutic benefits and reduced side effects compared to conventional treatments (Dewi *et al*., 2022). Phytochemicals, the bioactive compounds found in plants, often exhibit multiple mechanisms of action, which can target various pathways involved in disease progression (Salmerón-Manzano *et al*., 2020). This multi-target approach is particularly advantageous in complex diseases like cancer, where resistance to single-target therapies is a common challenge (Dewi *et al*., 2022).

The research using gas chromatography-mass spectrometry (GC-MS) identified a variety of components with significant features. For example, 1,1,3-triethoxypropane is significant in alcoholic beverages, while 2-[4-methyl-6-(2,6,6-trimethylcyclohex-1-enyl) hexa-1,3,5-trienyl] cyclohex-1-en-1-carboxaldehyde is characterized by its complex chemical structure (Qadir *et al*., 2022). Neophytadiene (NPT) is recognized for its ability to reduce anxiety, inflammation, and pain, as well as its potential to combat cancer (Gonzalez-Rivera *et al*., 2023). Ethyl palmitate demonstrates anti-inflammatory, antiviral, antimicrobial, and antioxidant activities (Díaz *et al*., 2023). Phytol is recognized for its anticancer, antimicrobial properties, and potential benefits in Alzheimer's treatment (Lakshmi *et al*., 2016). Ethyl linolenate exhibits antibacterial and anti-inflammatory properties (Chen *et al*.,2016). The study of octasiloxane contributes to understanding the diverse functions of these molecules (Khan *et al*., 2021). *In silico* studies focused on key cancer-related receptors, including progesterone receptor (PR), estrogen receptor alpha (ERα), and epidermal growth factor receptor (EGFR), revealed significant interactions with *L. interrupta* (Thomas *et al*., 2023). Docking simulations identified 2-[4-methyl-6-(2,6,6trimethylcyclohex-1-enyl) hexa-1,3,5-trienyl]cyclohex-1-en-1-carboxaldehyde as having strong binding affinities to these receptors, with docking scores of -6.611 kcal/mol for ERα (PDB ID: 3ERT), -4.744 kcal/mol for PR (PDB ID: 4OAR), and -3.950 kcal/mol for EGFR (PDB ID: 2J6M). These high binding scores suggest strong interactions with critical cancer-related targets and indicate the compound's potential as an effective therapeutic agent, particularly for estrogen-driven cancers such as luminal A breast cancer (Bertucci *et al*., 2009).

To validate these computational findings, we tested the effects of *L. interrupta* extract on luminal A breast cancer cell lines MCF-7 and T-47D. The extract exhibited IC_{50} values of 80.53 ± 0.428 µg/ml for MCF-7 cells and 107.51 ± 0.558 µg/ml for T-47D cells, compared to doxorubicin, which had IC_{50} values of 26.07 ± 15.70 µg/ml for MCF-7 cells and 35.74 ± 0.65 µg/ml for T-47D cells. These results underscore the potential of *L. interrupta* extract as a phytomedicine for targeting luminal A breast cancer cells (Al-Malki *et al*., 2020; Pal *et al*., 2019; Santhanam *et al*., 2022; Dhru *et al*.,2022). The differences in sensitivity between cell lines emphasize the importance of exploring plant-based compounds in cancer therapy and their potential to complement existing treatments (Arif *et al*., 2022). The

alignment of *in vitro* and *in silico* data underscores the relevance of the identified phytoconstituents in breast cancer therapy. One of the key advantages of plant-based medicines is their generally lower toxicity profile. Many conventional cancer treatments, such as chemotherapy, are associated with severe side effects that can significantly impact patients' quality of life. In contrast, plant-derived compounds often have fewer and less severe side effects, making them more tolerable for long-term use (Verma *et al*., 2022). For instance, compounds like neophytadiene and phytol, identified in *L. interrupta*, not only exhibit anticancer properties but also possess anti-inflammatory and antioxidant activities, which can help mitigate the adverse effects of cancer and its treatment. The ethanolic extract of *L. interrupta* demonstrates significant docking scores and considerable anticancer efficacy, indicating its potential as a valuable source for developing new therapeutic medicines.

5. Conclusion

Overall, this research underscores the potential of *L. interrupta* Chew. is a promising candidate for developing targeted therapies for luminal A breast cancer. The ethanolic extract underwent analysis employing gas chromatography-mass spectrometry (GC-MS), which identified many bioactive chemicals with significant characteristics. Computational docking studies of the extract against progesterone receptors (PR; PDB ID: 4OAR), estrogen receptors (ERα; PDB ID: 3ERT), and epidermal growth factor receptors (EGFR; PDB ID: 2J6M) revealed a significant affinity for ERα and PR, suggesting potential efficacy in treating luminal A breast cancer. The findings suggest that incorporating *L. interrupta* into therapeutic regimens for luminal A subtypes could be advantageous. Additionally, the increasing interest in natural and holistic health approaches aligns with the use of plant-based medicines. Research into the molecular mechanisms of phytochemicals emphasizes their potential for developing effective, safe, and affordable treatments, underscoring the importance of integrating these compounds into modern medical practices. *L. interrupta* could serve as an adjuvant therapy to enhance doxorubicin efficacy, potentially combined with other chemotherapeutics to combat resistance, delivered via targeted systems to optimize therapeutic outcomes, and included in complementary care to alleviate side effects. Furthermore, it warrants evaluation in clinical trials to rigorously assess its efficacy and safety, particularly as additional research clarifies its mechanisms of action. Despite the valuable insights provided by the study, it has limitations, including reliance on preclinical models, small sample sizes, and a lack of long-term data. Also, requires thorough scientific validation to establish its efficacy and safety, standardize treatments, understand underlying mechanisms, assess potential side effects, facilitate integration into conventional medicine, and support regulatory acceptance. Future research should prioritize *in vivo* evaluations, further explore the mechanisms of action, and compare *L. interrupta* with existing treatments to enhance its efficacy and address drug resistance. Ultimately, these efforts could pave the way for innovative therapies that significantly improve patient outcomes in breast cancer treatment.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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