INFORMATICS JOURNALS

Research Article

Journal of Natural Remedies
DOI: 10.18311/jnr/2026/52624

eISSN: 2320-3358 | Vol 26(2), 2026 | pp. 449-457

Molecular Docking of Phytoconstituents from *Pterospermum acerifolium* for Anticancer Activity

Sampada D. Dalvi and Vikas Shivaji Mugale*

Department of Pharmaceutical Chemistry, Marathwada Mitra Mandal's College of Pharmacy, (Affiliated to Savitribai Phule Pune University, Pune), Thergaon, Pune – 411033, Maharashtra, India; vikasmugale@gmail.com

Abstract

Background: Cancer is a leading global health concern, driving the search for safer and more effective therapeutic agents. Natural products remain a valuable source of novel anticancer agents. Medicinal plants represent a valuable source of anticancer compounds due to their diverse phytochemicals. **Aim:** The present study aimed to evaluate the anticancer potential of reported phytoconstituents from *Pterospermum acerifolium* using molecular docking and *in silico* ADMET analysis. **Methods:** Molecular docking was performed to predict the binding affinity and interaction profiles of reported Phytoconstituents present in *P. acerifolium* with selected cancer-related target proteins, including the human estrogen receptor alpha ligand-binding domain complexed with 4-hydroxytamoxifen (PDB ID: 3ERT), wild-type epidermal growth factor receptor complexed with AZD9291 (PDB ID: 4ZAU), fibroblast growth factor receptor 4 with an irreversible inhibitor (PDB ID: 4XCU), and the epidermal growth factor receptor tyrosine kinase domain complexed with erlotinib (PDB ID: 1M17). Docking was performed with BIOVIA Discovery Studio v.20 to predict binding affinities and interactions with 3ERT, 4ZAU, 4XCU and 1M17. The docking process involves protein (receptor) and ligand preparation, grid definition, simulation runs and analysis of binding poses. In addition, ADMET properties of selected phytoconstituents were predicted using the SWISSADME to evaluate their pharmacokinetic behaviour and drug-likeness. **Results:** The analysis indicated favourable absorption, lipophilicity, and low toxicity profiles, supporting potential use of Pterospermin A, B and C as an anticancer agent. **Conclusion:** The findings suggest that Pterospermin A and Pterospermin B possess significant anticancer potential and may serve as promising lead compounds for further experimental validation.

Major Finding: Pterospermin A and B demonstrated strong binding with multiple cancer targets. ADMET analysis supported favourable drug-likeness properties.

Keywords: Anticancer Activity, ADMET, Molecular Docking, Phytoconstituents, *Pterospermum acerifolium*, *In Silico* Study

(Article Chronicle: Article Received on: 14.10.2025; Revised on: 08.01.2026; Accepted on: 21.01.2026)

1. Introduction

Nature has long been an abundant source of medicinal products, with many useful drugs developed from plant origins. Natural resources not only provide therapeutic agents but also inspire modern drug discovery and the development of novel structural leads. Plant-based systems continue to play a vital role in healthcare across diverse cultures. A survey conducted in countries hosting WHO-Traditional Medicine Centres revealed that a significant proportion of plant-derived pure compounds used as drugs were employed for the same or related ethnomedical purposes, emphasising the close connection between traditional knowledge and modern pharmacology[1].

Cancer is a multifactorial and complex disease that remains a major global health challenge, accounting for millions of deaths each year. Despite advances in modern medicine, there is an urgent and continuing need for new therapeutic approaches to both prevent and treat this life-threatening condition. Current treatment modalities, including chemotherapy,

*Author for correspondence

radiotherapy, and synthetic drugs, though effective, are often associated with severe toxicity and undesirable side effects that compromise patients' quality of life. Consequently, the scientific community has increasingly turned its focus toward naturally derived compounds, which are considered safer and less toxic alternatives to conventional chemotherapeutics. The plant kingdom serves as a prolific source of structurally diverse bioactive compounds that have historically contributed to drug discovery and continue to inspire the development of novel anticancer agents. Many plant species have been shown to possess significant anticancer potential, with their secondary metabolites—such as alkaloids, terpenoids, phenolics, and flavonoids—exhibiting potent antioxidant, anti-inflammatory, and cytotoxic activities. The exploration of such phytochemicals offers a promising avenue for the development of safer, more effective, and affordable anticancer therapeutics derived from natural origins[2].

Among the diverse classes of bioactive plant metabolites, flavonoids represent one of the most ubiquitous and pharmacologically significant groups. Numerous preclinical and several clinical investigations have demonstrated that flavonoids possess significant therapeutic potential as anticancer agents. Epidemiological studies have further supported a protective role for diets rich in flavonoid-containing foods, correlating with a reduced risk of cancer incidence[3].

Pterospermum acerifolium (L.) Wild, belonging to the family *Sterculiaceae,* commonly known as Kanak Champa, has long been recognised in traditional medicine for its wide spectrum of therapeutic properties. Traditionally, the plant has been used as a general tonic and antitumor agent, as well as for the treatment of diabetes, gastrointestinal disorders, leprosy, blood diseases, bronchitis, cough, cephalic pain, migraine, inflammation, smallpox, and for its haemostatic and antimicrobial effects[4].

Modern pharmacological investigations have validated many of these traditional claims, demonstrating that *P. acerifolium* exhibits potent antioxidant, anti-inflammatory, hepatoprotective, antimicrobial, antimitotic, immunosuppressive, and anticancer activities. These biological effects are primarily attributed to its diverse phytochemical constituents, including alkaloids, glycosides, flavonoids, tannins, triterpenoids, and carbohydrates. Phytochemical analyses have further led to the isolation of several distinctive compounds, notably Pterospermin A, Pterospermin B, and Pterospermin C, which are believed to contribute significantly to the plant's pharmacological potential. Structurally, Pterospermins are characterised by the presence of a chromone ring system, a fused benzene and γ-pyrone framework, which plays a pivotal role in their biological activity. The presence of glycosidic linkages in these compounds enhances their solubility and bioavailability, thereby facilitating more effective interactions with biological targets. Notably, Pterospermin C contains an additional furan ring, which may further augment its anticancer potential by improving binding affinity with molecular targets. These structural attributes collectively suggest that *P. acerifolium* and its constituents could serve as promising molecular scaffolds for the development of new chemotherapeutic agents[5].

Molecular docking techniques play a crucial role in elucidating the interactions between bioactive plant-derived molecules and cancer-associated target proteins. Docking simulations predict the binding affinities and characterise the nature of ligand–receptor interactions at the molecular level, thereby providing valuable insights into their possible mechanisms of action. Such *in silico* approaches enable the visualisation and quantification of molecular interactions, which complement *in vitro* and *in vivo* studies. The integration of computational methods such as molecular docking with phytochemical characterisation and biological evaluation significantly accelerates the identification and optimisation of potent natural anticancer candidates from plants such as *P. acerifolium*[6,7].

The present study investigates the anticancer activity of Phytoconstituents of *P. acerifolium* (Pterospermin A, Pterospermin B and Pterospermin C) to provide a scientific basis for its therapeutic use as an anticancer agent.

2. Materials and Methods

2.1 Preparation of Macromolecule (Receptor)

This initial step involves preparing the target protein for docking. The three-dimensional (3D) structure of the protein is typically obtained from public

databases like the Protein Data Bank (PDB). The three-dimensional crystal structures of human estrogen receptor alpha (PDB ID: 3ERT), epidermal growth factor receptor (PDB IDs: 4ZAU and 1M17), and fibroblast growth factor receptor-4 (PDB ID: 4XCU) were retrieved from the Protein Data Bank and employed for molecular docking studies[8,9]. Detailed information on the selected target proteins is summarised in Table 1. The PDB file is cleaned to remove all non-essential components such as water molecules, co-crystallised ligands (if not part of the study) and other heteroatoms.

Hydrogenation and Charge Assignment: Polar hydrogen atoms are added to the protein structure, which is crucial for accurate hydrogen bond formation during docking. Partial atomic charges, such as Gasteiger charges, are then assigned to each atom. File Format Conversion: The prepared protein is converted into a specific file format required by the docking software, such as the Protein Data Bank, Partial Charge (Q), and Atom Type (T) format used by AutoDock Vina[10].

2.2 Preparation of Ligand (Small Molecule)

The ligand, or the molecule to be docked, must also be prepared similarly. The 3D structure of the ligand can be retrieved from chemical databases like PubChem or ZINC[11]. 3D Structure Optimisation: The ligand's structure is optimised to a low-energy conformation. This often involves geometry optimisation and conformational analysis. Hydrogenation and Rotatable Bonds: Non-polar hydrogen atoms are merged, and polar hydrogens are added. The software automatically identifies and defines the rotatable bonds of the ligand, which allows for conformational flexibility during the docking simulation. File Format Conversion: The prepared ligand is converted into a format compatible with the docking software, such as Protein Data Bank, Partial Charge (Q), and Atom Type (T).

2.3 Setting Up the Docking Simulation

This is the core phase where the docking parameters are defined. Defining the Active Site: The binding site on the protein where the ligand is expected to bind is specified. This is typically done by defining a grid box—a 3D rectangular space that encloses the active site. The coordinates (x, y, and z) and dimensions of this box are crucial for focusing the docking simulation on the area of interest and reducing computational time. Algorithm and Parameters: The docking software's search algorithm is selected (e.g., genetic algorithm, Lamarckian genetic algorithm). Other parameters, such as the number of docking runs and exhaustiveness, are set to control the thoroughness of the search.

2.4 Running the Docking Simulation

Once all the files and parameters are set, the molecular docking simulation is executed. The software uses its algorithm to search for various possible orientations (poses) and conformations of the ligand within the defined grid box. It attempts to find the most stable binding poses by minimising the overall energy of the protein-ligand complex.

2.5 Analysis of Docking Results

Scoring and Ranking: The docking results were analysed to identify the best binding poses based on binding affinity values. More negative binding

Table 1. Details of target proteins used in molecular docking studies

Sr. No.	Cancer Type/ Target	Protein Description	PDB ID	Resolution	Disallowed Region
1	Breast cancer	Human estrogen receptor alpha ligand-binding domain in complex with 4-hydroxytamoxifen	3ERT	Å	0%
2	Lung cancer	AZD9291 complex with wild-type EGFR	4ZAU	2.8 Å	0%
3	Liver cancer	Crystal Structure of FGFR4 with an Irreversible Inhibitor	4XCU	1.71 Å	0%
4	Colon cancer	Epidermal Growth Factor Receptor tyrosine kinase domain with 4-anilinoquinazoline inhibitor Erlotinib	1M17	2.6 Å	0%

energies indicated stronger and more stable interactions between ligand and receptor. Visual Analysis: The top-ranked poses are then visualised using molecular graphics software (like PyMOL or Discovery Studio) to inspect the specific interactions between the ligand and the amino acid residues in the active site. Key interactions, such as hydrogen bonds, hydrophobic interactions, and pi-stacking, are identified and reported. Validation: For validation, the docking protocol can be performed on a known co-crystallised complex to ensure the software can accurately reproduce the experimentally determined binding pose. The accuracy is often measured by the Root Mean Square Deviation (RMSD) between the docked pose and the original co-crystallised ligand. An RMSD value of less than 2.0 Å is generally considered an excellent result.

2.6 Prediction of ADMET

The ADMET properties (Absorption, Distribution, Metabolism, Excretion, and Toxicity) of the Pterospermins A, B and C were predicted using the SWISSADME online tool (https://www.swissadme.ch/index.php). The compounds were entered in SMILES format to calculate physicochemical properties, pharmacokinetics, and drug-likeness[12]. The ADMET and drug-likeness characteristics of Pterospermin A, B, and C were evaluated using the SWISSADME web tool, applying Lipinski's and Egan's rules for assessing oral bioavailability and pharmacokinetic suitability.

3. Results and Discussion

The data in Tables 2-4 illustrate binding interactions of Pterospermin A, Pterospermin B, and Pterospermin C with the selected cancer-associated target proteins (3ERT, 4ZAU, 4XCU, and 1M17). All ligands exhibited favourable interactions, forming multiple conventional hydrogen bonds with key amino acid residues. In addition, several C–H bond interactions contributed to the overall stability of the complexes. Among the ligands, Pterospermin A and Pterospermin B showed the most stable and energetically favourable binding conformations, with binding energies ranging between −8.2 and −8.8 kcal/mol. These interactions were primarily stabilised by hydrogen bonds with residues such as Glu353, Asp34, and Arg66, along with hydrophobic contacts involving Phe63, Phe404, and Leu387. In contrast, Pterospermin C demonstrated comparatively weaker binding affinities (−4.5 to −5.6 kcal/mol) and fewer hydrogen or C–H bond interactions, suggesting limited stability of the ligand–protein complex. Overall, the results indicate that Pterospermin A and B exhibit stronger binding potentials and could serve as promising candidates for further anticancer investigations.

Docking results were critically compared with co-crystallised reference inhibitors, revealing that Pterospermin A and B exhibit comparable binding affinities and interaction profiles, whereas Pterospermin C showed weaker binding.

Table 5 illustrates the drug-likeness radar map parameter diagrams of Pterospermin A, Pterospermin B, and Pterospermin C, while Table 6 summarises the predicted Lipinski's and Egan's rule parameters for the selected phytoconstituents. The ADMET analysis revealed that Pterospermin A possessed a molecular weight of 482.44 Da, six hydrogen bond donors, and ten hydrogen bond acceptors, thereby satisfying most of Lipinski's parameters with only one violation attributed to molecular size. Pterospermin B exhibited a molecular weight of 448.38 Da with seven hydrogen bond donors and eleven hydrogen bond acceptors, showing two Lipinski violations due to its higher polarity and hydrogen bonding potential. In contrast, Pterospermin C (MW 116.07 Da) completely adhered to both Lipinski's and Egan's rules, indicating a more favourable drug-like profile.

The calculated WLOGP values of 2.44, -0.24, and -0.7 for Pterospermin A, B, and C, respectively, suggest moderate lipophilicity and good membrane permeability. The Topological Polar Surface Area (TPSA) values of 170.05 and 190.28 for Pterospermin A and B indicate limited blood–brain barrier penetration but acceptable gastrointestinal absorption, whereas the lower TPSA of Pterospermin C (66.76) implies better passive diffusion and bioavailability. The radar maps of drug-likeness confirm that all three molecules lie within the optimal physicochemical space for oral bioavailability.

Table 2. Docking results of Pterospermin A with cancer targets

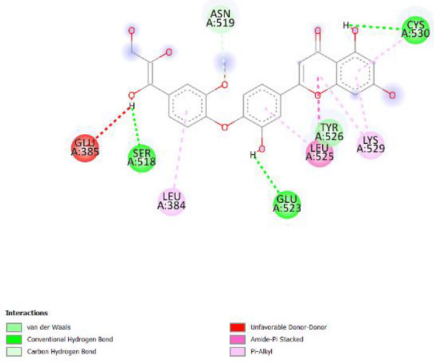
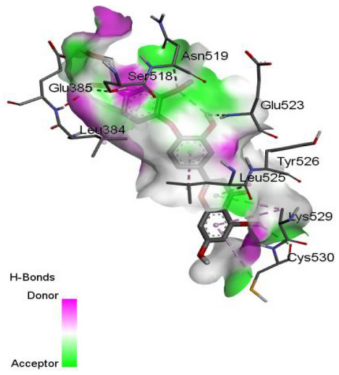
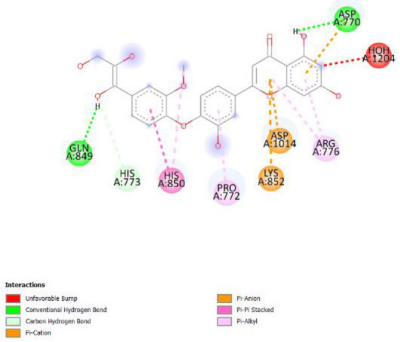
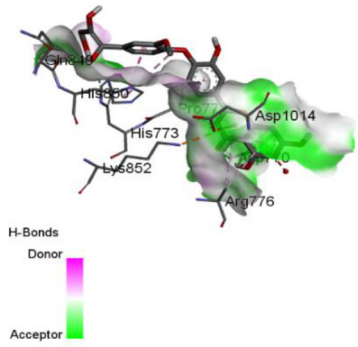
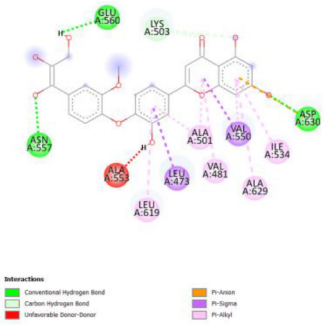
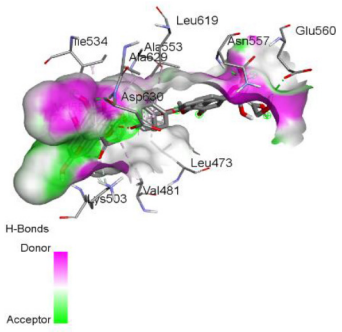
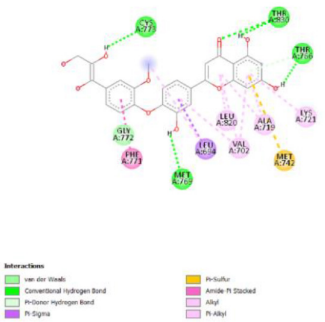
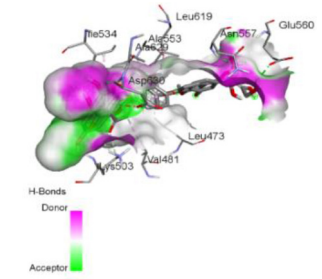
Sr. No.	Protein	Interaction		Binding affinity
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1	3ERT			-8.3
		Conventional Hydrogen Bond: SER A: 518, GLU A: 523, CYS A: 530	C-H Bond: No interaction	
2	4ZAU			-7.9
		Conventional Hydrogen Bond: ASP A: 770, GLN A: 849	C-H Bond: No interaction	
3	4XCU			-8.6
		Conventional Hydrogen Bond: GLUA:56O, ASNA:557, ASP:630	C-H Bond: LYSA:503	
4	1M17			-8.5
		Conventional Hydrogen Bond: CYSA:773, META:769, THRA:830, THRA:766	C-H Bond: GLYA:772	

Table 3. Docking results of Pterospermin B with cancer targets

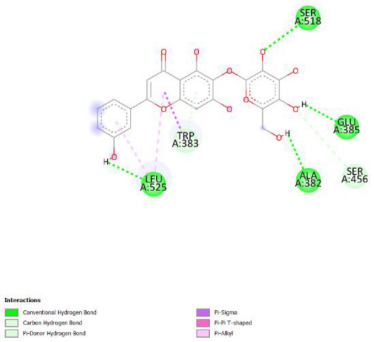
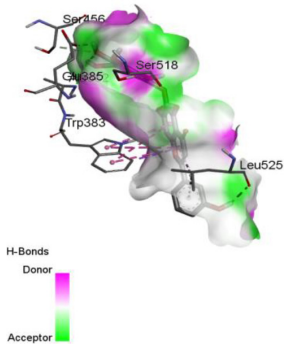
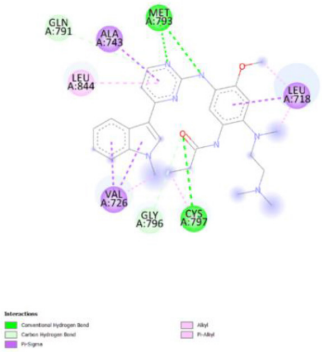
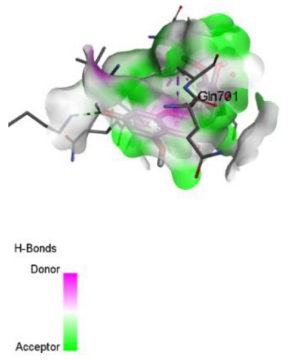
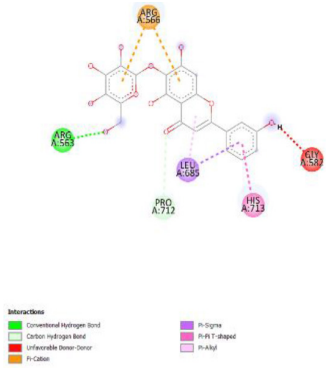
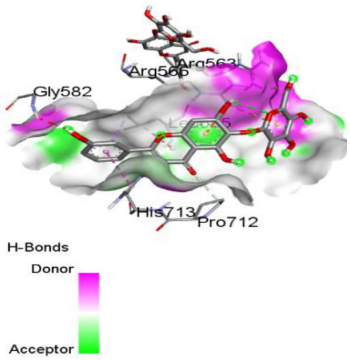
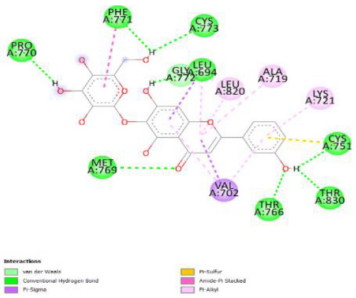
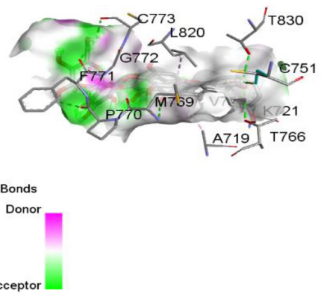
Sr. No.	Protein	Interaction		Binding affinity
		2D	3D	
1	3ERT			-8.2
		Conventional Hydrogen Bond: SER A: 518, GLU A: 523, CYS A: 530	C-H Bond: No interaction	
2	4ZAU			-8.7
		Conventional Hydrogen Bond: CYS A: 797, MET A: 793	C-H Bond: No interaction	
3	4XCU			-8.8
		Conventional Hydrogen Bond: ARGA:563	C-H Bond: PROA: 712	
4	1M17			-8.8
		Conventional Hydrogen Bond: PROA:770, PHEA:771,CYSA:773, ,META:769,CYSA:751,THRA:830,THRA:766	C-H Bond: GLYA:772	

Table 4. Docking results of Pterospermin C with cancer targets

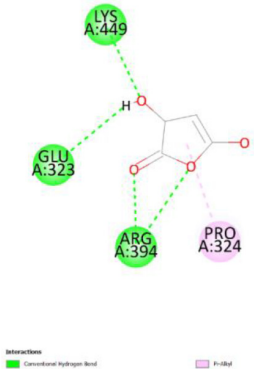
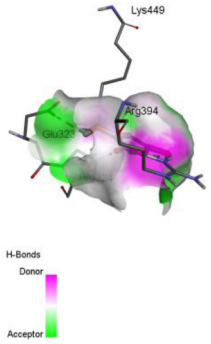
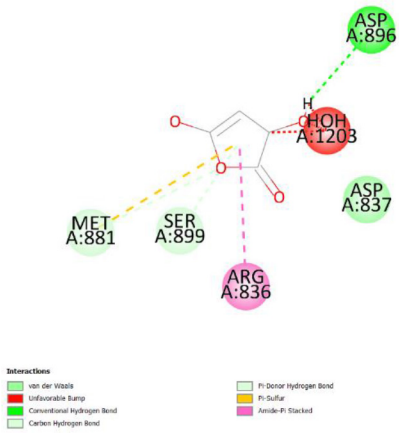
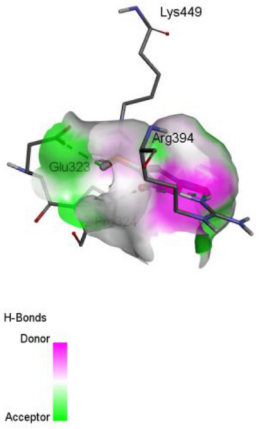
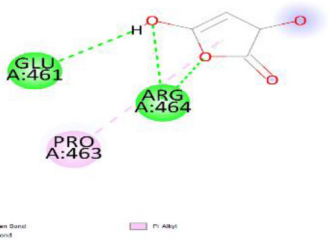
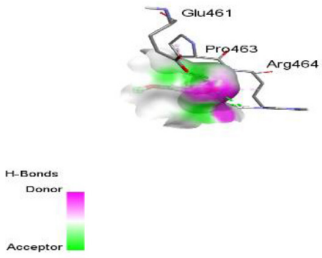
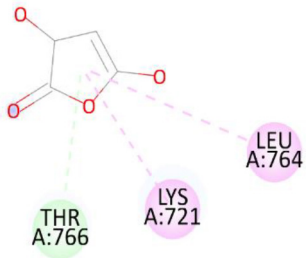
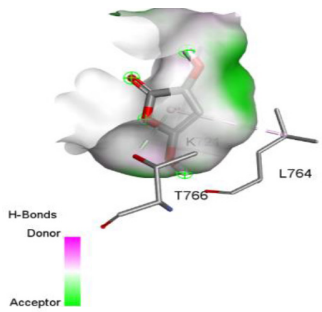
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		Conventional Hydrogen Bond: GLU A: 323, ARG A: 394, LYS A: 449	C-H Bond: No interaction	
2	4ZAU			-5.1
		Conventional Hydrogen Bond: ASP A: 896	C-H Bond: No interaction	
3	4XCU			-4.5
		Conventional Hydrogen Bond: GLUA:461, ARGA:464	C-H Bond: No interaction	
4	1M17			-4.5
		Conventional Hydrogen Bond: No interaction	C-H Bond: THRA:766	

Table 5. Drug-likeness Radar map parameter diagram of Pterospermin A, B and C

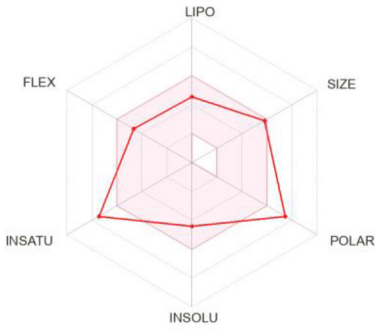
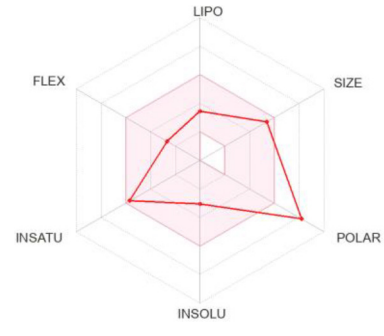
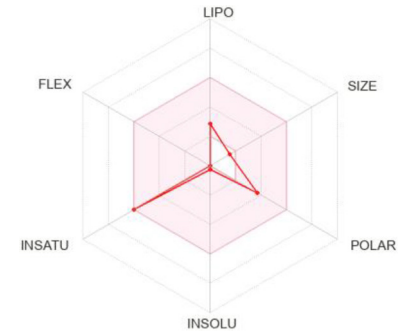
		
Pterospermin A	Pterospermin B	Pterospermin C

Table 6. Predicted Lipinski's and Egan's rule parameters for Pterospermin A, B and C

Compound	MW (DA)	H-bond donors	H-bond acceptors	TPSA	WLOGP	Lipinski violations	Egan violations
Pterospermin A	482.44	6	10	170.05	2.44	1	1
Pterospermin B	448.38	7	11	190.28	-0.24	2	1
Pterospermin C	116.07	2	4	66.76	-0.7	0	0

4. Conclusion

The molecular docking analysis of Pterospermin A, Pterospermin B and Pterospermin C derived from *Pterospermum acerifolium* revealed significant binding affinities toward the cancer-related targets 3ERT, 4ZAU, 4XCU, and 1M17. All three ligands interacted with key amino acid residues through hydrogen and hydrophobic bonds, enhancing complex stability. Among them, Pterospermin B showed the strongest binding affinities, recording −8.2 kcal/mol (3ERT), −8.8 kcal/mol (4XCU and 1M17), and −8.7 kcal/mol (4ZAU). Pterospermin A also displayed high affinity with binding energies of −8.3, −8.6, and −8.5 kcal/mol against 3ERT, 4XCU, and 1M17, respectively. These findings suggest that Pterospermin A and B possess substantial potential as anticancer agents, particularly against breast, lung, liver and colon cancers.

The ADMET analysis revealed that Pterospermin A, B, and C possess favourable pharmacokinetic and drug-likeness properties, supporting their potential as orally active candidates. Notably, Pterospermin C exhibited optimal absorption and no rule violations, indicating strong promise for further pharmacological evaluation. Future investigations should focus on *in vitro* cytotoxicity assays against relevant cancer cell lines to validate the predicted molecular interactions, followed by *in vivo* studies to assess therapeutic efficacy and safety.

5. References

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Author Contribution

All authors contributed equally to the conception, design, experimentation, data analysis, and writing of this manuscript. All authors have read and agreed to the published version of the manuscript.