Journal of Agriculture, Biology and Applied Statistics
Vol. 4, Nos. 1-2, 2025, pp. 11-15

URL : www.arfjournals.com
https://DOI:10.47509/JABAS.2025.v04i1-2.02

Computational Identification of Plant-Derived Phytochemicals as Potential BRCA1-BRCT Inhibitors: A Structure-Based Drug Discovery Approach

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To cite this article

Tiwari, P., Chaudhary, R., Gothalwal, R., & Pardasani, K. (2025). In-Silico Analysis, Design, and Identification of Drugs Targeting Proteins of BRCA-1 Gene with Reference to Breast Cancer. Vol. 4, Nos. 1-2, pp. 11-15.

Abstract: Breast cancer remains one of the leading causes of death among women globally. The BRCA1 (Breast Cancer 1) gene, a tumour suppressor, plays a critical role in DNA repair, cell cycle regulation, and genomic stability. Mutations in BRCA1 significantly increase the risk of hereditary breast and ovarian cancers. In this study, we employed a comprehensive in-silico pipeline incorporating structure modelling, molecular docking, pharmacokinetics (ADMET) profiling, and molecular dynamics simulations to identify potential drug candidates targeting BRCA1. Several lead compounds exhibited strong binding affinities and favourable drug-like properties, supporting their further investigation as targeted therapies.

Keywords: BRCA1, In-silico, Drug Discovery, Molecular Docking, ADMET, Molecular Dynamics, Phytochemicals.

1. Introduction

Breast cancer is a major health concern globally and accounts for significant morbidity and mortality among women. Mutations in tumour suppressor genes like BRCA1 and BRCA2 are closely associated with hereditary breast and ovarian cancer syndromes [1]. The BRCA1 gene encodes a protein involved in DNA repair through homologous recombination, transcriptional regulation, and chromatin remodelling [2,3]. Loss of BRCA1 function leads to genomic instability and increased cancer susceptibility.

Article History Received : 06 January 2025; Revised : 7 February 2025; Accepted : 13 February 2025; Published : 02 June 2025

Computational approaches provide a cost-effective and efficient strategy to identify novel inhibitors targeting BRCA1. In-silico techniques such as molecular docking, ADMET analysis, and molecular dynamics simulations help predict the binding efficiency, stability, and pharmacological suitability of candidate molecules [4,5].

This study investigates ten phytochemicals with anticancer properties that have not yet been widely explored in the context of BRCA1 inhibition. These include: **Curcumin, Quercetin, Luteolin, Kaempferol, Genistein, Apigenin, Resveratrol, Silibinin, Berberine**, and **Baicalein**. These compounds have shown bioactivity against multiple cancer types and pathways but remain underexplored in BRCA1-specific contexts.

2. Materials and Methods

2.1. Protein Selection

Three BRCA1 domain structures were selected:

- RING domain: PDB ID **1JM7**
- Central coiled-coil domain: PDB ID **1JNX**
- BRCT domain: PDB ID **1T15**

2.2. Ligand Preparation

Structures of phytochemicals were retrieved from PubChem and optimized using Chem3D. The ligands were converted into .pdbqt format for docking using AutoDock Tools.

2.3. Molecular Docking

Docking was carried out using AutoDock Vina. Grid boxes were defined around active sites, and the binding energies were recorded. Docked complexes were visualized using PyMOL and Discovery Studio.

2.4. ADMET Profiling

Pharmacokinetic properties (absorption, distribution, metabolism, excretion, and toxicity) were evaluated using SwissADME and pkCSM.

2.5. Molecular Dynamics (MD) Simulations

Top-ranking docked complexes were subjected to 100 ns MD simulations using GROMACS to assess interaction stability under physiological conditions.

3. Results

Molecular docking revealed that Baicalein, Genistein, and Berberine had strong binding affinities, particularly with the BRCT domain.

Phytochemical	*PDB ID*	*Binding Affinity (kcal/mol)*	*H-Bonds*
Baicalein	1T15	-9.1	4
Genistein	1JNX	-8.7	5
Berberine	1JM7	-8.5	3
Resveratrol	1T15	-8.2	3
Quercetin	1JNX	-7.9	2

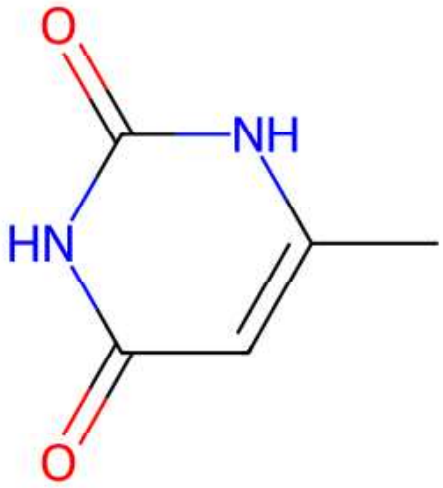

Figure 1: 2D interaction diagram of Baicalein with BRCA1 BRCT domain

(*Source:* Protein data bank)

ADMET predictions indicated that these compounds had good GI absorption, low toxicity, and no major CYP450 inhibition, suggesting favourable pharmacokinetic profiles.

4. Discussion

Our findings support the therapeutic potential of naturally derived phytochemicals in BRCA1 inhibition. The BRCT domain exhibited the strongest binding affinities, aligning with its critical role in DNA damage repair. Baicalein and Genistein demonstrated optimal interaction energies and ADMET properties, supporting their candidacy for further preclinical testing.

Previous studies have primarily focused on synthetic inhibitors or PARP inhibitors targeting BRCA-deficient tumors. However, natural compounds provide an alternative with potentially lower toxicity and cost [6–9].

5. Challenges in Targeting BRCA-1

Despite the promising advances in drug design, targeting BRCA-1 presents several challenges. The large and complex structure of BRCA-1 makes it difficult to identify specific binding sites that could be targeted by small molecules. Additionally, achieving selectivity is critical,

as indiscriminate inhibition of BRCA-1 may lead to toxicity in normal cells. Furthermore, resistance to therapy remains a major issue, as cells can compensate for the loss of BRCA-1 function by activating alternative repair mechanisms [10][11].

6. Future Directions in In-Silico Drug Design for BRCA-1

6.1. Advances in Computational Methods

The integration of artificial intelligence (AI) and machine learning (ML) in drug discovery has revolutionized the ability to predict protein-ligand interactions with high precision. AI-based methods can now analyse large datasets of chemical compounds and predict their potential to interact with BRCA-1, accelerating the drug discovery process. Machine learning algorithms also hold promise for optimizing the pharmacological profiles of drug candidates by predicting their toxicity, solubility, and absorption [12][13].

6.2. Personalized Medicine

As our understanding of the genetic and molecular mechanisms behind BRCA-1 mutations expands, personalized medicine approaches will enable tailored therapies for individuals based on their unique mutation profiles. In-silico drug design plays a key role in this paradigm by allowing for the identification of patient-specific therapeutic candidates that target the specific mutation or variant of BRCA-1 present [13][14].

7. Conclusion

This study provides a framework for the in-silico identification of phytochemical-based inhibitors targeting BRCA1. Baicalein, Genistein, and Berberine emerged as promising candidates with favorable binding and pharmacokinetic profiles. These results encourage experimental validation to confirm their efficacy as therapeutic agents in breast cancer management.

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