Computational Screening of Natural Compounds as Potential Inhibitors of Triple Negative Breast Cancer

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Abstract

Triple-negative breast cancer (TNBC) is a very aggressive subtype with few treatment options due to the lack of oestrogen, progesterone, and HER2 receptors. This study investigates the potential of natural substances as TNBC inhibitors utilising computational methods. Ten natural substances—Lycopene, Fucoxanthin, Cucurbitacin, Hesperidin, Ginsenosides, Lupenone, Cypripedin, Sesquiterpenes, Carotenoids, and Bilobetin—were chosen and their chemical structures optimised using vibrational frequency calculations with the DND basis set and the B3LYP function. Biological activity was predicted using the PASS program, and pharmacokinetic and toxicity profiles were evaluated using pkCSM. PyRx (v0.8) was used to dock against ULK2 (PDB ID: 6YID) and human CK2 alpha kinase (PDB ID: 3H30) to determine binding affinity. Ginsenosides and Bilobetin outperformed the other candidates in terms of ADMET properties such as drug-likeness, oral bioavailability, and low toxicity. The protein-ligand complexes' stability was further evaluated using 100 ns molecular dynamics simulations, which revealed persistent binding and negligible structural changes. The findings indicate that ginsenosides and bilobetin are promising natural inhibitors of TNBC targets, warranting more in vitro and in vivo research for therapeutic development.

Keywords: ADMET, Triple-negative breast cancer, Natural compounds, Molecular docking, Molecular dynamics.

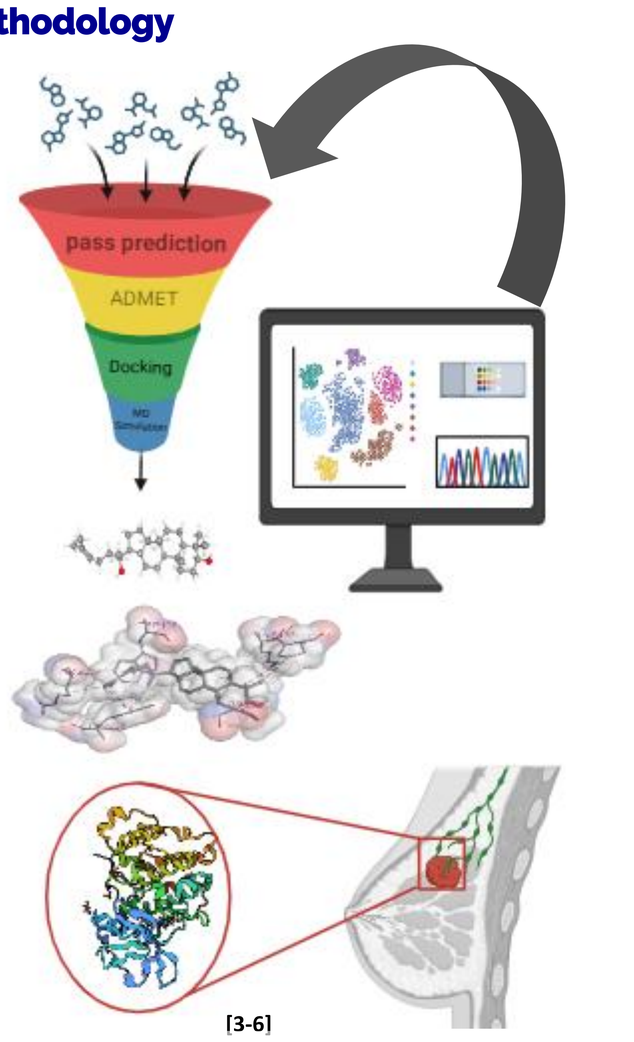
Introduction

Triple-negative breast cancer (TNBC) is an aggressive malignancy lacking ER, PR, and HER2 receptors, limiting treatment options and contributing to poor outcomes [1]. Chemotherapy remains the primary therapy despite severe side effects. This study investigates natural plant-derived compounds, particularly Ginsenosides, for their potential to inhibit TNBC targets using a comprehensive in silico approach, aiming to identify safer, targeted therapeutic alternatives [2].

Aim of the Study

To identify and evaluate natural compounds, especially Ginsenosides, as potential inhibitors of TNBC targets using molecular docking, ADMET analysis, and molecular dynamics simulations.

Methodology



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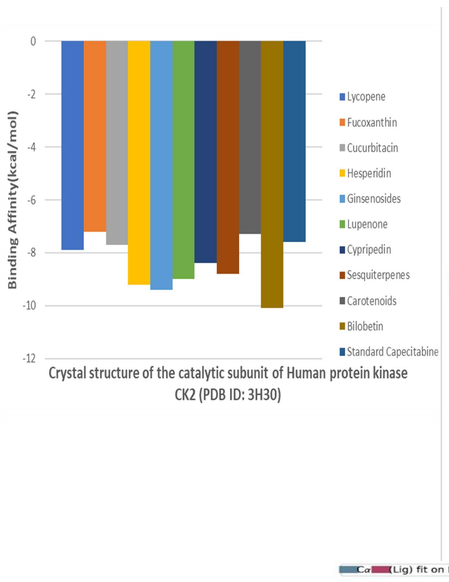
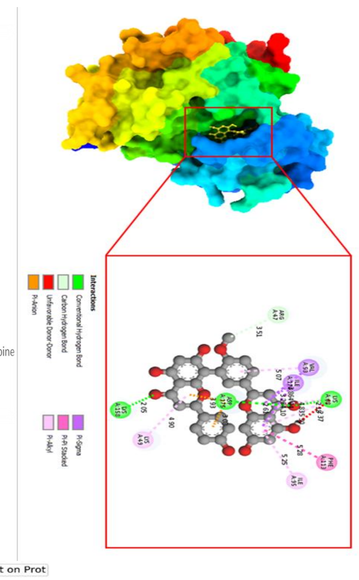
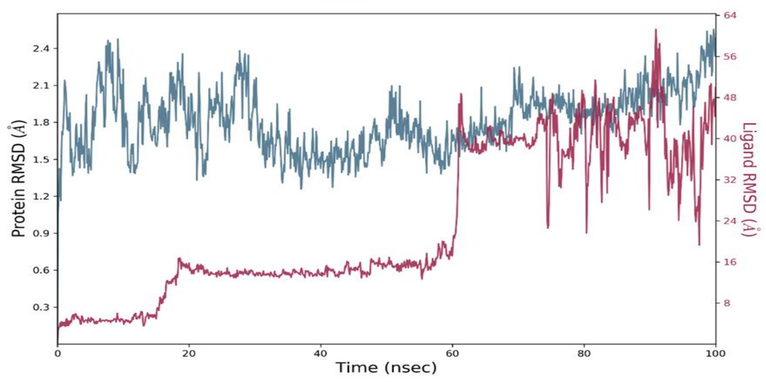
Result and Discussion

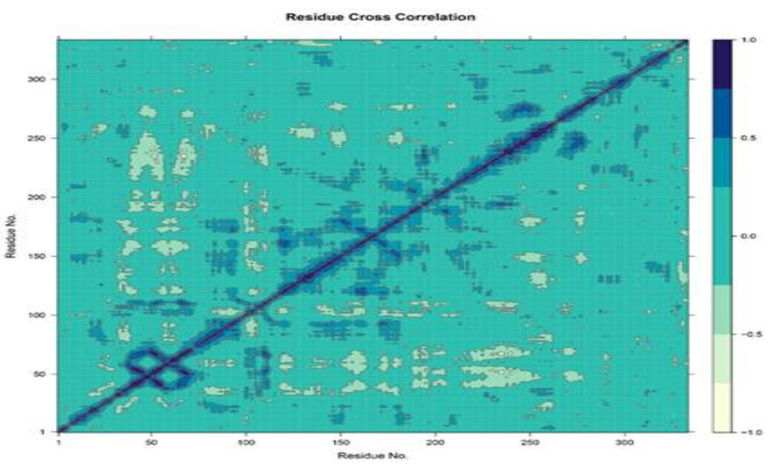
PASS and Lipinski Evaluation

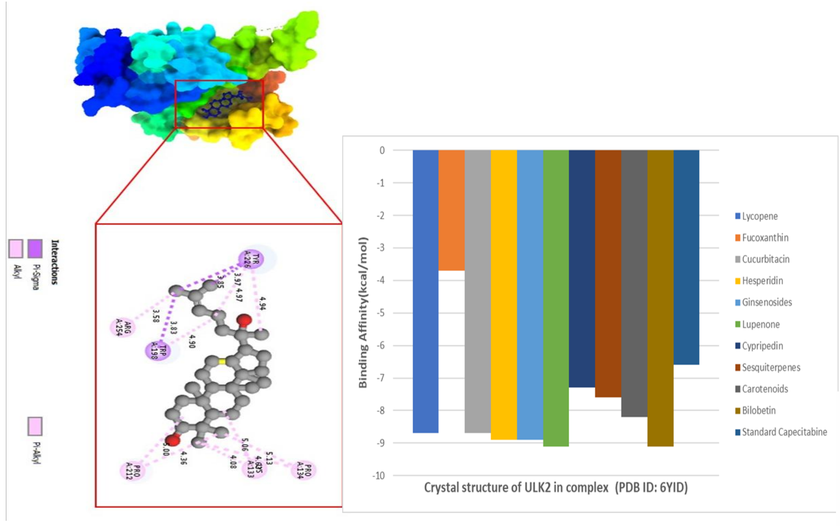
All compounds showed antineoplastic Pa scores >0.8. Except Hesperidin, all compounds complied with Lipinski's Rule, with

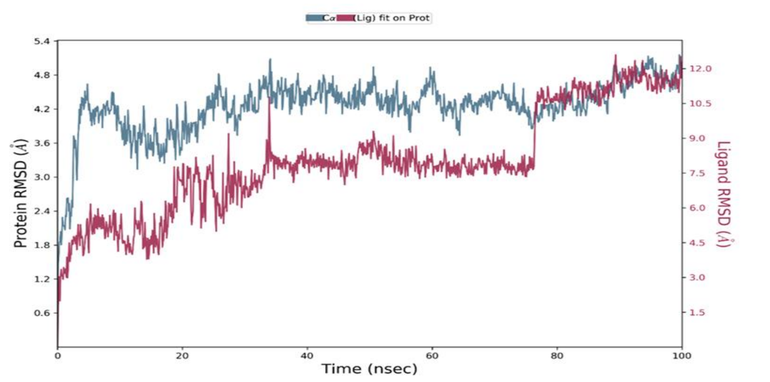


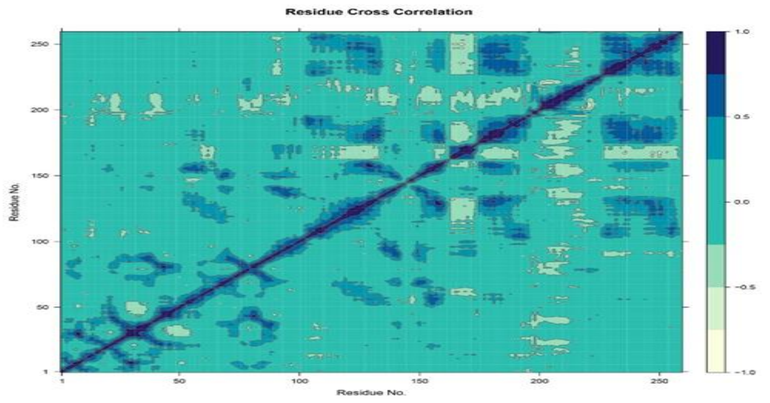












Drug-likeness Evaluation

CID	Name	Molecular weight	Hydrogen bond acceptor	Hydrogen bond donor	TPSA Å²	Lipinski rule		Bioavailability
						Result	violation	
446925	Lycopene	536.9	0	0	0.00	Yes	1	0.55
5281239	Fucoxanthin	658.91	6	2	96.36	Yes	1	0.55
5281316	Cucurbitacin	558.7	8	3	3.23	Yes	1	0.55
10621	Hesperidin	610.6	15	8	234.29	No	3	0.17
3086007	Ginsenosides	444.7	2	2	40.46	Yes	1	0.55
92158	Lupenone	424.7	1	0	17.07	Yes	1	0.55
174864	Cypripedin	284.26	5	1	72.83	Yes	0	0.85
667450	Sesquiterpenes	246.3	3	0	43.37	Yes	0	0.55
16061280	Carotenoids	717	6	4	99.38	Yes	1	0.55
5315459	Bilobetin	552.5	10	5	170.80	Yes	1	0.55

ADMET Profiling

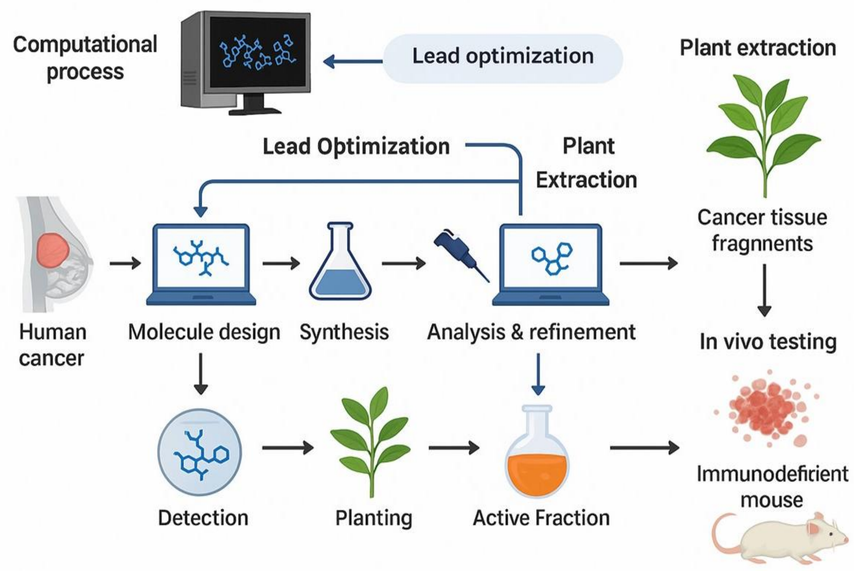
S/N	CID	Absorption		Distribution		Metabolism		Excretion		Toxicity		
		Water solubility Log S	Human Intestinal Absorption (%)	VDss (human)	BBB Permeability	CYP450 1A2 Inhibitor	CYP450 2D6 substrate	Total Clearance (ml/min/kg)	Renal OCT2 substrate	AMES toxicity	Skin Sensitization	Hepatotoxicity
01	Lycopene	-6.067	89.02	-0.208	Yes	No	No	1.949	No	No	No	No
02	Fucoxanthin	-6.436	90.671	-0.615	No	No	No	0.332	No	No	No	No
03	Cucurbitacin	-5.046	89.52	-0.348	No	No	No	0.137	No	No	No	No
04	Hesperidin	-3.014	31.481	0.996	No	No	No	0.211	No	No	No	No
05	Ginsenosides	-6.343	91.31	0.049	No	No	No	0.372	No	No	No	No
06	Lupenone	-5.828	98.467	-0.216	No	No	No	0.102	No	No	No	No
07	Cypripedin	-3.733	96.161	-0.304	No	Yes	No	0.501	No	Yes	No	No
08	Sesquiterpenes	-3.059	99.051	0.205	No	Yes	No	0.197	No	No	No	No
09	Carotenoids	-4.628	72.155	-1.418	No	No	No	1.227	No	No	No	No
10	Bilobetin	-2.893	86.049	-1.16	No	No	No	0.571	No	No	No	No

MD Simulation: Ginsenosides–ULK2 Complex:

Ginsenosides demonstrated stable binding with the ULK2 protein throughout the 100 ns simulation. RMSD analysis showed minor fluctuations after 20 ns, while RMSF peaks confirmed flexibility in certain residues. Persistent hydrogen bonds were observed with ARG130 and SER199, and high interaction frequencies were noted for TYR205 and GLN206. Stabilized SASA and Rg values indicated a compact complex. PCA revealed two dominant conformational states (PC1: 33.08%, PC2: 20.02%), and DCCM analysis highlighted strong intra-protein correlations, supporting dynamic but stable binding behavior.

MD Simulation: Bilobetin–CK2 Alpha Kinase Complex:

Bilobetin showed robust interaction with CK2 alpha kinase, maintaining backbone RMSD stability between 1.5–2.1 Å and ligand RMSD under 1.5 Å. RMSF identified flexible regions at residues 100, 200, and the C-terminus. Consistent hydrogen bonds formed with SER3, ARG14, and GLU115, while key interactions occurred with ARG14 and GLY46. Compactness was maintained (Rg ~4.5 Å), and PCA revealed clustered conformational states (PC1: 21.2%, PC2: 15.3%). DCCM indicated coordinated residue movements, confirming a stable and specific protein-ligand interaction.



In Silico Identification of Natural Product-Based Lead Compounds

Future Perspective: Bridging In Silico Discoveries to In Vivo Validation for Natural Anti-Cancer Therapeutics

- Identification of Ginsenosides and Bilobetin as TNBC inhibitors through in silico analysis.
- Isolation from plant extracts and development of total synthesis pathways.
- In vivo testing on TNBC-induced mice for efficacy and safety evaluation.CADD-based optimization if required for better therapeutic performance.

Goal: To develop natural product-based cancer therapeutics for clinical application.

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