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Original Article

Screening of Phytochemicals as PIP5K1α Protein Inhibitors for Breast Cancer Treatment: A Bio Computational Study

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ABSTRACT

Aim/Background: Breast Cancer (BC) is one of the most common cancers affecting women globally. PIP5K1α catalyzes PtdIns-4,5-P2 (PIP2), a Precursor to PtdIns-3,4,5-P3 (PIP3), required for AKT activation. Overexpression of this protein in BC cells suggests that it contributes to tumor progression. **Materials and Methods:** In the search for natural inhibitors of BC, PyRx0.8 tools were used to screen 261 compounds derived from *Withania somnifera* (*W. somnifera*) against the PIP5K1α enzyme, with ISA-2011B serving as a positive control. **Results:** Among them, quercetin, quinic acid, and alpha-D-galactose bind strongly to PIP5K1α, with affinities comparable or superior to ISA-2011B. In addition, these compounds interacted with the key active residues (such as Asp166, Arg227, and Val235) of PIP5K1α. Furthermore, these compounds possess good druglike properties, making them a promising candidate for developing PIP5K1α inhibitors for BC treatment. **Conclusion:** However, additional experimental validation is required to optimize these compounds as PIP5K1α inhibitors.

Keywords: Breast Cancer, PIP5K1α, *Withania somnifera*, Virtual Screening, Druglikeness.

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INTRODUCTION

Breast Cancer (BC) is among the most common cancers affecting women worldwide, accounting for around 0.57 million deaths in 2015. Every year, more than 1.5 million women are diagnosed with this disease, accounting for 25% of all female cancer cases globally. BC pathogenesis is a complex, multi-step process involving various cell types, making prevention difficult. Early detection remains one of the most effective ways to reduce BC-related death. In several industrialized countries, early screening and preventative initiatives have resulted in a 5-year relative survival rate of more than 80% (Sun *et al*., 2017).

Distant metastasis, the primary cause of BC-related death, is driven by a complex network of signaling pathways, many of which converge on the PI3K/AKT pathway (Coleman, 2002; Marino *et al*., 2013; Mundy, 2002). This pathway is responsible for regulating cell cycle progression, survival, metabolism, motility, and genomic stability (Fruman and Rommel, 2014). Mutations in PIK3CA or loss of PTEN, which result in constitutive activation of PI3K/AKT signaling, are common in ER^+ luminal and triple-negative basal-like BCs (Solzak *et al*., 2017). Therefore, addressing this pathway has become a top priority for medicinal development.

PIP5K1α catalyzes the production of PtdIns-4,5-P2 (PIP2), a precursor for PtdIns-3,4,5-P3 (PIP3), which is required for AKT activation (Loijens and Anderson, 1996; Shaw and Cantley, 2006). It is located upstream of the PI3K/AKT/PTEN axis. Overexpression of PIP5K1α has been discovered in the MDA-MB-231 BC cell line, suggesting its function in tumor growth (Yamaguchi *et al*., 2010). ISA-2011B, a selective PIP5K1α inhibitor, inhibits PI3K/AKT signaling by lowering AKT phosphorylation at Ser473, resulting in decreased tumor growth in a xenograft model of aggressive prostate cancer (Sarwar *et al*., 2016; Semenas *et al*., 2014).

Phytochemicals, or naturally occurring plant-derived substances, have a wide spectrum of therapeutic qualities and have been used in traditional medicine for millennia, highlighting their potential as innovative medication candidates (Atanasov *et al*., 2021). *W. somnifera* (ashwagandha), a fundamental component of Ayurvedic medicine, has historically been esteemed for its extensive health advantages, particularly its significant anticancer properties (Singh *et al*., 2021). The plant, rich in various phytoconstituents, especially withanolides and highly oxygenated alkaloids, has demonstrated considerable effectiveness against multiple cancers, particularly breast, colon, lung, and prostate cancer. Active compounds, including withaferin-A and withanolide-D, exhibit significant anticancer properties with minimal toxicity (Singh *et al*., 2021).

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Modern scientific approaches, including structural and computational biology, have advanced to the point that these bioactive compounds may be thoroughly investigated. Structural biology techniques have enabled the understanding of phytochemicals' three-dimensional architectures, allowing for molecular docking and virtual screening methodologies to uncover new pharmacologically active substances (Ourmazd *et al*., 2022). This study aimed to find *W. somnifera* phytochemicals as PIP5K1α inhibitors to manage the BC using the in-silico tools.

MATERIALS AND METHODS

PIP5K1α protein preparation

PIP5K1α protein (PDB ID: 5E3T) was retrieved from the Protein Data Bank (Muftuoglu *et al*., 2016). The protein structure was preprocessed by removing water and solvent molecules to retain only the essential residues for docking studies. The cleaned structure was then converted from pdb to pdbqt format using PyRx. Additionally, the co-crystallized ligand was retained as a positive control.

Phytochemicals library preparation

W. somnifera was chosen as the source of natural compounds. The PubChem database yielded 261 compounds in SDF format. The compounds underwent processing to ensure compatibility with docking studies. Each structure was subjected to energy minimization in PyRx to optimize its geometry and eliminate unfavorable conformations. After minimization, the optimized structures were converted to pdbqt format, which is required for subsequent docking simulations.

Virtual screening

Virtual screening, a computational technique for identifying structurally unique and possibly active lead compounds, is becoming more popular in drug development due to its higher calculation speed and lower cost (Guo *et al*., 2023). The prepared phytochemicals library was screened against the PIP5K1α protein using the PyRx0.8 tools (Dallakyan and Olson, 2015). The binding affinities for the most favorable poses were tabulated, and the interaction details were visualized using the Discovery Studio Visualizer.

Physicochemical and druglike properties

The top three candidates were subsequently assessed using DATAWARRIOR to calculate essential properties such as molecular weight, cLogP, cLogS, hydrogen bond acceptors/donors, and drug-likeness to verify adherence to Lipinski's rule of five. Toxicity endpoints, including mutagenicity, tumorigenicity, reproductive effects, and irritancy, were evaluated, and a DrugScore was computed to prioritize candidates.

RESULTS

In the search for natural inhibitors of BC, 261 compounds derived from *W. somnifera* were evaluated. Based on literary evidence, ISA-2011B was utilized as a positive control owing to its demonstrated effectiveness in BC models (Loijens and Anderson, 1996; Semenas *et al*., 2014). Figure 1 depicts the three-dimensional structure of the PIP5K1α protein (left) alongside the Molecular Interaction Atlas of ISA-2011B (right), demonstrating its multi-target potential, which includes anticipated interactions with PIP5K1α, LRRK2, DGKZ, LIN28A, GCH1, CAPN2, CASP8, CAMK2A, and KRAS. This multi-target profile highlights the appropriateness of ISA-2011B as a reference

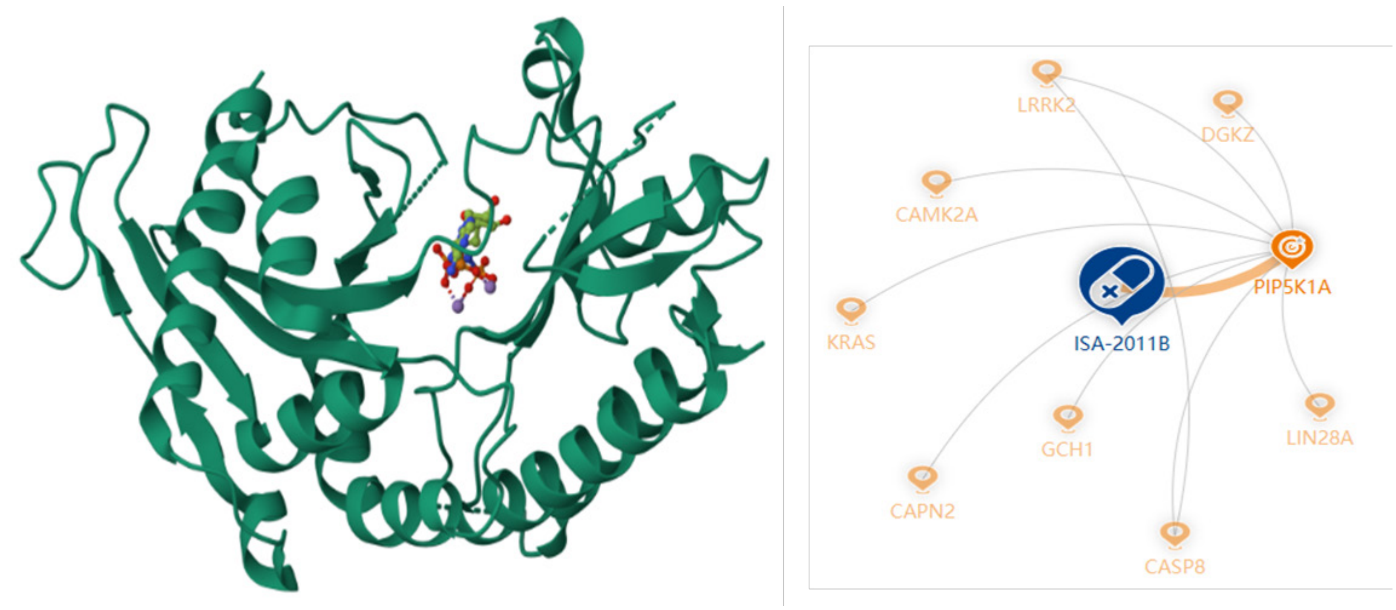

Figure 1: 3 D structure of the target protein PIP5K1α and its interaction with the control drug ISA-2011B.

compound. Comparative screening of 261 *W. somnifera*-derived compounds facilitated the assessment of binding affinities and pharmacological characteristics, identifying promising candidates for further exploration as potential BC inhibitors.

The virtual screening was performed using PyRx, with the active pocket identified via Discovery Studio Visualizer. The binding site coordinates were set to x = 8.920839, y = 112.384903, and z = 24.903032. Table 1 presents the top 10 compounds ranked by binding affinity alongside the control compound ISA-2011B (CID: 49853637).

The results indicate that compounds quercetin, quinic acid, and alpha-D-galactose demonstrate binding affinities comparable to or superior to the control, suggesting their potential as lead candidates for further development as natural BC inhibitors targeting PIP5K1α. Figure 2 presents a comprehensive interaction analysis of the three highest-scoring compounds, superimposed with the control compound (green) within the PIP5K1α binding site. Crucial interacting residues are emphasized, demonstrating both common and unique binding patterns.

A comprehensive 2D interaction analysis of the three selected compounds (quercetin, quinic acid, and alpha-D-galactose) in the PIP5K1α active site (Figure 3) revealed numerous hydrogen bonds, hydrophobic interactions, and non-covalent interactions. Each compound formed stabilizing interactions with essential residues (such as Asp166, Arg227, and Val235), indicating a strong binding mode. Quercetin had the highest binding affinity, which is explained by its extensive hydrogen bonding network.

The control compound (ISA-2011B) was found to interact with Asn152, Leu150, Ile148, Val162, Asp166, Val255, Met231, Lys234, Asn223, Leu225, Leu303, and Ther257 residues of PIP5K1α. Further, the interaction analysis of three selected compounds (quercetin, quinic acid, and alpha-D-galactose) showed that these compounds also bind to the majority of these residues, indicating that they bind to the same binding pocket of PIP5K1α as the control compound.

H-bonding had an essential role in the stability of the ligand-protein complex (Chen *et al*., 2016; Madushanka, Moura, Verma, and Kraka, 2023). Interestingly, quercetin was H-bonded with Asp166, Pro226, Val229, and Met231 residues of PIP5K1α; while Asp166, Val229, and Met231 residues of PIP5K1α was H-bonded with alpha-D-galactose (Figure 3). In addition, quinic acid was H-bonded with the Asp166 residue of PIP5K1α (Figure 3).

Further, compound quercetin possesses the highest molecular weight (302.237 g/mol) and a moderate cLogP (1.4902), accompanied by reduced solubility (cLogS = -2.491). Conversely, quinic acid and alpha-D-galactose possess lower molecular weights (192.166 and 180.155 g/mol) and demonstrate increased hydrophilicity, with cLogP values of -2.3347 and -2.6208, and cLogS values of -0.138 and 0.251, respectively. All three compounds meet the criteria for hydrogen bonding and exhibit no toxicity. Quinic acid is distinguished by its superior drug-likeness

Table 1: Binding affinities of the top 10 screened compounds.

Sl. No.	Compounds CID	Affinity (kcal/mol)
1	Quercetin	-8.1
2	Quinic acid	-7.9
3	Alpha-D-galactose	-7.9
4	Cuscohygrine	-7.7
5	AGN-PC-0NIHB1	-7.7
6	Atromentin	-7.5
7	Scopoletin	-6.9
8	Linoleic acid	-6.9
9	Withasomnine	-6.8
10	Esculetin	-6.8
11	Control_(ISA-2011B)	7.1

Table 2: Physiochemical and druglike properties of the top three compounds.

Property/compounds	Quercetin	Quinic acid	Alpha-D-galactose
Molecular weight	302.237	192.166	180.155
cLogP	1.4902	-2.3347	-2.6208
cLogS	-2.491	-0.138	0.251
H-Acceptors	7	6	6
H-Donors	5	5	5
Druglikeness	-0.082832	0.51019	-3.7768
Mutagenic	No	No	No
Tumorigenic	No	No	No
Reproductive Effective	No	No	No
Irritant	No	No	No
DrugScore	0.2417751	0.7992266	0.5043614

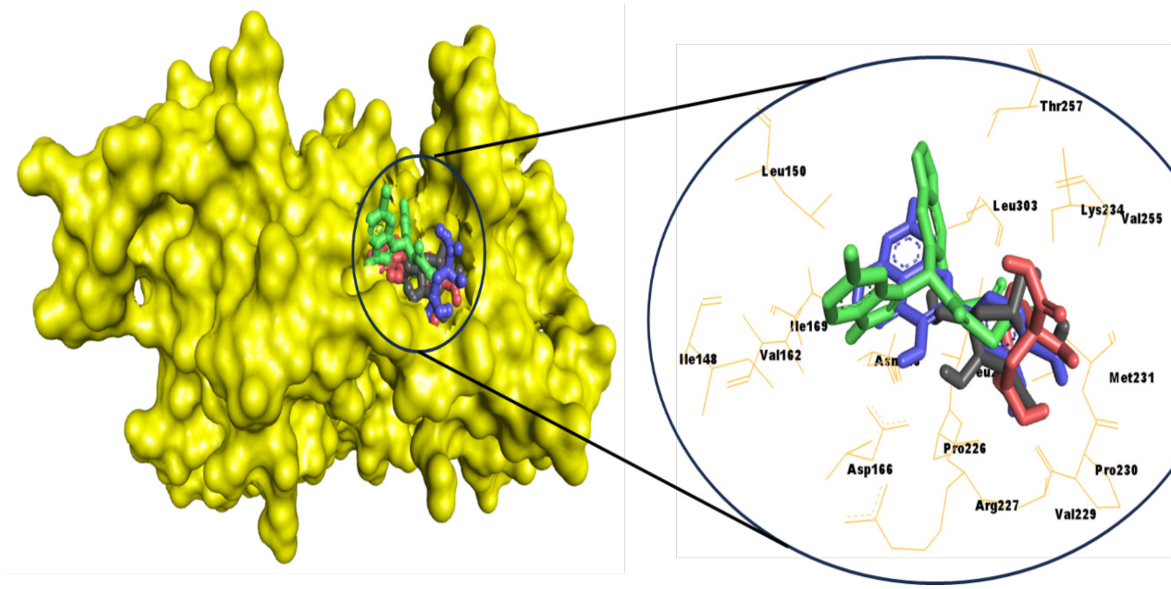

Figure 2: Superimposed view of the top three screened compounds (colored sticks) and the control compound (green) within the PIP5K1α binding site.

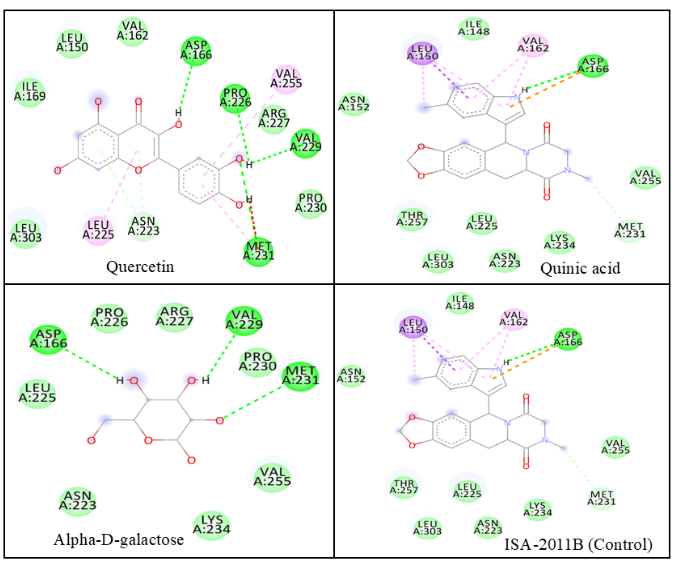

Figure 3: 2D interaction diagrams of the top three compounds with the PIP5K1α active site.

(0.51019) and the highest DrugScore (0.7992266), rendering it the most promising candidate for further development (Table 2).

DISCUSSION

Indian ginseng, also known as Indian winter cherry or Ashwagandha (*W. somnifera*), is a medicinal plant most commonly used for its root. The term "Ashwagandha" comes from the Sanskrit words "ashwa" (horse), which represents power, and "gandha" (fragrance), which refers to the distinctive odour of the fresh root (Singh *et al*., 2011). *W. somnifera*, which has long been utilized in Ayurveda to strengthen the neurological system, has received a lot of attention from scientists. Studies show that it has neuroprotective, sedative, adaptogenic, and sleep-enhancing properties. Furthermore, studies have found anti-inflammatory, antibacterial, cardioprotective, and anti-diabetic properties, as well as possible advantages for reproductive health and thyroid hormone regulation. These studies demonstrate Ashwagandha's medicinal potential in a variety of health disorders (Mikulska *et al*., 2023; Sharifi-Rad *et al*., 2021). This study found that *W. somnifera*-derived compounds quercetin, quinic acid, and alpha-D-galactose bind strongly to PIP5K1α active site residues and can be used as PIP5K1α inhibitors for BC treatment.

CONCLUSION

The present study screened the compounds derived from *W. somnifera* for their potential as BC inhibitors targeting the PIP5K1α protein. Quercetin, quinic acid, and alpha-D-galactose demonstrated strong binding to PIP5K1α protein and interacted with the key active site residues of PIP5K1α. Furthermore, these compounds possess good druglike properties, rendering them promising candidates for further PIP5K1α inhibitor development for BC treatment.

ABBREVIATIONS

BC: Breast cancer**; PDB:** Protein Data Bank; **W. somnifera:** *Withania somnifera.*

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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