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In-silico Analysis of Phytochemical Constituents from *Hemionitis arifolia* Against Breast Cancer Proteins

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ABSTRACT: The present study deals with the importance of phytochemical constituents of *Hemionitis arifolia* in treating breast cancer. This plant has many medicinal properties, such as antibacterial, hypoglycemic, antifungal, anti-inflammatory, antioxidant, and potent anti-cancer activities. Much research is to be done to know the mechanism involved. It has a very good healing property. We aimed to know the potential of the phytochemical constituents from *Hemionitis arifolia* against the breast cancer proteins. The two phytochemical constituents from *Hemionitis arifolia* topotecan, macdougallin, and the standard drug (Camptothecin) were used in this study. Based on the results obtained from Molecular docking analysis, all these phytochemical constituents have the best binding affinity towards breast cancer proteins EGFR and ER-α. From this, we can know the plant's usage and research in *Hemionitis arifolia* helps in the possibility of new drug development to treat breast cancer.

Keywords: *Hemionitis arifolia,* Camptothecin, Macdougallin, Topotecan, Molecular docking, ER-α, EGFR, Breast cancer.

INTRODUCTION

Cancer is one of the leading causes of death worldwide, with an expected 13.1 million deaths by 2030. Cancer is the second greatest cause of mortality worldwide, trailing only cardiovascular sickness. The type of cancer varies based on the location of the tumour. (Parveen *et al.,* 2015). Around 1.7 million women globally are diagnosed with breast cancer. Despite this, many studies have been done to understand breast cancer and develop novel strategies for prevention. However, the majority of the existing treatments include the use of cytotoxic drugs and chemotherapy. However, the function of chemotherapy is still unclear (Middleton *et al.,* 2018). The primary reason for the side effects of chemotherapy is the inability of drugs to target cancer cells (Weinberg and Chandel 2015).

India is blessed with a rich history of traditional medical systems that have been practiced for over 3,000 years. For a few decades, plants and their derived compounds have shown increased attention as potential medical sources. The secondary metabolites present in the plant extracts, such as phenolic components, increase biological activity. These compounds from medicinal plants are showing great interest as they have therapeutic activities.

Pteridophytes are often called the “reptile group” of plants, as they are the first vascular plants. In native populations, mostly because of their scarcity when compared to the flowering plants. Sadly, their medicinal uses are not known. Still, pteridophytes are most useful for our planet’s diversity (Ahmad *et al.,* 1998). The endemic and extensively dispersed species on India's western ghats is *Hemionitis arifolia* (Burm.f.) T. moore, which belongs to the *Hemionitidaceae* family. It has been used to treat menstrual irregularities, burns, infertility, and flatulence. *Hemionitis arifolia* frond juice has been used to treat burns and is a folk remedy for diabetes. Its hypoglycemic and anti-diabetic qualities were tested on rats. Alkaloids, flavonoids, phenols, tannins, and saponins are the compounds that provide *Hemionitis arifolia* its therapeutic value (Sureshkumar *et al.,* 2021). *Hemionitis arifolia* methanolic extract contained phenols, saponins, tannins, steroids, flavonoids, glycosides, and carbohydrates, according to preliminary phytochemical screening (Rakkimuthu *et al.,* 2018).

Estrogens are bound by the ligand-inducible nuclear hormone receptor known as estrogen receptor α (ER, or ESR1). About 70% of breast cancers express ER, which is essential to the growth and spread of these malignancies. Since ER contributes to the development of ER-positive (ER+) breast cancer, endocrine treatments, such as aromatase inhibitors (AI), selective estrogen receptor modulators, and selective estrogen receptor degraders, are typically used to treat these tumors.

In breast cancer, particularly triple-negative breast cancer (TNBC), EGFR is also abundantly expressed. It is essential for controlling and preserving the biological traits of breast cancer, including invasion, metastasis, proliferation, and stemness (Li *et al.,* 2022). In this study, using *in silico* analysis, we are identifying the best phytochemical constituents of *Hemionitis arifolia* plant extract against both ER-α and EGFR proteins.

MATERIALS AND METHODS

Preparation of proteins and ligands. The proteins used in this study were ER-α and EGFR; their 3D structure was retrieved from the Protein Data Bank PDB (https://www.rcsb.org/) database. The other ligands and water molecules were removed, and the pure protein was prepared for molecular docking analysis. The grid has specific parameters for ER-α, such as 40 × 40 × 40 with spacing 0.375 and axes of X= 27.43, Y=-2.031, and Z= 26.269. For EGFR 40x40x40 with spacing 0.375 and axis of X= 23.24, Y= -0.45, and Z= 56.12.

The two phytochemical constituents (Topotecan and Macdouglallin)from *Hemionitis arifolia* methanolic extract and the control drug (Camptothecin)were selected for this study. All the selected ligands were downloaded from the PUBCHEM database (https://pubchem.ncbi.nlm.nih.gov/).

Molecular docking analysis. The ligands selected for this study obey Lipinski's rule of 5. The list of ligands along with their PubChem IDs selected for this study is shown in Table 1, and the 3D structure of the pure proteins is shown in Fig. 1. The structure of the ligands was shown in Fig. 2. The molecular docking analysis were performed using autodock vina (Pradhan and Dubey 2021) and the results were visualized using BIOVIA Discovery Studio (Fitrilia *et al.,* 2020).

RESULTS AND DISCUSSION

From the results obtained, the three ligand molecules selected from *Hemionitis arifolia* were listed, and their structures are shown in Table 1 and Fig. 2. The proteins used are also shown in Fig. 1. The molecular docking was performed using AutoDock Vina, and the results are shown in Fig. 3 and 4. The docking score and interacting residues of these proteins with ligands are tabulated in Table 2. Based on the results of the present study, when compared with camptothecin, Topotecan has shown (-9.3 Kcal/mol) binding affinity towards the EGFR protein and (-8.3 Kcal/mol) towards ER-α protein. Whereas, Macdougallin has shown (-7.7 Kcal/mol) binding affinity towards the EGFR protein and (-8.6 Kcal/mol) towards ER-α protein. Nowadays, (Oberhoff *et al.,* 2001) results suggested that for patients with breast cancer and CNS metastases, topotecan combined with initial chemotherapy is a successful and well-tolerated treatment. Based on the study (Salazar *et al.,* 2011) Macdougallin isolated from *Myrtillocactus geometrizans* had shown potent anti-cancer activity on various human cancer cell lines. So, the phytochemical constituents from *Hemionitis arifolia* have many other beneficial medicinal values. Recently, the silver nanoparticles were synthesized by using *Hemionitis arifolia*, and the drug (tamoxifen) was loaded, which has shown potent anti-cancer activity against breast cancer cell lines (Varadharajaperumal *et al.*, 2021).

Table 1: The list of ligands with their PubChem IDs.

Sr. No.	Ligand Name	PubChem ID
1.	Topotecan	60700
2.	Macdougallin	23258271
3.	Camptothecin (standard)	24360

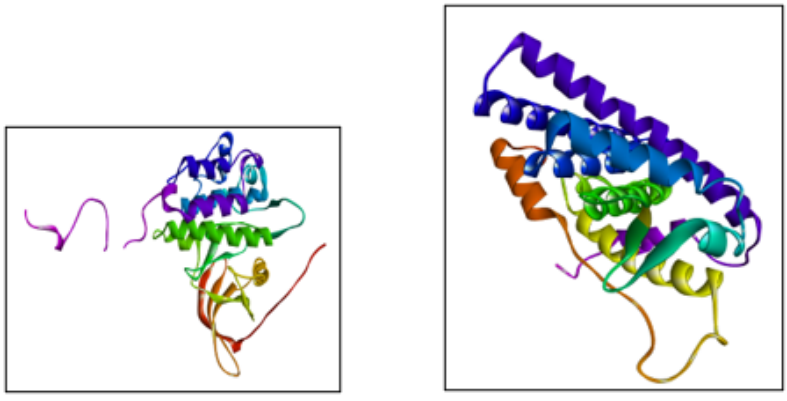


Fig. 1. The structure of pure proteins used in this study.

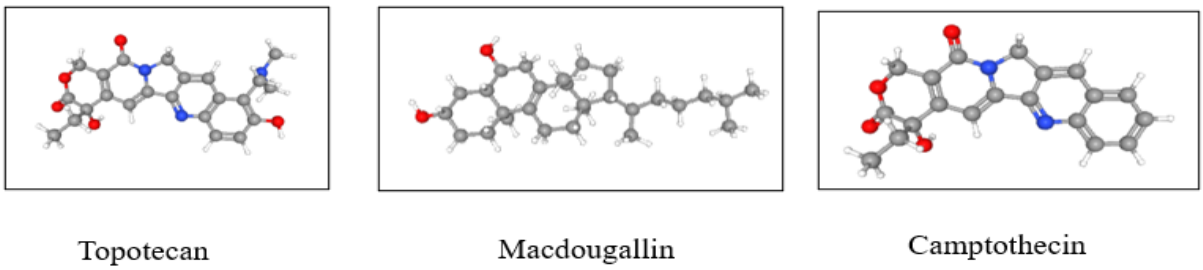
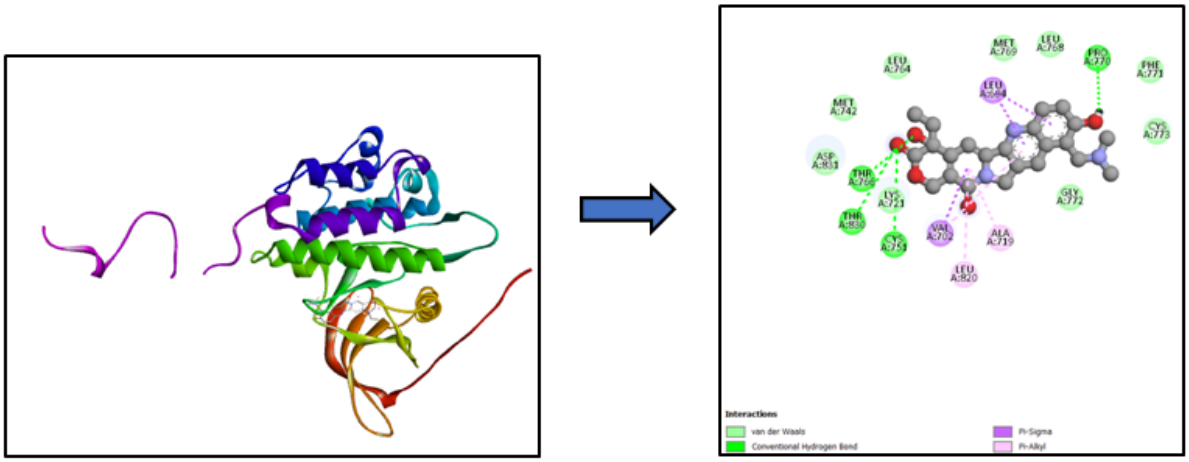
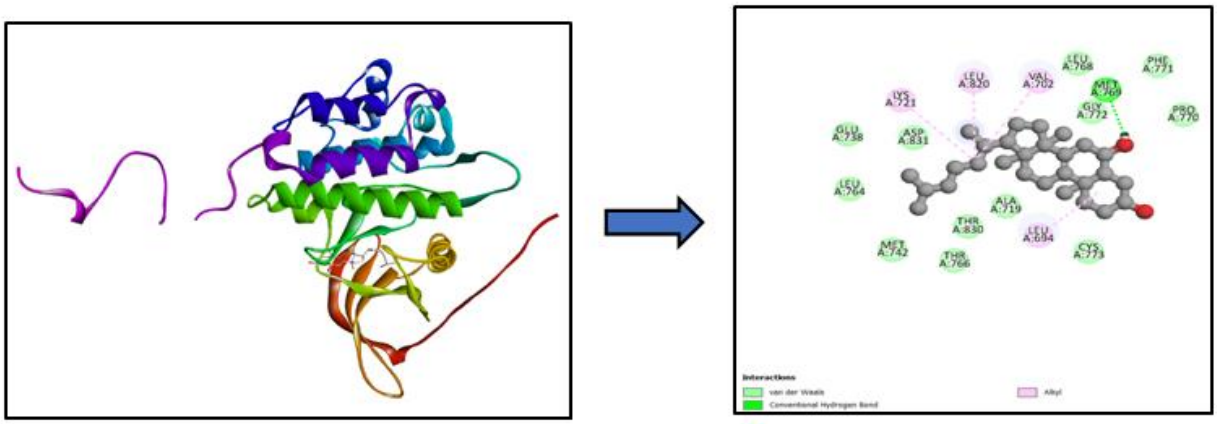


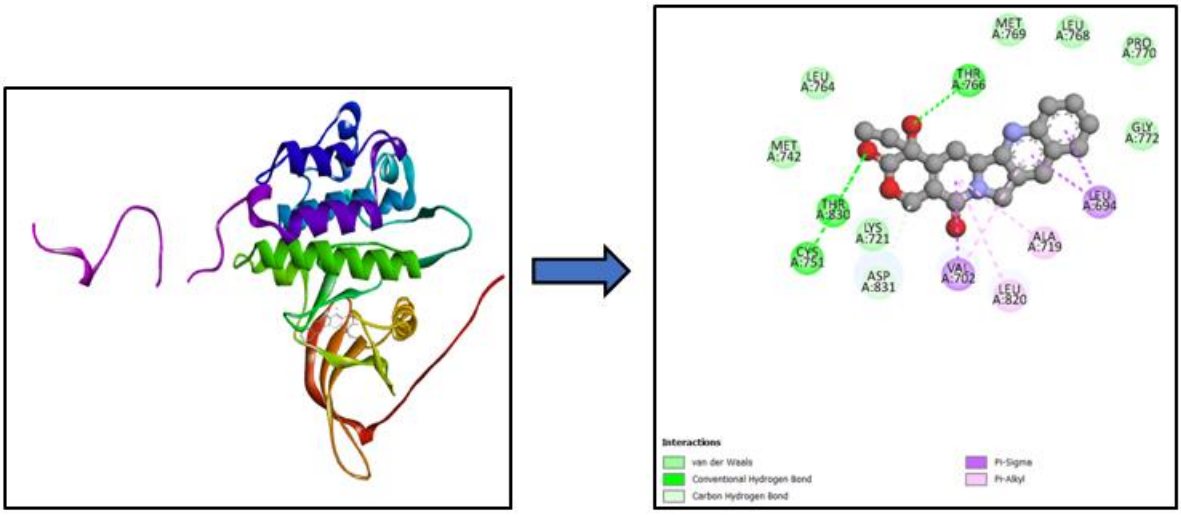
Fig. 2. The 3D structure of the ligands.



(A) The EGFR protein with the ligand Topotecan and its interacting residues

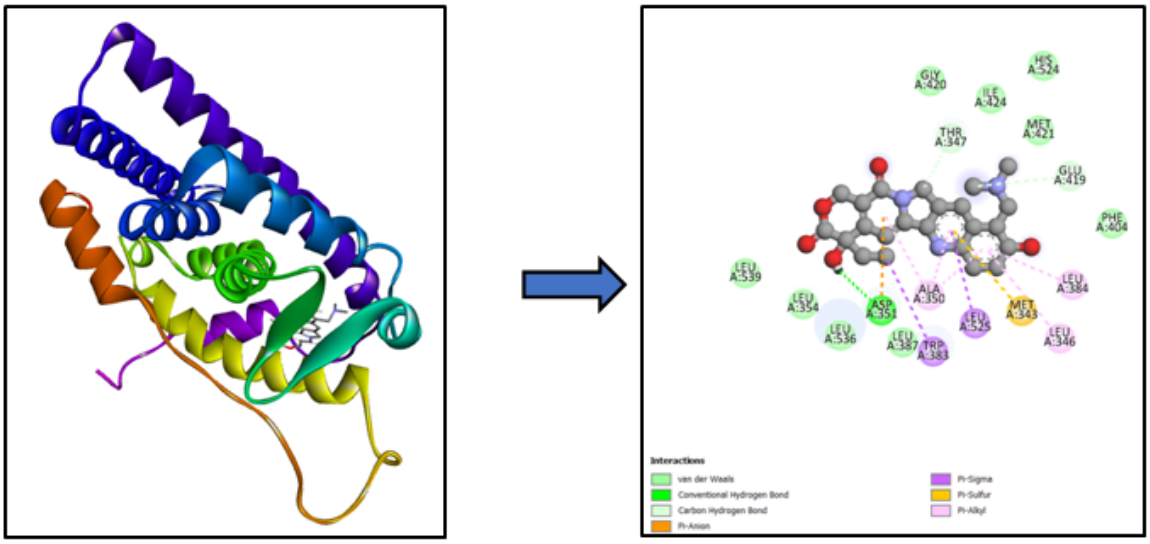


(B) The EGFR protein with the ligand Macdougallin and its interacting residues

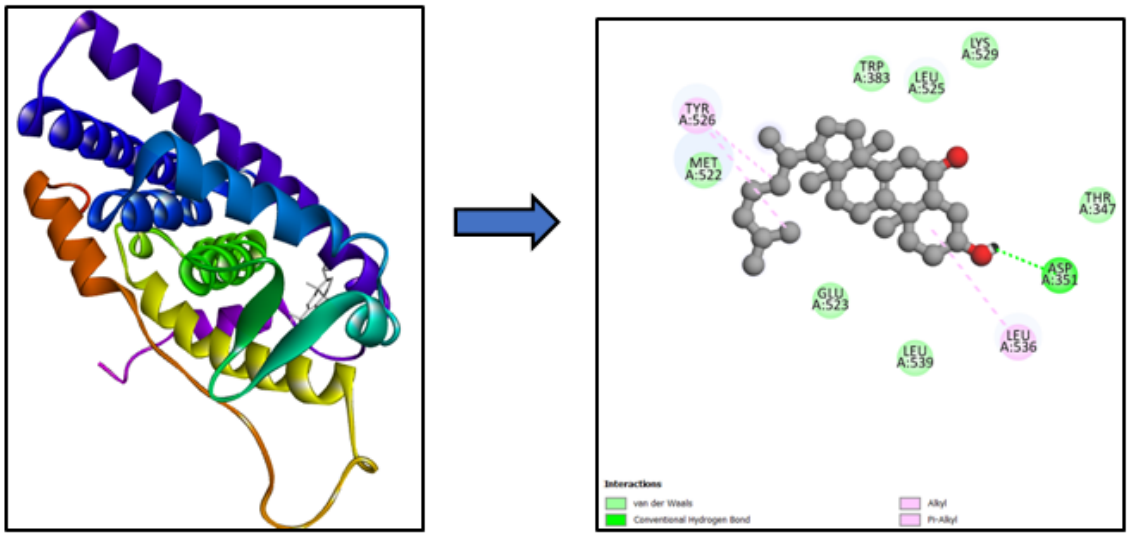


(C) The EGFR protein with the ligand Camptothecin and its interacting residues

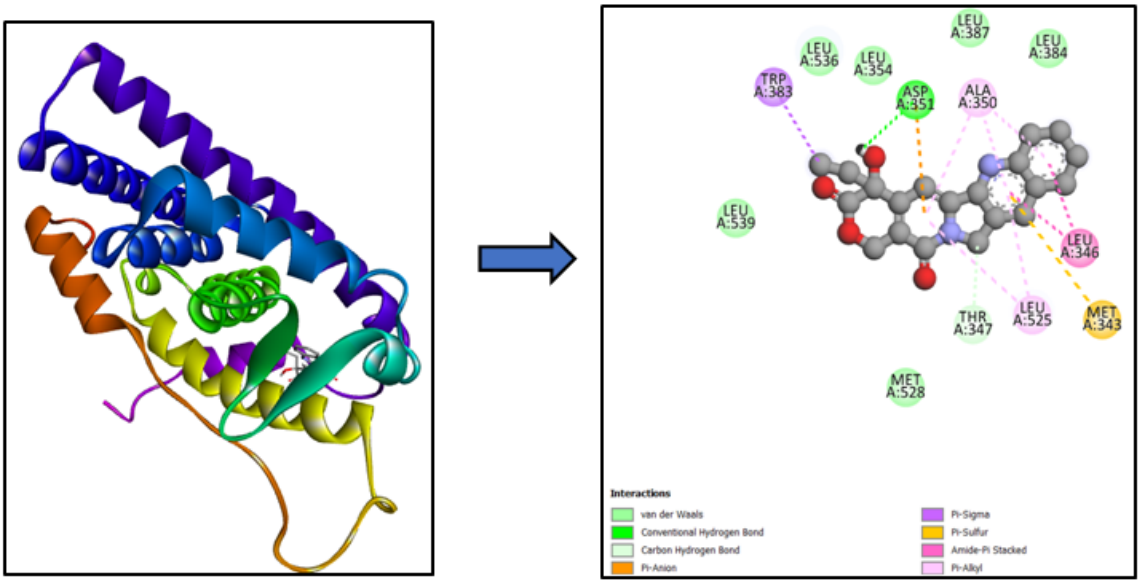
Fig. 3. The EGFR protein with its interacting residues.



(A) The ER-α protein with the ligand Topotecan and its interacting residues



(B) The ER-α protein with the ligand Macdougallin and its interacting residues



(C) The ER-α protein with the ligand Camptothecin and its interacting residues

Fig. 4. The ER-α protein with its interacting residues.

Table 2: The protein with its ligand's docking score and its interacting residues.

Protein	Ligand Name	Docking score (Kcal/mol)	Interacting residues
EGFR	Topotecan	-9.3	ASP831,MET742,LEU764,LEU694, MET769,LEU768,PRO770,PHE771, CYS773,GLY772,ALA719,LEU820, VAL702,CYS751,LYS721,THR830.
	Macdougallin	-7.7	GLU738,LYS721,LEU820,VAL702, LEU768,GLY772,MET769,PHE771, PRO770,ASP831,LEU764,MET742, THR766,THR830,ALA719,LEU694, CYS773.
	Camptothecin	-9.7	LEU764,THR766,MET769,LEU768, PRO770,GLY772,LEU694,ALA719, LEU820,VAL702,ASP831,LYS721, THR830,CYS751,MET742.
ER-α	Topotecan	-8.3	LEU539,LEU354,LEU536,ASP351, LEU387,TRP383,ALA350,LEU525, MET343,LEU346,LEU384,PHE404, GLU419,MET421,HIS524,ILE424, THR347,GLY420.
	Macdougallin	-8.6	TRY526,MET522,GLU523,LEU539, LEU536,ASP351,THR347,LYS529, LEU525,TRP383.
	Camptothecin	-8.4	LEU539,TRP383,LEU536,LEU354, ASP351,ALA350,LEU387,LEU384, LEU346,MET343,LEU525,THR347 MET528.

CONCLUSIONS

From the present study, it was concluded that the bioactive compounds identified from *Hemionitis arifolia,* i.e., especially topotecan and macdougallin, exhibited stronger binding affinities to breast cancer proteins compared to the standard drug, camptothecin. This *in silico* analysis provides valuable insights into the identification of the best phytochemical constituents. Future research will focus on isolating these compounds from *Hemionitis arifolia* and then performing in vitro analyses to further evaluate their therapeutic potential.

FUTURE SCOPE

As there is not much research conducted on this type of pteridophytes, *Hemionitis arifolia.* This study highlights its historical use of medicine in various forms was used as decoction for many years. Isolation of specific phytochemicals and conducting in vitro studies can pave the way for uncovering additional medicinal properties of this plant, contributing valuable insights for future therapeutic applications.

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Conflict of Interest. None.

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