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Molecular Docking of *Saraca asoca* (Ashoka) Phytocompounds for Ovarian Cancer Therapy

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Abstract

Objective: *One of the top five cancers that causes death in women is ovarian cancer, with increases awareness till date the rate of survival is unpredictable. Even though there are advance treatments introduced, chemotherapy is most suggested to the ovarian cancer patients but the rate of relapses increased and the tumors get resistant towards the drugs. This present study is to evaluate the interaction of phytocompounds from Saraca asoca an Indian medicinal plant with VEGF protein that is essential for metastasis of the tumor cells by docking studies.* ***Methods:*** *The In-silico study involved retrieval of phytocompounds of Saraca asoca from IMPPAT database and analysed for the pharmacokinetic properties by ADME analysis. These phytocompounds are evaluated with the target 3V2A protein by PyRx and BIOVIA Discovery studio to deduct the binding affinity of the ligand and protein.* ***Result:*** *Among the 11 phytocompounds after the ADME and docking results showed that (–)–epicatechin was ideal phytocompound for 3V2A protein associated with ovarian cancer.* ***Conclusion:*** *(-)-epicatechin can be a promising alternative for ovarian cancer treatment further research to be done to analysis their effect.*

Keywords: Ovarian cancer, VEGF, *Saraca asoca*, ADME and molecular docking

INTRODUCTION

Germ cells, gonadal stromal cells, and epithelial cells comprise the female gonad or ovaries. Although ovarian cancer can arise from any of these cell types, the majority of ovarian cancers are caused by cancers with epithelial differentiation [1]. According to reports, among women with gynecological cancer diagnoses, ovarian cancer ranks fifth in terms of cancer-related deaths. Due to its silent and ambiguous signs, which have a negative impact on the disease's prognosis, ovarian cancer is typically discovered when it has progressed [1, 2]. Despite widespread knowledge of this specific cancer type, the early diagnostic challenges have kept the survival rate mostly unchanged. Approximately 21,750 new cases of ovarian cancer were recorded in 2020, which amounts to 1.2% of all cancer diagnoses. Of all of these cases, 13,940 deaths were estimated to be attributed to the disease. Common symptoms of ovarian cancer are abdominal bloating, abdominal pain, frequent urination, and altered bowel movements. The disease is known to be associated with risk factors, family history, ovulation, endometriosis, and dietary factors in addition to these indefinite symptoms, which should also be considered in high-risk situations [1, 3].

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In ovarian cancer, the tumor microenvironment contains various components that assist in tumor cell proliferation. Tumor growth is accompanied by angiogenesis to provide vascular support, which is essential for the tumor growth. VEGF, generally known as VEGF, is one angiogenetic factor that plays a significant role in the vascularization of both normal and malignant tissue. Through promoting angiogenesis and enhancing vascular permeability, which results in malignant effusion, VEGF contributes to the advancement of ovarian cancer [3–6].

The original tumors of ovarian cancer are typically limited to the ovaries; however, during metastasis, the tumor cells undergo epithelial mesenchymal transition in order to acquire motility. VEGF is a crucial factor in this process. The cancerous cells are released from the damaged tumor into the peritoneum, where they undergo spheroidal differentiation to make sure that they survive. In order for them to survive, these spheroids transform into invasive mesenchymal cells, which are subsequently delivered via intraperitoneal fluid across the peritoneal cavity and gets implanted on the peritoneal wall, abdominal organs, and pelvic mesothelium. Ascites development is linked to ovarian cancer, and one of the most noticeable behaviors in the disease is peritoneal seedings and peritoneum carcinomatosis. It has been proven that patients with ovarian cancer had increased VEGF levels and the development of significant ascites. They go through a reverse transition and breakdown at the implanted site to start the metastatic growth process. Due to matrix breakdown and their mutual association, VEGF and matrix metalloproteinases cause ovarian cancer to disseminate peritoneally. Nuclear factor kappa B (NF-kB) regulates the transcription of VEGF and IL-8, which are expressed in ovarian cancer and contribute to the EMT and invasiveness of the spheroids [5, 7]. VEGFR-1 and VEGFR-2 are the two most significant members of the VEGF family that are involved in angiogenesis. While VEGFR-2 harmonizes the angiogenic and enhances the permeability effect of VEGF, VEGF-1 controls angiogenesis by ligand-trapping and choosing bone-marrow derived cells, such as monocytes, towards tumor vasculature. A well-defined VEGFR-2 mediated pathway directly promotes the formation of tumors on ovarian cancer cells [8, 9].

Currently, platinum-based chemotherapy and surgery are the standard of care; nevertheless, the side effects of chemotherapy have led to the development of chemotherapy resistance. The investigation of primary and maintenance treatments has thus far yielded substantial advances in extending the disease-free interval, with the poly (ADP-ribose) polymerase (PARPS) inhibitor playing a major role in achieving this goal. Even while the recurrence window may be longer than expected, the disease seems certain to return, especially in more advanced stages [2, 10]. International guidelines assist in directing patients away from surgery and towards chemotherapy [11]. Nevertheless, ovarian cancer patients typically experience a recurrence and progressive disease as a result of their resistance to the current chemotherapy treatment. Additionally, the chemotherapy drugs that are prescribed are synthetic and have toxicity effects on both cancer cells and healthy cells. According to recent studies, naturally derived phytocompounds from plants are less likely to be harmful to healthy cells and are cytotoxic to cancer cells, suggesting that they might be used as an alternate cancer therapy [1, 12]. The selected plant in this study is "*Saraca asoca*" (Ashoka), which is an effective Ayurvedic medicine in treating menorrhagia, dysfunctional uterine bleeding, reproductive disorders, other gynaecological problems, tumors etc. *Saraca asoca* (Ashoka) possesses pharmacological properties that include anti-inflammatory, antibacterial, antioxidant, and anti-tumor activities. [13]. By these historical backgrounds of *Saraca asoca,* we hypothesize that it can be an effective alternative for ovarian cancer by reducing the tumor proliferation activity by preventing the VEGF activity in ovarian cancer.

METHODS

Protein Extraction: PDB ID- 3V2A (VEGFR-2)

Selection of proteins is an important step in molecular docking studies. Vascular endothelial growth factor receptor 2 from the Protein Data Bank (PDB ID: 3V2A) is selected and downloaded for further analysis as the target protein by reviewing the appropriate literature [9].

Structure Validation

The structure validation of 3V2A is done in the SWISS-MODEL workspace tool; the protein's secondary structure prediction is obtained after uploading the protein, and a Ramachandran plot will be generated to evaluate the protein structure quality [14]. The target protein undergoes the removal of impurities like heteroatoms and water molecules by the BIOVIA Discovery Studio visualizer.

Retrieval of Phytocompounds from *Saraca asoca*

After a review of the literature, the plant's medicinal qualities are thoroughly studied, and its phytocompounds are obtained from the IMPPAT website, a digital repository for phytocompounds

derived from Indian medicinal plants [15]. The 3D SDS structures and their canonical SMILES were obtained from the PubChem database (http://pubchem.ncbi.nlm.nih.gov/) [16].

ADME Analysis

Drug likeness evaluation is done by using the Webtool SwissADME. This tool helps in compute the physiochemical descriptors and also predicts the ADME parameters (absorption distribution metabolism excretion), pharmacokinetics qualities, and druglike nature. The selected canonical SMILES of the phytocompounds retrieved from the PubChem are pasted and analyzed [17].

DOCKING

The computer-aided approach in the development of drugs has become an enhanced method that can be used to develop medicine made from phytochemicals extracted from plants with medicinal properties. Currently, molecular docking is a useful method for creating and evaluating medications. The determination of ligand-receptor binding positions and binding affinity can be confirmed by in-silico based docking studies. It gives the information of the interactions in accordance with their binding energy in kcal/mol which is achieved by PyRx, a virtual screening software for computational drug discovery and also has embedded programs like Open Babel, AutoDock Wizard and Vina Wizard [18]. The ligands which follow Lipinski rule of five and the protein structure which was obtained from BIOVIA Discovery were uploaded in the PyRx [19]. The ligand energies are reduced and grid formation are done the by Open Babel program "CSV" format file is downloaded which contains the docking score of all the by the ligand and selected which meets the criteria.

RESULTS

Protein Extraction

PDB ID – 3V2A (vascular endothelial growth factor receptor 2) and structure validation.

Protein selected has two chains (A and B) with the molecular weight of 102.11 kDa and atom count of 2,114. In the 3D protein structure, the red coloured three spring shaped is the alpha helix and the blue strands denotes the beta sheets (Figure 1).

The structure validation is carried out in SWISS MODEL. The protein's secondary structure is represented in the four quadrants of the Ramachandran plot graphically. The plot shows the protein residues which are energetically favourable and it also shows that 91.33% residues are in the favoured region which indicates the quality of the protein (Figure 2). The protein molecule is loaded in BIOVIA Discovery to check for the presence of impurities like heteroatoms and water molecule to avoid steric clashes and non-specific interaction that could lead to incorrect results. After analysing it was found that there were no impurities found in the protein and it is saved as auto dock for further analysis.

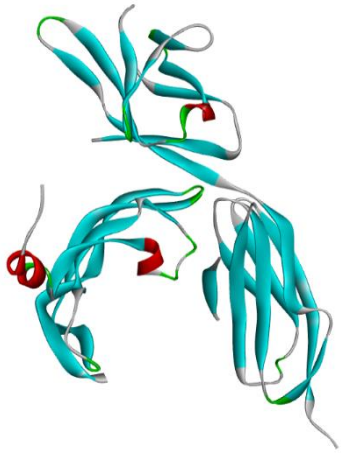

Figure 1. Represents the 3V2A protein.

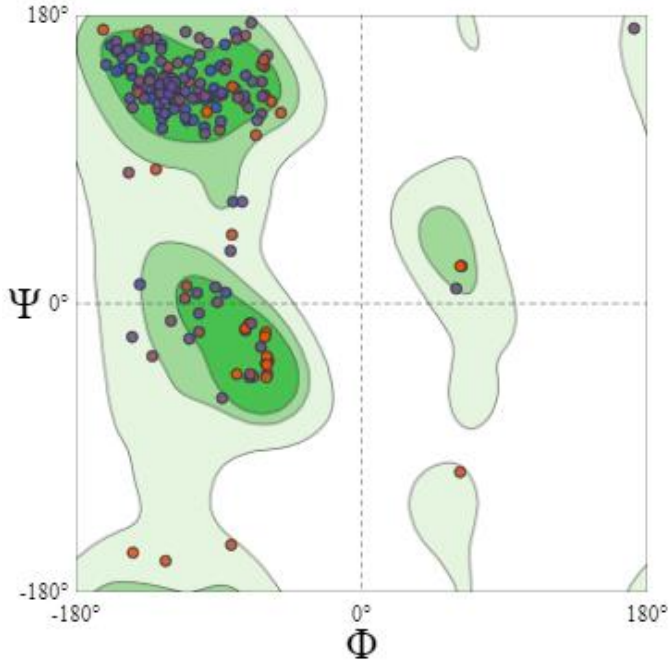

Figure 2. Ramachandran plot represent the amino acid residues of 3V2A in phi-psi angle.

Retrieval of Phytocompounds from *Saraca asoca*

Eleven (11) phytochemicals from the selected plant *Saraca asoca* from the bark of the plant was retrieved from the IMPPAT database and are listed in Table 1. Also, their canonical SMILES are obtained from PubChem database for ADME analysis to narrow down the docking ligands for the target protein.

Table 1. List of phytoligands extracted from IMPPAT.

Molecule Number	Phytocompound Name
1	Leucopelargonidin
2	Catechol
3	1-Octacosanol
4	Procyanidin B2
5	Leucocianidol
6	Tannic acid
7	Ergometrine
8	Stigmast-5-en-3-ol
9	beta-Sitosterol
10	Cianidanol
11	(-)-Epicatechin

ADME Analysis

ADME is crucial for the development and discovery of new drugs. Human pharmacokinetics with drug-like matter which has specific composition and properties is an alternative method to reduce clinical trial failure. The phytocompounds were analysed using the Lipinski "Rule of Five," which states that a molecule's molecular weight should not exceed 500 Da, that its hydrogen bond donors should not exceed 5, and its hydrogen bond acceptors should not exceed 10 and Log p not more than 5. In Table 2, the ligands 3, 4, 5, 6, 8, and 9 do not fulfil Lipinski rule of 5. The molecules 1, 2, 7, 10, and 11 meet the Lipinski rule of 5 and are suitable for future research.

DOCKING

The narrowed down 5 ligands, i.e., leucopelargonidin, catechol, ergometrine, cianidanol and (-)-epicatechin 3D structures are downloaded in SDF format (Figure 3) for the docking simulation by open-

Bable program. The ligand docking results for the protein 3V2A are obtained from the PyRx system in CVS format. The CVS file contains the binding energies of the various position of the protein-ligand interaction. The molecule 11, i.e., (-)-epicatechin has lowest binding affinity and it is selected for visualisation in BIOVIA (3D) and ligplot+ (2D) in Figure 4. Table 3 shows the binding affinity for the ligands with protein 3V2A. By visualising the 2D structure result, the (-)-epicatechin forms five hydrogen bonds with 3V2A protein at Phe47, Asn253, Lys286, Leu277 and Asp276 amino acid residues. The Pi-Alkyl interaction at the Ile46 residue was also visible in the findings.

Table 2. Lipinski analysis.

Molecule No.	Ligand	Molecular Weight (<500Da)	Hydrogen Bond Doner (<5)	Hydrogen Bond Acceptor (<10)	MLOGP (<5)
1	Leucopelargonidin	290.27	5	6	–0.02
2	Catechol	110.11	2	2	0.79
3	1-Octacosanol	410.76	1	1	7.07
4	Procyanidin B2	578.52	10	12	–0.26
5	Leucocianidol	306.27	6	7	–0.56
6	Tannic acid	1700.17	25	46	3.791
7	Ergometrine	325.4	3	3	1.27
8	Stigmast-5-en-3-ol	414.71	1	1	6.73
9	beta-Sitosterol	414.71	1	1	6.73
10	Cianidanol	290.27	5	6	0.24
11	(-)-Epicatechin	290.27	5	6	0.24

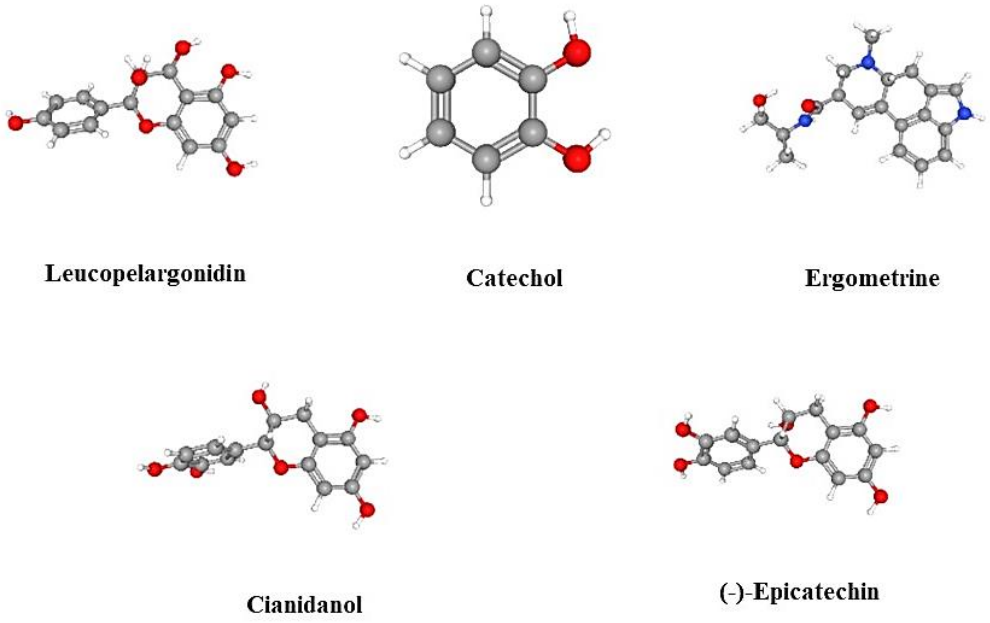

Figure 3. Represents the 3D structure of the 5 selected ligands, i.e., leucopelargonidin, catechol, ergometrine, cianidanol and (-)-epicatechin 3D from *Saraca asoca* downloaded from PubChem database.

Table 3. Binding affinity of ligands with 3V2A protein.

Molecule No.	Ligand	Binding Affinity (kcal/mol)
1	Leucopelargonidin	–6.2
2	Catechol	–4.9
7	Ergometrine	–6.8
10	Cianidanol	–6.4
11	(-)-Epicatechin	–6.9

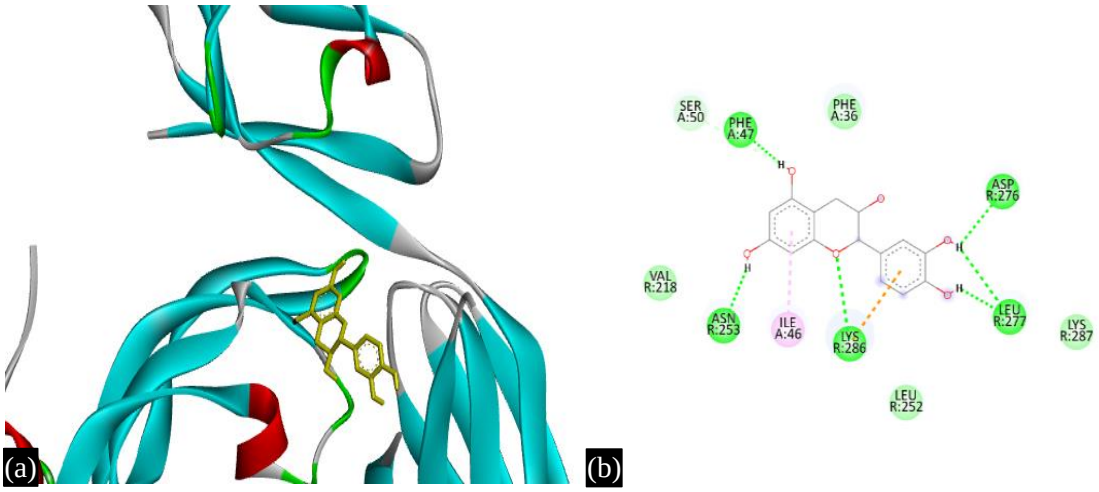

Figure 4. (a) Shows the 3D visualisation of the protein-ligand binding where the ligand is represented in yellow colour. (b) Shows the 2D diagram of the protein-ligand interaction along with the interacting amino acids. Pi-Alkyl interaction is shown by pink dotted lines, and hydrogen bonding is represented by green dotted lines.

DISCUSSION

Ovarian cancer is most lethal malignant neoplasm among female reproductive tract and high rate of death in females due to late detection. Their molecular and genetic profiles these cancer makes it difficult to design treatment due to their varied response [20]. On the other hand, VEGF has a major contribution in ovarian cancer in their growth and well-established progression. Peritoneal carcinomatosis is the pattern by which ovarian cancer is spread along by ascites formation in which VEGF is essential for the progression of the disease [5]. Platinum-based chemotherapy is the prime choice considered for ovarian cancer patients. Extensive research has demonstrated that although ovarian cancer initially appears to respond favourably to platinum-chemotherapy, prolonged exposure increases the risk of relapse. As a result, advanced stage tumors are unable to respond to chemotherapy due to multidrug resistance [21]. There's history of therapeutic plants which are anti cancerous and these naturally derived phytocompounds can be an alternative for painful treatments and reduce toxicity towards other cells. *Saraca asoca* which commonly known as Ashoka, is an old Indian Ayurvedic remedy for gynaecological complications and infection like uterine pain, tumors, bacterial infections, circulatory problems and all of the plant's part is considered valuable [22]. The bark part of the plant is used as a tonic for females which contains tannin, flavonoids, sterol, alkaloids and other calcium compounds and used for the treatment of menstrual disorders which includes excessive bleeding, uterine spasm [23]. In this point of view *Saraca asoca* is an ideal plant for this current study. According to the results of this study, the phytocompound (-)-epicatechin possesses the highest binding affinity (-6.9) towards the 3V2A protein, which is a protein involved in the growth of tumors in ovarian cancer. Additionally, (-)-epicatechin complies with the Lipinski rule of five, having a molecular weight of 290.27, a hydrogen bond donor of 5, hydrogen acceptor of 6, and a log value of 0.24, which shows potential drug likeness. Some studies have reported that (-)-Epicatechin has health benefits like antibacterial, anti-inflammatory and also as a cardio protector [24, 25]. In a breast cancer research with

(-)-epicatechin, the study showed that (-)-epicatechin showed anti-cancer properties that inhibited the growth of breast cancer cells and induced apoptosis [26]. Molecular and therapeutics findings of (-)-epicatechin in cancer results that (-)-epicatechin interfere in cancer signalling pathway and makes the cells vulnerable to apoptosis and also showed a protective response towards non-cancerous cells [27]. The present findings are parallel with other studies which validates that (-)-epicatechin has therapeutic potential by following all the Lipinski rule of five criteria and also from the docking results it shows high binding affinity towards the 3V2A which is an initial success in blocking the protein activity in the ovarian cancer. As (-)-epicatechin is an inhibitor of cell proliferation that has been proved in previous studies, it can be a novel potent drug as an alternative for ovarian cancer treatment by further clinical trials to study their anti-cancer effect towards the 3V2A protein and their mechanism.

CONCLUSIONS

The present study of the interaction of phytocompounds of *Saraca asoca* with 3V2A protein is analysed by implementing In-silico techniques to obtain the ideal phyto-ligand and it is found that (-)-epicatechin meets all the pharmacological parameters. (-)-epicatechin fulfils Lipinski's rule of five physiochemical criteria which shows drug likeness towards the target protein which ordains the carcinogenesis in ovarian cancer. Clinical trials are necessary to verify the efficacy and safety of the phyto-ligand in addition to the results of the current investigation. However (-)-epicatechin can be an alternative treatment for ovarian cancer by further future experimental/ in vivo confirmation.

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Authors Contribution

Each author has contributed equally.

Conflict of Interest

There's no conflict of interest among the authors.

Abbreviations

EMT	:	Epithelial-mesenchymal transition
IL-8	:	Interleukin-8
MMPs	:	Matrix metalloproteinases
NF-kB	:	Nuclear factor kappa B
PARPS	:	Poly (ADP-ribose) polymerase
VEGF	:	Vascular endothelial growth factor
VEGF A	:	Vascular endothelial growth factor A
VEGFR-1	:	Vascular endothelial growth factor receptor 1
VEGFR-2	:	Vascular endothelial growth factor receptor 2

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