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PHARMACOINFORMATICS AND MOLECULAR DOCKING STUDIES ON *PSORALEA CORYLIFOLIA* (L.) DERIVED SEED COMPOUNDS AGAINST TUMOR INDUCED CANCER PROTEIN

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ABSTRACT

Background: *Psoralea corylifolia* (Linn.) belongs to the family Fabaceae and is widely distributed tropical and sub-tropical areas. The seeds of *P.corylifolia* have found in rich amount of secondary metabolites. There is an increasing recognition that Pharmacoinformatics and molecular docking technologies can be effectively used for drug discovery and drug development from *P.corylifolia* Phytocompounds.

Objectives: Using pharmacoinformatics and molecular docking techniques, the current study aimed to identify the phytocompounds from *Psoralea corylifolia* seeds that inhibit the EGFR protein. The findings additionally validate the anticancer properties of the seed's bioactive components.

Methods: The identified biological compounds of *P.corylifolia* species were investigated for virtual screening analysis, ADMET and Molecular docking analysis.

Results: Seven major biological compounds were selected for virtual screening analysis to find out the drug - likeness activity. Out of these seven compounds five compounds are drug - likeness in nature. Based on the ADMET analysis, Isopsoralen showed a low toxicity level and it represents the Lipinski rule of five. The molecular docking results of Isopsoralen interact with target protein used in the study showed the docking energy was obtained against tumor induced cancer protein -10.9505kcal/mol.

Conclusion: The result was concluded that, *P.corylifolia* seeds derived compound Isopsoralen was showed significant tumor induced anti-cancer activity. Pharmacoinformatics and molecular docking study was providing valuable inputs to developing the active component Isopsoralen into potential drug in future.

Keywords: ADMET; Docking; Pharmacoinformatics; Phytocompounds; *P.corylifolia*.

INTRODUCTION

Plants are the first medicines for mankind and hundreds of plant species are harvested for their medicinal properties all over the world. In spite of modern development of sophisticated pharmaceutical chemicals to treat illnesses, medicinal plants remain an important tool for treating illness. Medicinal and Aromatic Plants (MAPs) utilization and conservation has attracted global attention[1]. *Psoralea corylifolia* (Linn.) contains a variety of bioactive

compounds, including flavonoids, coumarins and alkaloids, which have been shown to exhibit anti-cancer properties.

Pharmacoinformatics is new emerging information technologies like neuroinformatics, immunoinformatics, bioinformatics, Metabolomics, chemo-informatics, toxico-informatics, cancer informatics, genome informatics, proteome informatics, biomedical informatics are basic tools provided for the purpose of drug discovery. There is an increasing recognition that information technology can be effectively used for drug discovery. In the field of molecular modelling, docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules using for example scoring functions. In the context of molecular modelling, docking means predicting the bioactive conformation of a molecule in the binding site of a target structure[2].

Pharmacokinetics and toxicity issues are responsible for more than half of all failures in the clinical trials. Hence the first part of the virtual screening evaluates drug-likeness of small molecules, drug like molecules exhibit favourable absorption, distribution, metabolism, excretion, toxicological (ADMET) parameters[3]. Database collections of known drugs are typically used to extract knowledge about structure properties of potential drug molecules. Molecular weight, lipophilicity, charges is profiled to extract simple counting rules for an ever-relevant description of ADMET related parameter. Pharmacokinetics has emerged as an integral part of drug development, especially when identifying a drug's biological properties. Understanding of pharmacokinetic and metabolism characteristics of the drug compounds is needed in designing appropriate human clinical trials[4].

Over the decades, many plant-based immune toxins have been developed with the goal of targeting the broad range of cancers reliant upon epidermal growth factor receptor overexpression. Many examples demonstrate excellent anti-cancer properties in preclinical development, and several EGFR-targeted immune toxins have progressed to human trials[5]. However, very little is known about pharmacoinformatics based studies of *P. corylifolia* species which is growing in Tamil Nadu and it is also familiarly called as Babchi or Bakuchi that has been traditionally used in Ayurvedic medicine to treat various diseases. One particular phytochemical of interest is Isopsoralen, a natural compound that is found in high concentrations in the *P.corylifolia* seeds[6]. This study is mainly focused on to comparing the divergence of biological compounds and activities of these compounds were studied with virtual screening, Absorption, Distribution, Metabolism, Excretion and Toxicity analysis, Protein-ligand interaction through molecular docking analysis with tumor induced EGFR protein (Protein Data Bank ID: 3G5Z).

Materials and Methods

Structure Preparation of *P.corylifolia* Compounds from seeds

The bioactive compounds, Isopsoralen, Dihydroxy coumestan, Isobavachin, Beta caryophyllene oxide, Cyclooctene, 3,3 dimethyl oxiran and n-Hexa decanoic acid were obtained from methanolic seed extract of *P.corylifolia* by GC-MS[7]. A total of seven bioactive compounds structure were obtained from Pubchem, and all these compounds were being studied. The ligand structures were constructed using Chem Sketch, a free chemically intelligent drawing interface program created by Advance Chemistry Development, Inc. (http://www.acdlabs.com) (Table 1). After the generation of the ligand molecules and completion of the three-dimensional optimizations, the results were saved. SDF file format (a file format that stores data about a molecule's atoms, bonds, connectivity, and coordinates).

Virtual Screening Analysis

According to Lipinski rule of five[8], the Pub Chem chemical database's, .SDF format was used to get the structural coordinates of chemicals originating from plants. The compounds were filtered using the Lipinski rule of five for drug similarity prior to screening. PyRx is a virtual screening tool that uses Auto Dock and Auto Dock Vina software, which are built-in, to discover the best chemical. PyRx uses the Open Babel program to view the ligands and protein. The ligands and the protein target were first energy minimized, then charged, and then moved to pdbqt format to aid in docking with Auto Dock Vina[9].

In-Silico pharmacokinetics

The pharmacokinetic properties such as Absorption, Distribution, Metabolism and Excretion (ADME) toxicity for the compound were computed by utilizing the ADMET under calculate molecular properties in BIOVIA Accelrys Discovery Studio v4.5. In 2020, Wu et al 2020 revealed that the undesired pharmacokinetics properties can lead to

failures of most drugs in the later pipeline during the drug development process. In the course of drug discovery process, addressing these issues beforehand at the early stages.

Discovery Studio Visualizer

The results were visualized using BIOVIA Accelyrs Discovery Studio 2022 Visualizer. The discovery studio visualizer is also a free viewer that is designed to offer an interactive environment for viewing and editing molecular structures, sequences, X-ray reflection data, script and other data. Discovery Studio is designed for use in the Life Sciences, with a focus on the study of biologically relevant structures. These ranges from small molecules such as drugs and inhibitors to larger molecules such as proteins and nucleic acid biopolymers to form typically determine function of molecular systems.

RESULTS

The PyRx virtual screening software can be used to apply high throughput virtual screening approaches for computational screening. After identification, the seven (07) primary active compounds were chosen for this computational screening investigation. The chemicals' 2D structures were obtained using the online PubChem program (Figure 1). The basis for virtual screening was Lipinski's rule of drug-likeness receptors, which was used to separate screening into two categories: structural screening and screening using major active molecules as templates for ligand-based virtual screening.

High throughput virtual screening revealed that five compounds were exhibited a drug-likenes character. The substances are Dihydroxy Coumestan, Isobavachin, Cyclo Octene, Beta-Caryophyllene Oxide, and Isopsoralen. Virtual screening revealed the binding affinities of the corresponding compounds, which were -6.7, -6.3, -6.0, -5.6, and -5.7 (Table 2).

Screening of compounds through Pharmacokinetics properties

The pharmacokinetics and metabolism characteristic of the drug of compounds is needed in designing of new drug for the appropriate human diseases. Total of five compounds were filtered with total number of seven major compounds through high throughput virtual screening method. The computational techniques such as ADMET predictions, molecular dynamics studies to design and analyse five potential biological compounds were studied the ADMET properties.

By using the pkCSM program (http://biosig.unimelb.edu.au/pkcsm), attributes were analysed based on ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity). Out of these five compounds, the compound isopsoralen represented the Lipinski rule of five and had a very low toxicity level, as indicated by the data (Table 3-A & B). It also showed a Log P value of -0.054. Using tumor induced cancer proteins in GC-MS analysis of *P.corylifolia*, the compound isopsoralen was chosen for molecular docking investigation.

Molecular Docking Analysis

The compound Isopsoralen (Figure 2) interacted with tumor induced EGFR cancer protein (Figure 3). The Glycine and Serine were bind amino acids sites of 43 and 99 respectively with vanderwaals interaction. The conventional hydrogen bond interactions were observed pheneylalanine 44 and 98 of amino acids binding sites, lysine 42 and glutamine 38 binding sites. The Pi-Alkyl interaction was identified with the binding site of leucine 36 amino acid. The protein tyrosine was bind with amino acid site of 87 with Pi-Pi interaction. The above amino acids were involved in docking analysis (Figure 4,5) and the observed docking energy in -10.9505kcal/mol (Table 4).

DISCUSSION

To find inhibitory medications against a particular cancer, diabetes, or other infections, structure-based drug design is becoming more and more significant, efficient, and essential. Using in-silico drug design, researchers are trying to identify more potent lead compounds against the Epidermal growth factor receptor (EGFR), a crucial component in the advancement and development of several human cancers[10].

In order to generate drug-like molecules, it is imperative to discover important phytocompounds from medicinal plants using structure-based virtual screening (SBVS)[11]. The PyRx is an excellent virtual screening tool for screening phytocompounds against disease target proteins. The present study performed virtual screening for seven (07) primary active compounds of *Psoralea corylifolia* seed. Among the 7 phytocompouds, the prominent binding affinity was represented by Isopsoralen, followed by Dihydroxy Coumestan, Isobavachin, and Beta. Caryophyllene Oxide and Cyclo Octene. The present findings revealed that the selected phytocompounds, i.e., in Isopsoralen,

Dihydroxy Coumestan, Isobavachin, Beta. Caryophyllene Oxide and Cyclo Octene may have potential inhibitory action against EGFR. The present findings were also supported by Mustafa et al. 2023[12], who reported that phytochemicals such as liquoric acid, berbamine, obamegine, and isotetrandrine showed inhibitory properties against EGFR by virtual screening,

Effectiveness, appropriate pharmacokinetics, and toxicity profile are the main factors that determine a successful drug development process. The main reason for the expensive and late failure of medication development is the poor ADMET profile and the potential for toxicity. Therefore, such basic requirements need to be thoroughly examined at the outset of the drug discovery process[13]. In the present study, Isopsoralen, Dihydroxy Coumestan, Isobavachin, Beta. Caryophyllene Oxide and Cyclo Octene were examined for *in-silico* ADMET predictions. Out of these five compounds, isopsoralen represented in the Lipinski rule of five and had a very low toxicity. This result indicates that Isopsoralen may be a good candidate for inhibiting EGFR with low toxicity risk.

Several human malignancies progress and develop abnormally as a result of EGFR. EGFR is responsible for 50–60% of lung adenocarcinoma, colon cancer, and breast cancers[14]. To effectively target EGFR for cancer treatment, several drugs are administered alone or in addition to chemotherapy for colorectal, non-small-cell lung, and breast cancers[15]. Nowadays, a lot of research is being done using molecular docking to examine how ligands and proteins interact[16]. It is possible to use these in-silico interactions to find protein modulators or other modulators in the human system.

CONCLUSION

The data presented showed that five of the seven compounds that were chosen exhibited binding affinity, based on high throughput virtual screening. The Isopsoralen compound exhibited a significant degree of binding affinity. Based on the analysis of the ADMET qualities for five different compounds, including its features related to absorption, distribution, metabolism, excretion, and logP values, Isopsoralen was determined to be a harmful free/less chemical. Using docking studies, the Isopsoralen functions as a ligand molecule to connect with cancer (tumor) - induced proteins. It demonstrated the activity against tumor induced proteins based on the docking energy of Isopsoralen with selected protein. The results were concluded that *P.corylifolia* seeds derived compounds were showed anti-cancer activity. Finally, the Molecular docking studies were providing valuable inputs to develop the active components into potential drugs in future in thefield of drug research and development.

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Conflicts of Interest

Authors have no conflicts of interest to declare

Author Contribution

Material preparation, data collection and writing original draft preparation by B. Priyadharshini. Review and editing by M. Prakash.

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Compound Name	Pubchem ID	Hydrogen		Canonical Smiles
		Donor	Acceptor	
Iso Psoralen	11508879	5	9	C1=COC2=CC(=C(C=C21)C=CC(=O)O)OC3C(C(C(C(O3)CO)O)O)O
Dihydroxy Coumestan	13964267	3	7	CC(C)(CCC1=C(C(=CC2=C1C3=C(O2)C4=C(C=C(C=C4)O)OC3=O)O)OC)O
Isobavachin	11609510	2	4	CC(=CCC1=C(C=CC2=C1OC(CC2=O)C3=CC=C(C=C3)O)O)C
Beta. Caryophyllene Oxide	6604672	0	1	CC1(CC2C1CCC3(C(O3)CCC2=C)C)C
Cyclo Octene	102239663	4	4	CC(C)C1=C2C(=C(C=C1)OC)[Se]SC3=C(C=CC(=C3[Se]S2)OC)C(C)C
3,3 Dimethyl oxiran	61068	0	5	C[Si](C)(CCCOCC1CO1)O[Si](C)(C)CCCOCC2CO2
n-Hexadecanoic acid	985	1	2	CCCCCCCCCCCCCCCC(=O)O

Table 1: Structure of physical and chemical properties of the selected ligand Phytocompounds for docking analysis

Species Name	Compound Name	Binding Affinity	RMSD/UB	RMSD/LB
PC	Isopsoralen	-6.7	3.576	3.113
	Dihydroxy Coumestan	-6.3	5.594	3.113
	Isobavachin	-6.0	5.887	2.229
	Beta. Caryophyllene Oxide	-5.6	31.197	2.844
	Cyclo Octene	-5.7	31.687	27.844

Table 2: Virtual Screening results of *P. corylifolia* species derived compounds

Compound Name	Distribution			Metabolism		Excretion
	VD_{SS} human	Fraction unbound (%)	BBB permeability	CYP3A4 substrate	CYP1A2 inhibitor	Total Clearance
Isopsoralen	0.403	21.11	0.702	0.013	0.053	1.669
Dihydroxy Coumestan	0.821	15.86	0.005	0.101	0.952	6.419
Isobavachin	0.646	1.37	0.040	0.192	0.787	18.276
Beta. Caryophyllene Oxide	1.469	11.13	0.745	0.361	0.107	15.503
Cyclo Octene	4.163	1.58	0.541	0.680	0.698	10.038

Table 3(A): ADMET Properties of GC-MS derived compounds from the selected *P.corylifolia* species

Compound Name	Toxicity					
	AMES toxicity	hERG II inhibitor	Oral rat acute toxicity (LD50)	*T.pyriformis* toxicity	Minnow toxicity	Log P value
Isopsoralen	0.054	0.048	0.251	3.102	3.387	-0.054
Dihydroxy Coumestan	0.342	0.005	0.111	4.280	4.560	3.548
Isobavachin	0.209	0.054	0.474	4.973	7.059	4.715
Beta. Caryophyllene Oxide	0.055	0.019	0.093	4.373	4.951	4.474
Cyclo Octene	0.334	0.027	0.939	5.570	8.502	6.213

Table 3(B): ADMET Properties of GC-MS derived compounds from the selected *P.corylifolia* species

Diseases/ Proteins	PDB ID	Docking energy (kcal/mol)	Interactions	Amino acid	Amino acid binding site
Cancer	3G5Z	-10.9505	Conventional hydrogen bond	Lysine	42
				Glutamine	38
				Phenyl Alanine	44, 98
			Vander Waals	Glycine	99
				Serine	43
			Pi-Alkyl	Leucine	36
			Pi-Pi Interaction	Tyrosine	87

Table 4: Molecular docking results of Isopsoralen (Ligand Molecule) interact with target protein

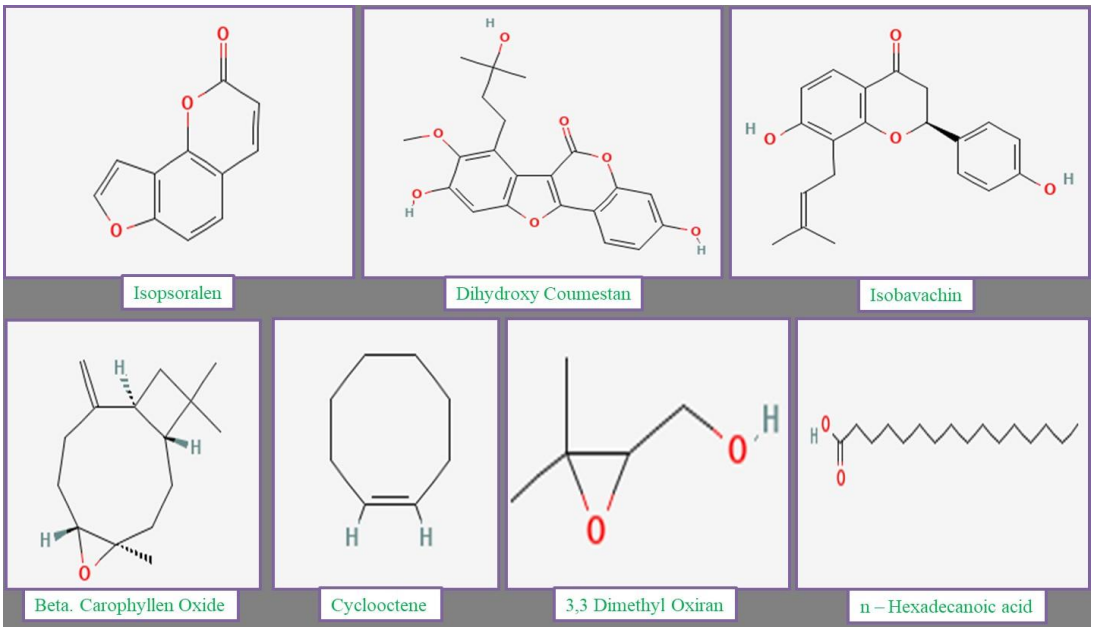

Figure 1: 2D Structure of the selected Phyto (ligand) compounds for docking analysis

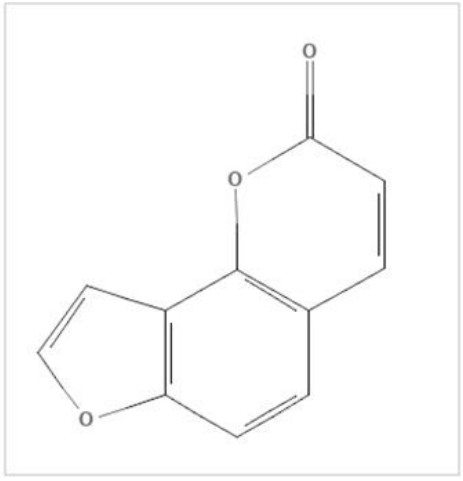

Figure 2: 2D structure of Isopsoralen

Figure 3: 3D Structure of tumor induced cancer protein

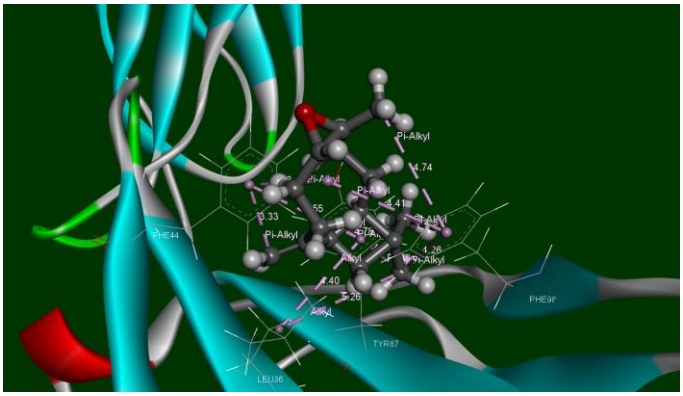

Figure 5. 3D Structure of ligand molecule interaction with target protein