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Selective plant alkaloids as potential inhibitors of PARP in pancreatic cancer- An *in silico* study

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Pancreatic cancer is recognized as the fourth leading cause of death. Treatment cost for pancreatic cancer remains very high. So, searching for novel plant compounds with potent anticancer activity is required. Computer-aided drug design has gained importance recently. Using these techniques drugs for specific targets can be predicted *in silico*. In this present study, PARP from pancreatic cancer was chosen as the target, and plant alkaloids from the literature were selected as ligands. First, the alkaloid was screened for their drug-likeness and pharmacokinetics properties, and violations of Lipinski's rule were rejected. Docking studies were carried out to analyze the compounds with the best binding affinity, and the best compound was selected for analyzing toxicity profiles. Compounds with toxic endpoints were rejected and final lead compounds were identified; the identified leads were again screened for bioavailability and molecular target predictions. The results are compared with control drugs. All compounds showed drug-likeness and pharmacokinetics except, Geissospermine. From docking studies, 15 compounds showed the best binding affinity of –6.0 to –8.8 Kcal/mol. Atropine, ephedrine, theobromine, theophylline, actinidine, and pinidine have no toxic endpoints. These compounds were predicted as final lead compounds. Leads also possesses oral bioavailability, which was predicted by radar plot. The identified hits were analyzed for molecular targets. Atropine, ephedrine, theobromine, theophylline, actinidine, and pinidine were predicted as hit among 21 compounds but further *in vitro* and *in vivo* studies are required to validate its action.

Keywords: CADD, Molecular docking, Molecular targets, PARP, Plant alkaloids

Bioinformatics has gained much importance in the past years. Using bioinformatics tools, fast prediction of lead compounds from thousands of compounds in high throughput mode can be achieved in a short span of time[1]. Due to the rapid development in computer-aided drug design, new drugs are designed and discovered, and many success stories of drug design were also reported[2]. In normal conventional drug discovery, it takes more than 12 years to discover a new drug, and costs greater than $1.8 million. But the computational methods are less time-consuming and cost-effective[3]. The phytochemicals present in various plant species were investigated as potential inhibitors for various diseases using *in silico* studies[4-6]. One of the important secondary metabolites present in plants is alkaloids[7]. Since ancient days, plants containing alkaloids have been used as medicine. Alkaloids are known to contain more than 12,000 different structures and belong to a class of Nitrogen-containing compounds[8]. Alkaloids possess greater pharmacological activity. There are more than 20 various classes of alkaloids present and more than 27,000 alkaloids were identified so far[10]. Alkaloids were known for their anticancer, antibacterial, antiviral, antifungal, anti-inflammatory activities, *etc*[11-13].

Natural plant alkaloids such as Atropine, Codeine, Morphine, *etc* were reported for various pharmacological activities[14]. Over the past two decades, more alkaloids have been reported for their anticancer activities. A few alkaloids isolated from plants for their pharmacological activity are in preclinical trials [15]. Vinca alkaloids from plants are the most widely used antineoplastic drugs[16]. Pancreatic cancer is the fourth leading cause of death in the world. The average survival period for pancreatic cancer is 17-23 months, even at early diagnosis as well as surgery[17]. Treatment for pancreatic cancer remains costly[18], so the search for a natural compound possessing anticancer activity against pancreatic cancer is desirable.

Poly (ADP-ribose) Polymerase (PARP) is an important protein that plays a role in the base excision repair (BER) pathway, more specifically in single-strand breaks (SSBs)[19]. If PARP is inhibited, the BER pathway gets impaired, and SSBs become double-

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strand breaks (DSBs)[20]. This PARP is the major target in cancer treatment. Inhibition or blocking the PARP can make the cancer cell unable to repair the damaged DNA and eventually cause them to die[21]. So, in this study, PARP is selected as a target for pancreatic cancer. The FDA has approved some PARP inhibitors for various cancer treatments[22].

In this study, various plant alkaloids from the literature were selected and analyzed for their drug-likeness and pharmacokinetics properties *in silico*. After analysis, docking studies were carried out between alkaloids and selected target proteins of cancer. Finally, toxicity profiles of compounds with the best binding affinity were screened. Finally, the identified lead compounds were analyzed for molecular targets.

Materials and Methods

Ligand selection

22 plant alkaloids from various plants were selected from literature[11,23,24]. The 3D structure of the alkaloids was downloaded from the PubChem database in Simulation Description Format (SD Format). The Canonical SMILES of the compounds were also noted. Olaparib was used as a control drug[25].

In silico Drug likeness and ADME analysis of the alkaloids

The drug-likeness and pharmacokinetics of the alkaloids were determined by submitting their SMILES to the swiss ADME (http://www.swissadme.ch/index.php) web server. violation of Lipinski's rule of five, *i.e* Molecular weight, Number of hydrogen bond donors, number of hydrogen bond acceptors, and LogP were predicted. Rotatable bonds, molar refractivity, and topological polar surface area (TPSA) were also considered in this study. Pharmacokinetic properties namely absorption, distribution, metabolism, and excretion (ADME), were predicted. Gastrointestinal tract absorption, blood-brain permanent, cytochrome P450 and its isoenzymes inhibitions are the properties considered for ADME screening[26]. Compounds having more than 1 violation of Lipinski's rule were rejected for further analysis.

Protein

The 3D structure of the target protein PARP was downloaded from RCSB PDB(http://www.rcsb.org/pdb/home/home.do). Crystal structure of PARP catalytic domain in complex with novel inhibitors, PDB ID: 4HHY.

Docking studies

First the downloaded ligands from PubChem in sdf format were converted to pdb format using open babel. Docking studies were carried out between selected alkaloids and target receptors using auto dock 4.2.6. Docking was performed based on previously reported protocol[27]. Protein is prepared by the removal of water molecules and adding hydrogen atoms and Kollman's charges. The protein is set rigid and the ligand is made flexible by allowing all the rotatable bonds to rotate. Gasteiger charges were also computed to the ligand. Grid coordinates of existing ligands were noted to set the grid for docking. And the existing ligand was removed from the active site to carry out docking. Lamarckian genetic algorithm used for obtaining docking results. From the obtained 10 conformations, one with the best possible binding affinity was selected. The selected ligand with the best conformation was saved and visualized in BIOVIA Discovery studio v21.1.0.20298.

Toxicity analysis

The compounds with the best binding affinity were selected for further toxicity analysis. Using the ProToxII web server toxicity profiles of the compounds were evaluated[28]. The compounds were analyzed for Lethal Dose 50 (LD50 mg/Kg), Acute toxicity classes, Hepatotoxicity, carcinogenicity, Immunogenicity, Mutagenicity, and cytotoxicity. Compounds with toxic endpoints were rejected and the rest of the compounds were selected for further analysis.

Bioavailability radar and Molecular target analysis

For determining the bioavailability of the identified lead compounds, the Swiss ADME web server was used.(http://www.swissadme.ch/index.php)[27].

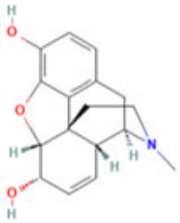
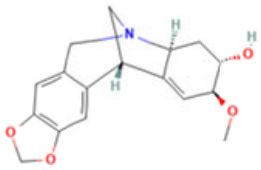
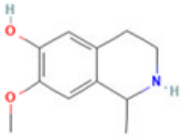
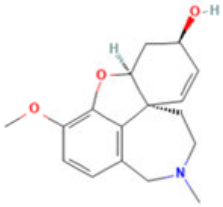
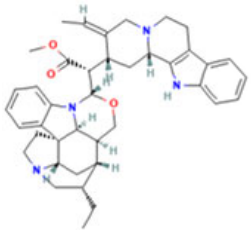
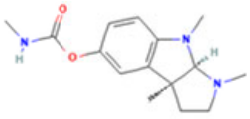
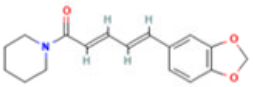
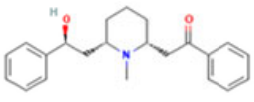
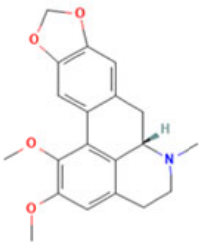
To analyze the molecular target of the lead compounds. Swiss Target prediction web server is used. SMILES of lead were submitted in order to analyze the target proteins. This prediction is helpful in analyzing the molecular mechanism of the lead[29].

Results and Discussion

Drug - likeness and ADME screening

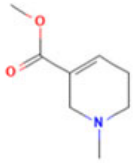
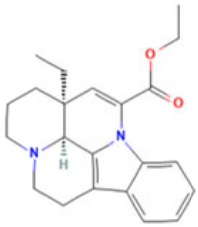
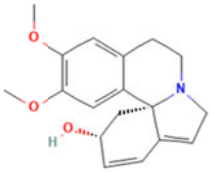
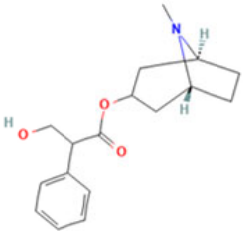
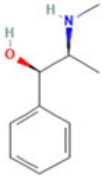
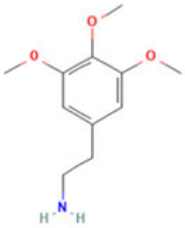
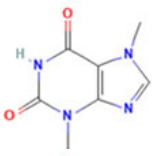
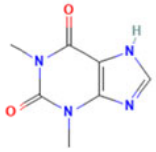
To analyze the drug-like nature of Selected 21, Lipinski's rule of Five was used, which determines the probability of the compounds acting as drugs. Compounds having more than one violation of the following were rejected, molecular weight of the compound less than 500 Da, hydrogen bond donor less than 5, hydrogen bond acceptor less than 10, and log P not greater than 5[30]. Table 1 represents the plant alkaloids, PubChem ID, and 2D structure. Table 2 represents the drug-likeness of the compounds.

Table 1 — Pubchem 1D and 2D structure of Alkaloids

No	Compounds	Pubchem Id	2D structure
1	Morphine	5288826	
2	Montanine	11087935	
3	Salsoline	46695	
4	Galantamine	9651	
5	Geissospermine	5281401	
6	Physostigmine	5983	
7	Piperine	638024	
8	Lobeline	101616	
9	Nantenine	197001	

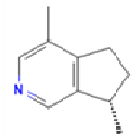
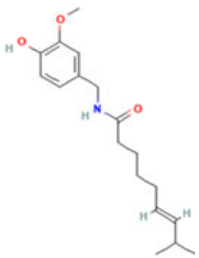
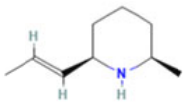
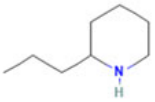
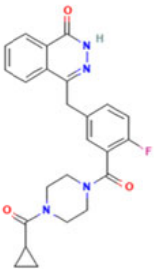
(*Contd.*)

Table 1 — Pubchem 1D and 2D structure of Alkaloids (*Contd*.)

No	Compounds	Pubchem Id	2D structure
10	Arecoline	2230	
11	Vinpocetin	443955	
12	(+)-erythravine	11231853	
13	Atropine	174174	
14	Ephedrine	9294	
15	Mescaline	4076	
16	Theobromine,	5429	
17	Theophylline	2153	

(*Contd*.)

Table 1 — Pubchem 1D and 2D structure of Alkaloids (*Contd.*)

No	Compounds	Pubchem Id	2D structure
18	Actinidine	68231	
19	Capsaicin	1548943	
20	Pinidine	5281689	
21	Coniine	9985	
C	Olaparib	23725625	

Among the screened compounds Geissospermine was found to violate Lipinski's rule of five with 2 violations. All 20 compounds were predicted to possess drug-like properties. Violation of Lipinski's rule of five results in poor permeability and absorption of drugs.It was found that molecular weight, NHBA, and NHBD were in the acceptable range for all compounds. The optimum TPSA of a compound should be 0-140Å, compounds possessing TPSA of 140 or greater than 140 were found to have poor absorption. The TPSA of all compounds was found below 140, indicating good absorption [31].

The optimum Log P for a drug should be 0<LogP<3. The Log P of 18 compounds ranges between 0.04 to 3.64, except Geissospermine, with log P of 4.59, Theobromine and Theophylline, log P -1.04, Indicating poor membrane permeability. Based on this analysis, oral bioavailability and intestinal absorption of drugs is possible.

Pharmacokinetics

All the compounds were predicted to be actively absorbed by the gastrointestinal tract (GIA). Except for Arecoline, Theobromine, and Theophylline all other compounds are permanent of the blood-brain barrier. P-glycoprotein (p-gp) causes efflux of the drug and this p-gp is overexpressed in cancer cells. If a drug acts as a substrate of p-gp, the treatment becomes ineffective[32,33]. Morphine, Galantamine, Geissospermine, Physostigmine, Nantenine, Erythravine, and control drug Olaparib act as substrates of p-gp and the rest of the compounds are not substrates of p-gp. Cytochrome P450 (Cyc P450) isoenzymes such as CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4 are important for the

Table 2 — Drug likeness of Selected Plant alkaloids

No	Phytochemicals	Mol. weight	Hydrogen bond donor	Hydrogen bond Acceptor	Rotatable bond	LogP	MR	TPSA	Lipinsiki's rule of 5 violation	Bioavailability Score
1	Morphine	285.34	2	4	0	0.82	82.27	52.93	0	0.55
2	Montanine	301.34	1	5	1	0.87	83.13	51.16	0	0.55
3	Salsoline	193.24	2	3	1	0.9	59.11	41.49	0	0.55
4	Galantamine	287.35	1	4	1	1.32	84.05	41.93	0	0.55
5	Geissospermine	632.83	1	5	5	4.59	196.22	61.04	2	0.17
6	Physostigmine	275.35	1	3	3	1.01	84.93	44.81	0	0.55
7	Piperine	285.34	0	3	4	2.51	85.47	38.77	0	0.55
8	Lobeline	337.46	1	3	6	3.53	105.44	40.54	0	0.55
9	Nantenine	339.39	0	5	2	2.48	98.02	40.16	0	0.55
10	Arecoline	155.19	0	3	2	0.04	46.08	29.54	0	0.55
11	Vinpocetin	350.45	0	3	4	3.44	107.82	34.47	0	0.55
12	erythravine	299.36	1	4	2	1.53	88.38	41.93	0	0.55
13	Atropine	289.37	1	4	5	1.55	84.51	49.77	0	0.55
14	Ephedrine	165.23	2	2	3	1	49.79	32.26	0	0.55
15	Mescaline	211.26	1	4	5	1.21	58.4	53.71	0	0.55
16	Theobromine	180.16	1	3	0	-1.04	47.14	72.68	0	0.55
17	Theophylline	180.16	1	3	0	-1.04	47.14	72.68	0	0.55
18	Actinidine	147.22	0	1	0	2.44	46.64	12.89	0	0.55
19	Capsaicin	305.41	2	3	10	3.64	90.52	58.56	0	0.55
20	Pinidine	139.24	1	1	1	1.71	49.51	12.03	0	0.55
21	Coniine	127.23	1	1	2	1.55	45.17	12.03	0	0.55
C	Olaparib	434.46	1	5	6	1.94	125.21	86.37	0	0.55

Table 3 — Pharmacokinetics of selected alkaloids

No	Compounds	ESOL Log S	ESOL Class	GIA	BBB Permeant	p-gp substrate	CYP1A2 inhibitor	CYP2C19 Inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	iLOG P
1	Morphine	-2.3	Soluble	High	Yes	Yes	No	No	No	Yes	No	2.69
2	Montanine	-2.21	Soluble	High	Yes	No	No	No	No	Yes	No	2.85
3	Salsoline	-2.13	Soluble	High	Yes	No	No	No	No	No	No	2.26
4	Galantamine	-2.93	Soluble	High	Yes	Yes	No	No	No	Yes	No	2.64
5	Geissospermine	-7.36	Poorly soluble	High	Yes	Yes	No	No	No	No	No	5.01
6	Physostigmine	-2.57	Soluble	High	Yes	Yes	No	No	No	Yes	No	2.83
7	Piperine	-3.74	Soluble	High	Yes	No	Yes	Yes	Yes	No	No	3.38
8	Lobeline	-4.26	Moderately soluble	High	Yes	No	Yes	No	No	Yes	No	3.32
9	Nantenine	-4.21	Moderately soluble	High	Yes	Yes	Yes	Yes	Yes	Yes	Yes	3.54
10	Arecoline	-0.89	Very soluble	High	No	No	No	No	No	No	No	2.26
11	Vinpocetin	-4.6	Moderately soluble	High	Yes	No	No	Yes	Yes	Yes	Yes	3.28
12	erythravine	-2.78	Soluble	High	Yes	Yes	No	No	No	Yes	No	2.81
13	Atropine	-2.67	Soluble	High	Yes	No	No	No	No	Yes	No	2.85
14	Ephedrine	-1.62	Very soluble	High	Yes	No	No	No	No	No	No	2.25
15	Mescaline	-1.61	Very soluble	High	Yes	No	No	No	No	No	No	2.37
16	Theobromine	-0.98	Very soluble	High	No	No	No	No	No	No	No	1.22
17	Theophylline	-1.46	Very soluble	High	No	No	No	No	No	No	No	0.53
18	Actinidine	-2.66	Soluble	High	Yes	No	Yes	No	No	No	No	2.15
19	Capsaicin	-3.53	Soluble	High	Yes	No	Yes	No	No	Yes	Yes	3.15
20	Pinidine	-1.89	Very soluble	High	Yes	No	No	No	No	No	No	2.64
21	Coniine	-1.73	Very soluble	High	Yes	No	No	No	No	No	No	2.43
C	Olaparib	-3.7	Soluble	High	No	Yes	No	Yes	Yes	Yes	Yes	2.84

metabolism of drugs. If the drug is an inhibitor of Cyc P450, accumulation occurs, or if it acts as a substrate, more metabolisms occur[34]. Geissospermine showed 2 violations of Lipinski's rule so it was rejected for further study. Table 3 represents the pharmacokinetics of the selected alkaloids.

Docking results analysis

PARP is one of the major targets for anticancer drug development. In this present study, PARP was chosen as the target (Pdb ID; 4HHY) and the interaction between PARP and plant alkaloids was studied with a standard drug as a control. The 3D structure of PARP is represented in (Fig. 1). Molecular docking studies were carried out between compounds possessing drug-like properties and PARP. The 2D representation of PARP with selected compounds was shown in (Fig. 2). The binding affinity between the alkaloids and PARP, number of hydrogen bonds, amino acids involved in hydrogen bond formation, hydrogen bond length, van der waal interaction, and other interactions like Carbon hydrogen, pi anion, Pi-sulfur, Pi-Pi stacked and pi-alkyl bond were also noted and represented in (Table 4).

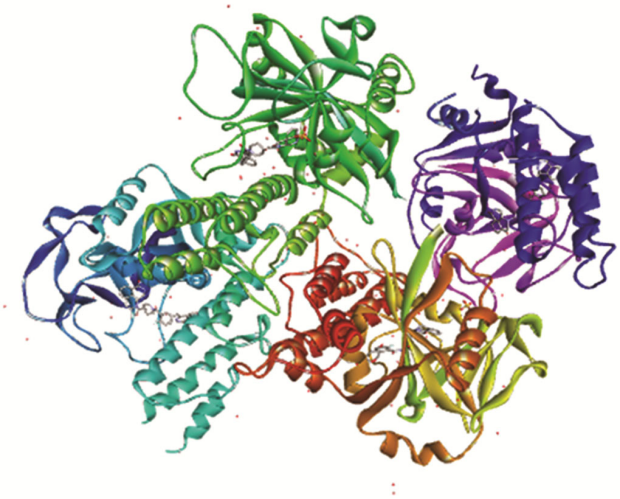


Fig. 1 — 3D structure of Poly(ADP-ribose) Polymerase (PARP) (PDB ID : 4HHY)

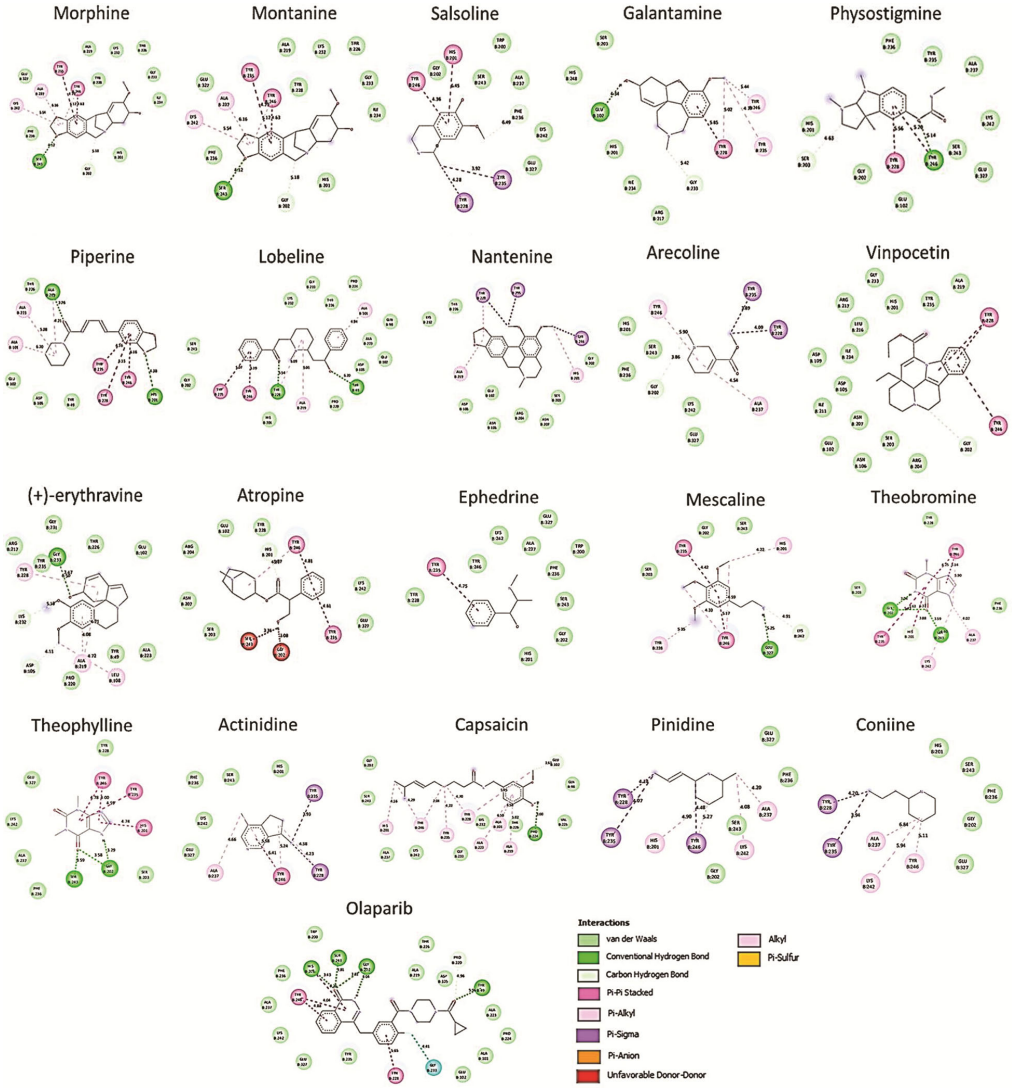


Fig. 2 — 2D interaction Structure of alkaloids with PARP

Table 4 — Binding affinity of alkaloids with PARP

No	Compound	Binding affinity	No. of H bond	Hydrogen bond	Carbon Hydrogen / Pi-anion /Pi-Sulfur / Pi-Pi stacked / Pi- Alkyl bond	Van der waals
1	Morphine	-8.3	1	Gly233(3.77)	Thr226, Ala219, Ala223	Ala101, Gln98, Glu102, Lys232, Tyr228, Ile234, Tyr235, Asp105, Tyr49, Pro220
2	Montanine	-10.2	1	Ser243(4.12)	Lys242,Ala237, Tyr235, Tyr246, Gly202	Phe236, Glu327, Ala219, Tyr228, Lys232, Thr226, Gly233, Ile234, His201
3	Salsoline	-7.6	-	-	Tyr246, His201, Phe236, Tyr235, Tyr228	Ala237, Lys242, Glu327, Gly202, Ser243, trp200
4	Galantamine	-7.7	1	Glu102(4.34)	Tyr228, Gly233, Tyr246, Tyr235	Ser203, His248, His201, Ile234, Arg217
5	Geissospermine	-9.6	2	Ala210 (4.06,3.45)	Ala223, Pro224, Ala101, Arg217, His201, tyr246, Ile218	Gln98, glu102, Asp105, Tyr49, Thr226, Lys232, Leu216, Pro220, Ser203, Ile211, Tyr228, Gly233, Asn207, Ile234, Tyr235
6	Physostigmine	-8.1	1	Tyr246(5.14)	Ser203, Tyr228	His201, Gly202, Glu102, Ser243, Glu327, Lys242, Ala237, Tyr235, Phe236
7	Piperine	-9.3	2	Ala219(3.76), His201(4.38)	Ala223, Ala101,Tyr235, Tyr228, Tyr246	Thr226, glu102, Asp105, Tyr49, Gly202, Ser243
8	Lobeline	-9.6	3	Tyr228(3.54), Tyr49(6.20)	Tyr235, Tyr246, Ala219, Ala101	His201, pro220, Asp105, Glu102, Ala223, Gln98, Pro224, Thr226, Gly233, Lys232
9	Nantenine	-8.7	-	-	Tyr228, Tyr235, Tyr246, Hia201, Ala219	Lys232, Thr226, Asp105, Glu102, Asn106, Arg204, Asn207, Ser203, Gly202
10	Arecoline	-5.6	-	-	Gly202, Tyr246, Tyr235, Tyr228, Ala237	His201, Ser243, Phe236, Lys242, Glu327
11	Vinpocetin	-8.8	-	-	Tyr228, Tyr246, Gly202	Ala219, Tyr235, His201, Gly233, Arg217, Leu216, Ile234, Asp109, Asp105, Ile211, Asn207, Glu102, Asn106, Ser203, Arg204
12	(+)-erythravine	-7.9	1	Gly233(3.47)	Ala219, Leu108, Tyr228, Asp105, Lys232	Arg217, Tyr235, Pro220,Tyr49, Ala223, Thr226, Glu102
13	Atropine	-8.4	-	-	Ser243, Gly202, Tyr246, His201, Tyr235	Tyr228, Lys242, Glu327, Ser203, Asn207, Arg204, Glu102
14	Ephedrine	-6.3	-	-	Tyr235	Tyr228, Tyr246, Lys242, Ala237, Glu327, Phe236, Trp200, Ser243, Gly202, His201
15	Mescaline	-6.1	1	Glu327(5.25)	Tyr235, His201, Tyr246, Tyr228, Lys242	Ser203, Gly202, Ser243
16	Theobromine,	-6.8	3	Gly202(3.04,5.43), Ser243(3.59)	Tyr246, Tyr235, His201, Lys243, Ala237	Ser203, Tyr228, Phe236
17	Theophylline	-6.7	3	Ser243(3.59), Gly202(3.58,3.29)	Tyr246, Tyr235, His201	Ser203, Phe236, Ala237, Lys242, Glu327, Tyr228
18	Actinidine	-7.4	-	-	Ala237, Tyr246, Tyr228, Tyr235	Glu327, Lys242, Phe236, Ser243, His201
19	Capsaicin	-8.2	1	Pro224(3.00)	His201, Tyr246, Tyr235, Ala223, Tyr228, Ala101, Ala219, Glu102	Gly202, Ser243, Ala237, Lys242, Gly233, Lys232, Thr226, Gln98, Val225
20	Pinidine	-6	-	-	Tyr228, Tyr235, His201, Tyr246, Lys242, Ala237	Glu327,Phe236,Ser243,Gly202

(*Contd*.)

Table 4 — Binding affinity of alkaloids with PARP

No	Compound	Binding affinity	No. of H bond	Hydrogen bond	Carbon Hydrogen / Pi-anion /Pi-Sulfur / Pi-Pi stacked / Pi- Alkyl bond	Van der waals
21	Coniine	-5.6	-	-	Tyr228, Tyr235, Ala237, Lys242, Tyr246	His201, Ser243, Phe236, Gly202, Glu327
C	Olaparib	-13	5	His201(3.43), Ser243(3.81), Gly202(3.81,3.04), Tyr49(5.96)	Tyr246,tyr228,Gly233, Pro220	Trp200, Phe236, Ala237, Lys242, Glu327, Tyr235, Thr226, Ala219, Asp105, Ala223, Ala101, Glu102, Pro224

Table 5 — Toxicity profiles of alkaloids

S. No	Compound	LD_{50} (mg/Kg)	Acute toxicity class	Hepatoxicity	Carcinogenicity	Immunogenicity	Mutagenicity	Cytotoxicity
1	Morphine	335	4	Inactive	Inactive	Inactive	Inactive	Inactive
2	Salsoline	1000	4	Inactive	Inactive	Active	Inactive	Inactive
3	Galantamine	85	3	Inactive	Inacitve	Active	Inactive	Active
4	Physostigmine	2	1	Inactive	Inactive	Inactive	Inactive	Inactive
5	Nantenine	401	4	Inactive	Active	Active	Active	Active
6	Vinpocetin	503	4	Inactive	Inactive	Inactive	Inactive	Inactive
7	(+)-erythravine	80	3	Inactive	Inactive	Active	Inactive	Inactive
8	Atropine	380	4	Inactive	Inactive	Inactive	Inactive	Inactive
9	Ephedrine	40	4	Inactive	Inactive	Inactive	Inactive	Inactive
10	Mescaline	800	4	Inactive	Inactive	Active	Active	Inactive
11	Theobromine,	837	4	Inactive	Inactive	Inactive	Inactive	Inactive
12	Theophylline	127	3	Inactive	Inactive	Inactive	Inactive	Inactive
13	Actinidine	500	4	Inactive	Inactive	Inactive	Inactive	Inactive
14	Capsaicin	47	2	Inactive	Active	Active	Active	Inactive
15	Pinidine	700	4	Inactive	Inactive	Inactive	Inactive	Inactive
C	Olaparib	500	4	Inactive	Inactive	Inactive	Inactive	Inactive

The binding affinity of alkaloids ranged from −5.6 to −13 Kcal/mol. The compounds possessing low binding affinities ranging from −6 to −8.8 Kcal/mol were morphine, salsoline, galantamine, physostigmine, nantenine, vinpocetine, erythravine, atropine, ephedrine, mescaline, theobromine, theophylline, actinidine, capsaicin and pinidine. These compounds were found to fit well in the active site of PARP, forming a stable complex. Morphine forms one hydrogen bond with amino acid gly233 of the target protein with a binding affinity of −8.3 Kcal/mol, galantamine forms one hydrogen bond with glu102 with a binding affinity of −7.7 Kcal/mol, physostigmine forms 1 hydrogen bond with Tyr246 with a binding affinity of −8.1 Kcal/mol, erythravine forms one hydrogen bond with gly233 with binding affinity −7.9 Kcal/mol, mescaline forms one hydrogen bond with Glu327 with a binding affinity of −6.1 Kcal/mol, theobromine forms three hydrogen bonds, two bonds withgly 203, ser243 with −6.8 Kcal/mol, theophylline forms three hydrogen bonds, one withser 243, two bonds with gly202 with a binding affinity of −6.7 to −8.2 Kcal/mol, capsaicin forms one hydrogen bond with pro224 with a binding affinity of −8.2 Kcal/mol. Salsoline, nantenine, vinpocetine, atropine, ephedrine, actinidine, and pinidine forms no hydrogen bond but forms other types of interaction with amino acids present in active sites. The 15 selected compounds were screened for further study. Previous study on molecular interaction of Phenol, 2,4, bis (1,1- dimethylethyl)-(7311) isolated from from *Plumbago zeylanica* showed better interaction with MMPs whose dysfunction may results in cancer[35].

Toxicity analysis

For a compound to be selected as an ideal therapeutic agent, it should not show any toxicity[36]. The toxicity profiles of the compounds predicted using proToxII were represented in (Table 5). The lethal dose (LD50) of the compounds ranges from 2 to 837 mg/kg and the acute toxicity classes were 2,3 and 5. The compounds with one or two toxic endpoints are salsoline, galantamine, physostigmine, nantenine, erythravine, mescaline and capsaicin and these compounds were rejected. Morphine and vinpocetine possess class 1 and

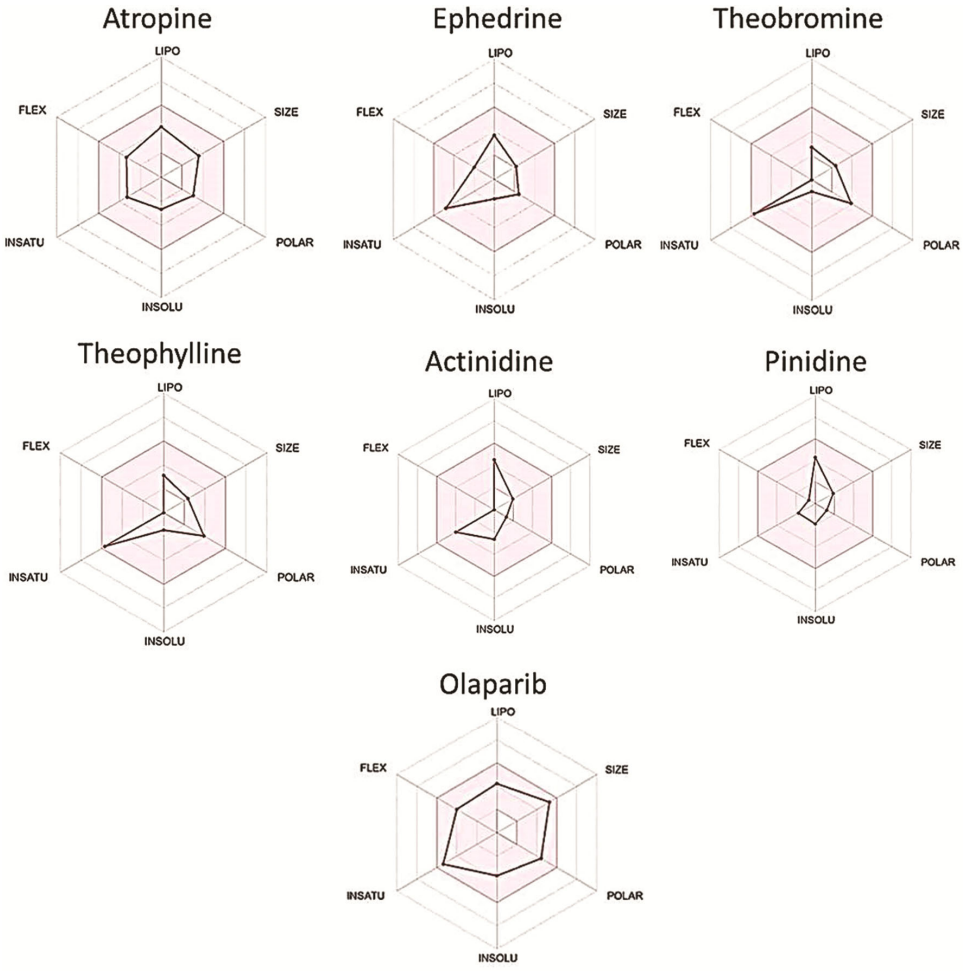


Fig. 3 — Radar plot of lead compounds

3 toxicities, so these compounds were rejected. Atropine, ephedrine, theobromine, theophylline, actinidine, and pinidine are the compounds with no toxic endpoint predicted. And these compounds were considered as hits among the screened compounds.

Radar plot and Molecular target analysis

The radar plot of the hits or lead compounds was represented in (Fig. 3). The pink region of the plot shows the optimum range, it is necessary for the compounds to fall in the pink region of the plot. All the hits were found to be orally bioavailable as they fall in the pink region. FLEX (flexibility) and Polar (Polarity) determine bioavailability. All 6 compounds were predicted to possess oral bioavailability[34]. Molecular targets of hits were also predicted. The results for each of the compounds were represented in a pie chart with separate targets for each compound. Figure 4 represents the molecular targets of lead compounds, elucidating their potential therapeutic interaction.

Sepay *et al.* (2022) conducted previous investigations on flavonoids' interaction with EGFR, emphasizing the significance of molecular docking studies in predicting compound potential as inhibitors for specific molecular targets, reinforcing our use of molecular docking to explore phytochemicals from *Acronychia pedunculata* as potent HER2 inhibitor in colorectal cancer[37].

Our research aligns with the findings of Kadri and Aouadi (2020), who previously utilized the bioavailability radar plot to assess oral bioavailability. Our results also confirm the favorable oral bioavailability characteristics of the identified compounds. The consistency between our study and related research enhances the credibility of our findings and underscores the potential of these alkaloids as safe and promising candidates for further investigation[38].

Conclusion

PARP is a major therapeutic target for many cancers. In this study, PARP was selected as a target

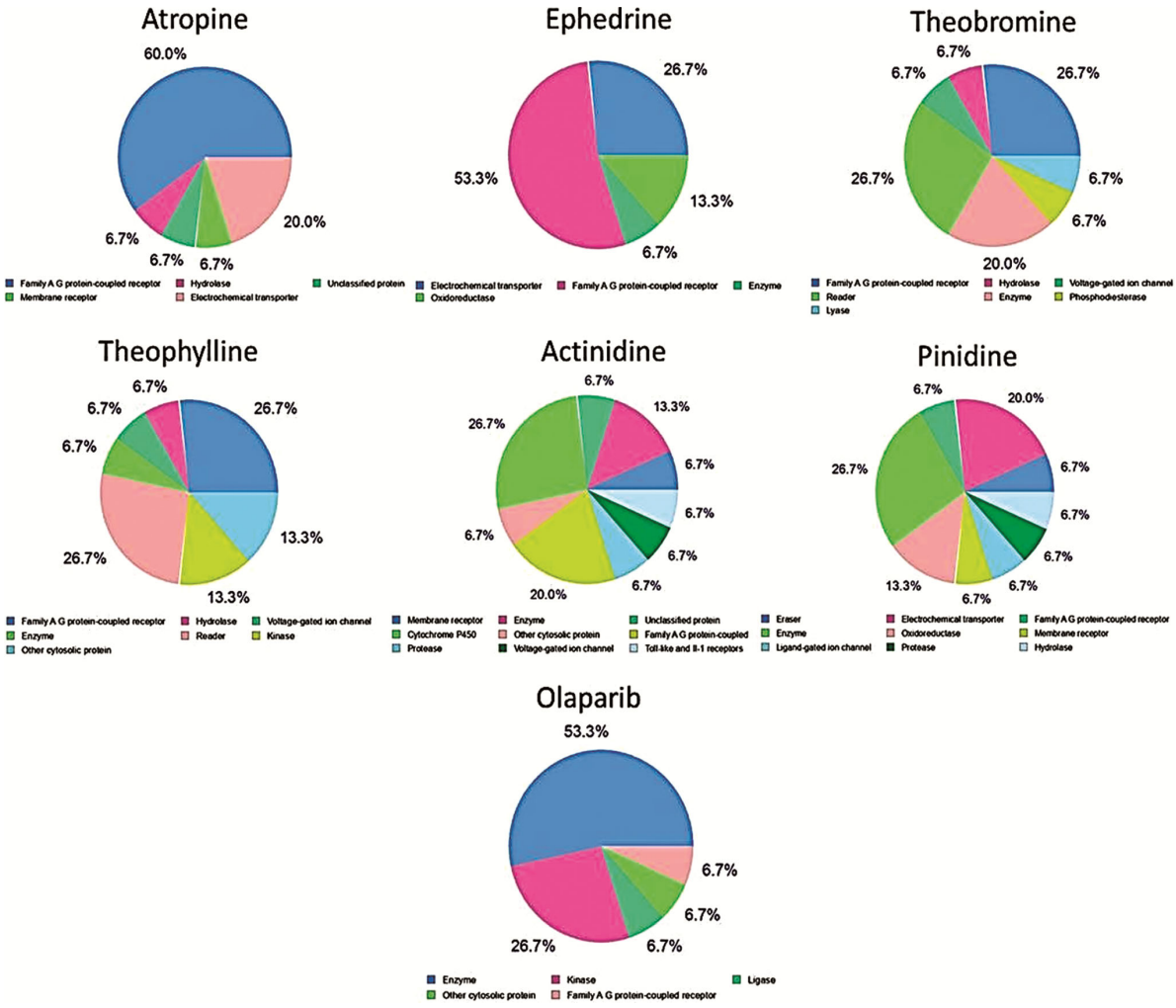


Fig. 4 — Varied Molecular targets of lead compounds elucidating their potential therapeutic interactions

in pancreatic cancer and natural plant alkaloids were screened for its inhibition activity against PARP. Among 21 compounds, Geissospermine violates Lipinski's rule. Docking studies between PARP and alkaloids showed that 15 compounds showed the best binding affinity, these 15 compounds were screened for further toxicity analysis.9 compounds showed toxicity and 6 compounds were found to be nontoxic in nature. Identified 6 hits were screened for bioavailability and molecular targets. Analyzing the results of lead with the control drug, it was found to be significant. This preliminary *in silico* analysis identified lead compounds possessing drug-like properties and good binding affinity towards PARP, but validation of the identified lead alkaloids necessitates subsequent studies involving the isolation of these compounds from plants and conducting *in vitro* and *in vivo* investigations in the future.

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Conflict of interest

All authors declare no competing interests.

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