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Original Article

In Silico Techniques Unveil the Anticancer Potential of Himalayan Pteridophytic Compounds via PI3K Inhibition

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Abstract

Introduction Inhibiting the signaling protein/gene involved in cancer progression may affect the signaling cascade and could be a possible targeted approach against progressive cancer. The present study aims to evaluate the anticancer potential of bioactive compounds from selected Himalayan pteridophytes by targeting the phosphoinositide 3 kinase (PI3K) pathway using in silico techniques.

Materials and Methods In the present study, we identified various Himalayan pteridophytes via literature search from different search engines like Google Scholar, Science Direct, PubMed, etc. Among all, four Himalayan pteridophytes were chosen whose bioactive constituents were already identified by gas chromatography–mass spectrometry (GC-MS) analysis. Molecular docking via PyRx software was performed against two PI3K target proteins (PDB ID: 5OQ4 and PDB ID: 3OAW) for determining the binding affinity of selected bioactive constituents against cancer. Drug likeliness and toxicity assessment were also carried out by using Swiss ADME and ProTox-II.

Results and Discussion Molecular docking study identified 12 bioactive molecules with favorable binding affinities (ranging from –7.3 to –10.00 kcal/mol) against PI3K pathway. Among 12 constituents, 3 molecules named as PC-2 (Matteucinol), PC-4 (Matteuorienate-A), and PC-9 (flavan-4-ol) have binding affinity more than the reference compounds. These results suggest that these constituents may serve as a promising candidate for further in vitro and in vivo studies in cancer therapeutics. The selected bioactive compounds demonstrate promising anticancer activity via PI3K inhibition, warranting further experimental validation and development as potential cancer therapeutics.

Keywords
- phosphoinositide 3-kinase
- anticancer activity
- molecular docking
- pteridophytes

Introduction

Cancer is a serious disease in which cells multiply and grow uncontrollably. It occurs due to mutation in genes that cause cellular alteration and malignant transformation. The increase in the incidence of cancer is with age, as the mechanism of cell repair is less effective when a person grows older.[1] Globally, it has become the second most regular cause of death after cardiovascular diseases.[2] Major risk factors for cancer are excessive alcohol consumption, extreme tobacco use, harmful chemical exposure, radiation, air pollution, etc. Cancer works through many pathways

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such as phosphoinositide 3 kinase (PI3K), Wnt, Janus kinase/signal transducers and activators of transcription (JAK-STAT) pathway, Notch signaling pathway, etc. PI3K pathway is involved in various cellular functions, which comprise cell cycle, cell growth, and cell proliferation.[3] Various studies have been conducted using in silico methods for the inhibition of cancer cells/PI3K pathway.[4]

Anticancer therapy aims to target cancer cells and halt their proliferation while leaving normal cells alone to divide.[5] But there are side effects in the treatment of cancer like hair loss, neutropenia, etc. Therefore, a need to discover new anticancer therapies resulting from plant sources involving fewer side effects than conventional synthetic medications. Many species of plant have been picked for anticancer activity, and one of them is pteridophyte flora.[6] Research found that pteridophytes are successful against cervical, breast, brain, ovary, colorectal, liver, lung, pancreas, gastric, blood, squamosal cell cancers.[7] There are several phytoconstituent that have notable activity against cancer, which is performed in several in vitro and in vivo studies. Kaempferol, caffeic acid, rutin, coumaric acid, apigenin, etc., are some of the known pteridophytic constituents that showed efficacy in the treatment of cancer. In the present study, various pteridophytes have been investigated based on traditional usage as well as phytoconstituents already reported in the literature. *Matteuccia struthiopteris*, *Cyathea contaminans*, *C. phalerata*, and *Abacopteris penangiana* were the cryptograms having good revelation of bioactive constituents as well as have antioxidant, antiproliferative, and anti-inflammatory properties as reported in the literature. The present study aims to investigate the anticancer activity of these plants against the PI3K pathway through the in silico method.

Materials and Methods

Search Criteria and Inclusion Criteria

Some Himalayan pteridophytes were identified by literature search through different databases like PubMed, PubChem (https://pubchem.ncbi.nlm.nih.gov/), Google Scholar, and Science Direct. From this, four Himalayan pteridophytes were chosen whose molecular constituents were identified by gas chromatography–mass spectrometry (GC-MS) analysis.[8–10] These selected pteridophytes have 40 bioactive compounds, whose three-dimensional (3D) structures were prepared through ChemDraw 16.0 program and smile codes were generated for activity prediction and molecular docking.

Protein Preparation

It is an important step for identification and preparation of proteins for docking. In this study, two target proteins (PDB ID: 5OQ4 and PDB ID: 3OAW), which are PI3K inhibitors, were downloaded from the RCSB Protein Data Bank (https:/www.rcsb.org/) and prepared with the help of BIOVIA Discovery Studio Visualizer (https://discover.3ds.com/discovery-studio-visualizer-download), through which water molecules, heteroatoms, and co-ligand were removed from the active position and saved in the .pdb format.[11]

Ligand Preparation

2D structures of recognized 40 phytoconstituents were prepared and the smile codes were generated for predicting activity. Furthermore, the 2D structure of these ligands was converted into a 3D structure and saved in the .pdb Format.[12]

Molecular docking is an effective tool used for the prediction of the binding affinity of ligand molecules with the prepared target protein.[13] Docking helps determine the finest binding alignment of ligands with respective target molecules. From RCSB Protein Data Bank, protein structures (PDB ID) were downloaded and docking was performed using PyRx software (https://pyrx.sourceforge.io/).[14] First, the prepared protein was loaded into PyRx and converted to macromolecules and then selected bioactive compounds were grided. Further, the compound was docked to generate the docking score to predict the binding energies of the protein–ligand complex. The binding energy is represented as a negative value in kilocalories per mole (kcal/mol). The compounds that have good binding affinity are chosen for further analysis and visualization.

Visualization of Protein–Ligand Complex

Visualization of docked protein–ligand complex was done through BIOVIA Discovery Studio Visualizer (https://d9iscover.3ds.com/discovery-studio-visualizer-download), which provides 2D and 3D structures of the complex with interacting bonds and bonding distance. The protein–ligand 2D plots were used to identify various interacting amino acid residues, hydrophilic interactions, hydrophobic interactions, hydrogen bonds, and van der Waal forces,[15] whereas 3D structures help understand the molecular arrangement and how the protein and ligand are bonded to each other.

ADMET Prediction

Tools such as Swiss ADME (http://www.swissadme.ch/) predict pharmacokinetic parameters like P-glycoprotein (Pgp) substrate, gastrointestinal (GI) absorption, blood–brain barrier (BBB) permeation, CYP2D6, CYP3A4, CYP2C9, CTP1A, CYP2C19, and Log Kp (cm/s). Physicochemical parameters like hydrogen bond donors, hydrogen bond acceptors, heavy atoms, number of aromatic heavy atoms,[16] number of rotatable bonds, molecular weight, molecular formula, molar refractivity, and topological polar surface area (TPSA) were also calculated. Drug-likeness parameters like Lipinski's, Veber's, and Ghose's rules were also calculated via Swiss ADME. Toxicity prediction through Prediction of Toxicity II (PROTOX-II) revealed hepatotoxicity, carcinogenicity, immunogenicity, mutagenicity, cytotoxic, and LD-50 value estimate.[17]

Results and Discussion

Earlier research extended the importance of the PI3K pathway in cell division and the mechanism of action is well known. To discover a new potent anticancer agent, 40 phytoconstituents were identified on which molecular docking was done as they are PI3K pathway inhibitors. By molecular docking, the binding affinity of the selected phytoconstituents can be seen. The results for the docking studies are given in ►**Table 1**.

Table 1 Docking score of bioactive compounds

Phytoconstituents	Source	PDB-5OQ4		PDB-3OAW	
		Docking score (kcal/mol)	Interaction with amino acids	Docking score (kcal/mol)	Interaction with amino acids
PC-1	*Matteuccia struthiopteris*	−7.9	ASP A:964, ILE A:968, ILE A:963, THR A:887, LYS A:890, SER A:806, LYS A:807, ALA A:805, TYR A:867, ILE A:879, ILE A:831, MET A:953, ASN A:951, ASP A:950, ALA A:889, GLN A:893	−7.9	ASP A:632, ILE A:1029, SER A:1032, LEU A:564, MET A:1036, CYS A:633, LYS A:1045, PRO A:566, ASN A:565, LYS A:591, PHE A:635, LEU A:567, PRO A:590, SER A:594
PC-2	*Matteuccia struthiopteris*	−8.9	GLN A:291, HIS A:295, TRP A:292, TRP A:201, ARG A:690, PHE A:694, LEU A:657, LEU A:660, GLN A:846, PHE A:698, GLY A:868, ARG A:849	−8.7	GLN A:291, HIS A:295, TRP A:292, TRP A:201, ARG A:690, PHE A:694, LEU A:657, LEU A:660, GLN A:846, PHE A:698, CYS A:869, ARG A:849, GLY A:868, TYR A:787
PC-3	*Matteuccia struthiopteris*	−8.3	MET A:953, TYR A:867, VAL A:882, ILE A:963, ASP A:964, ILE A:879, GLU A:880, MET A:804, PRO A:810, PHE A:961, ILE A:881, ILE A:831, LEU A:838, ASP A:836, ASP A:841, LYS A:833	−8.1	ASP A:422, LEU A:423, LYS A:421, PRO A:424, LEU A:354, TYR A:608, ASN A:639, GLU A:638, PHE A:473, LYS A:425, LEU A:529, VAL A:604, TRP A:355, ALA A:605, GLN A:601
PC-4	*Matteuccia struthiopteris*	−9.3	LYS A:298, GLU A:856, GLN A:291, TYR A:210, ASP A:861, GLU A:852, ASP A:654, HIS A:658, LEU A;657, PHE A:694, ARG A:849, ARG A:690, PRO A:866, TYR A:867, GLY A:868, GLU A:880, TYR A:787, ASP A:788, TRP A:292, ARG A:277, HIS A:295	−10.0	PRO A:208, GLU A:856, THR A:203, ARG A:294, LEU A:211, GLU A:852, LYS A:298, TYR A:210, ASN A:299, HIS A:295, GLN A:291, TRP A:201, ASP A:654, HIS A:658, ARG A:690, PHE A:694, LEU A:657, GLN A:846, ARG A:849, PHE A:698. ILE A:870, CYS A:869
PC-5	*Matteuccia struthiopteris*	−7.4	TRP A:201, TRP A:292, GLN A:291, HIS A:658, ARG A:690, ARG A:849, GLN A:846, PHE A:694, PHE A:698, TYR A:787, GLY A:868, CYS A:869, ILE A:870	−7.3	GLN A:291, HIS A:658, HIS A:295, TRP A:201, TRP A:292, TYR A:787, GLN A:846, LEU A:846, PHE A:698, ARG A:849, PHE A:694, ARG A:690, LEU A:657, ASP A:654
PC-6	*Matteuccia struthiopteris*	−8.7	HIS A:295, TRP A:292, TRP A:201, GLN A:291, ARG A:690, PHE A:694, LEU A:657, LEU A:660, PHE A:698, GLN A:846, ARG A:849, GLY A:868	−8.1	ASN A:639, GLU A:638, TYR A:608, LYS A:425, TRP A:598, ASP A:422, PRO A:424, VAL A:604, GLN A:601, LYS A:421, TRP A:355, LEU A:423, LEU A:529, PHE A:473, PRO A:530
PC-7	*Cyathea contaminans*	−7.6	PHE A:694, PHE A:698, ILE A:870, CYS A:869, ARG A:849, GLY A:868, TYR A:787, ASP A:788, TRP A:201, ARG A:690, LEU A:657, GLN A:846	−7.5	GLN A:893, PHE A:902, ASN A:898, GLN A:892, THR A:899, PHE A:1087, ALA A:889, VAL A:1091, LEU A:1090, GLN A:1083, ASN A:949, ASP A:950
PC-8	*Cyathea phalerata*	−8.3	GLU A:880, TYR A:787, GLY A:868, ARG A:849, PHE A:694, MET A:842, CYS A:869, ILE A:870, GLN A:846, PHE A:698, ARG A:690, ASP A:788, TYR A:867, PRO A:866	−8.3	ASP A:654, TRP A:201, HIS A:658, PHE A:694, ARG A:690, ARG A:849, GLY A:868, GLU A:880, TYR A:787, CYS A:869, ILE A:870, PHE A:698, GLN A:846, LEU A:657
PC-9	*Abacopteris penangiana*	−8.5	TYR A:867, ILE A:963, MET A:953, ILE A:881, VAL A:882,	−8.4	ASN A:639, GLU A:638, PHE A:473, LYS A:425, LEU A:529,

(*Continued*)

Table 1 (*Continued*)

Phytoconstituents	Source	PDB-5OQ4		PDB-3OAW	
		Docking score (kcal/mol)	Interaction with amino acids	Docking score (kcal/mol)	Interaction with amino acids
			GLU A:880, PHE A:961, ILE A:879, ASP A:964, ILE A:831, PRO A:810, SER A:806, MET A:804, LYS A:833		ASP A:637, TRP A:355, PRO A:424, TYR A:608, ALA A:605, GLN A:601, VAL A:604
PC-10	*Abacopteris penangiana*	−7.7	ARG A:849, PHE A:694, PHE A:698, ILE A:870, CYS A:870, CYS A:869, GLY A:868, TYR A:787, ASP A:788, PRO A:789, LEU A:657, ARG A:690, TRP A:201, HIS A:658	−7.7	PHE A:694, PHE A:698, ARG A:849, GLN A:846, ARG A:690, HIS A:658, LEU A:657, TRP A:657, TRP A:201, ASP A:654
PC-11	*Abacopteris penangiana*	−8.2	ILE A:963, ILE A:831, TRP A:812, ALA A:885, MET A:953, ILE A:881, VAL A:882, PHE A:961, GLU A:880, TYR A:867, MET A:804, ILE A:879, ASP A:964, ASP A:836, LYS A:833, ILE A:968	−8.3	ASP A:654, HIS A:658, TRP A:201, PHE A:694, ARG A:849, ARG A:690, GLU A:880, GLY A:868, TYR A:787, CYS A:869, ILE A:870, PHE A:698, GLN A:846, LEU A:657
PC-12	*Abacopteris penangiana*	−8.0	ARG A:849, TYR A:787, GLY A:868, ILE A:870, CYS A:869, PHE A:698, PHE A:694, GLN A:846, ARG A:690, LEU A:657, ASP A:654, HISA:658, TRP A:201	−7.8	CYS A:869, ILE A:870, PHE A:694, PHE A:698, ARG A:849, GLN A:846, HIS A:658, LEU A:657, ASP A:654, TRP A:201, ARG A:690, TYR A:787, GLY A:868

Through docking, 12 compounds were recognized with a good binding affinity toward the PI3K pathway (PDB ID: 5OQ4). Some of these compounds revealed higher binding affinities as compared to the reference compound, that is, 5-(4,6-dimorpholin-4-yl-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine (−8.4 kcal/mol), shown in ►**Fig. 1**. Furthermore, docking studies of the same phytoconstituents on the PI3K pathway (PDB ID: 3OAW) revealed binding affinities higher as compared to the reference compound, that is, 2-amino-4-methyl-8-(1-methylethyl)-6-(1H-pyrazol-4-yl)ptridin-7(8H)-one (−8.1 kcal/mol), shown in ►**Fig. 1**. Among 12 compounds, 4 phytoconstituents (PC-2, PC-4, PC-6, and PC-9) exhibited higher binding affinity toward the cancerous protein (PDB ID: 5OQ4) when compared with reference.

Similarly, in other cancer protein (PDB ID: 3OAW), five phytoconstituents (PC-2, PC-4, PC-8, PC-9, and PC-11) exhibited higher binding affinity when taken into comparison with the reference. Visualization was done through the BIOVIA Discovery Studio Visualizer and results of 3D interactions are shown in ►**Figs. 2** and **3**. The binding affinity and specificity of ligands to their target proteins rely heavily on molecular interactions, particularly those involving acid residues. Amino acid residues and molecular interactions

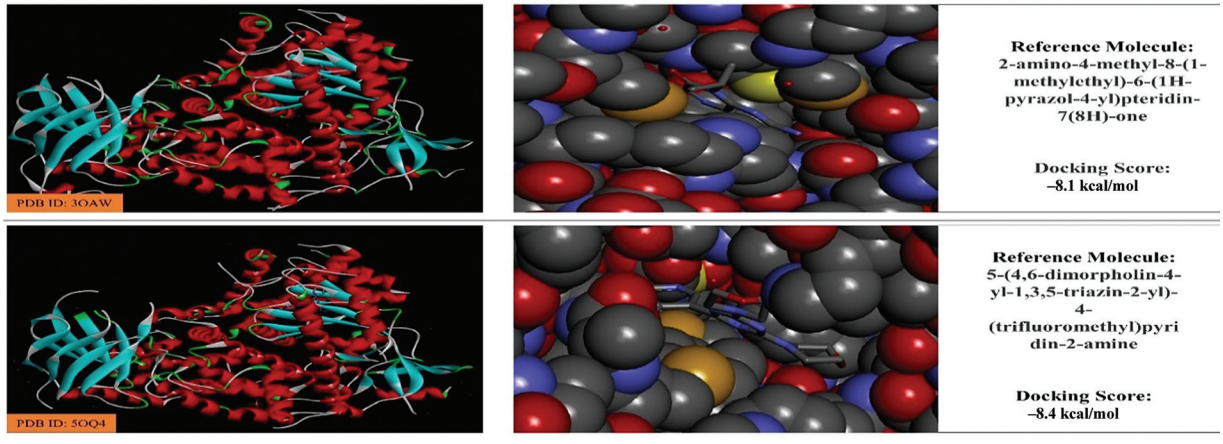

Fig. 1 Structure of proteins of PI3K pathway with their reference compounds and their docking score.

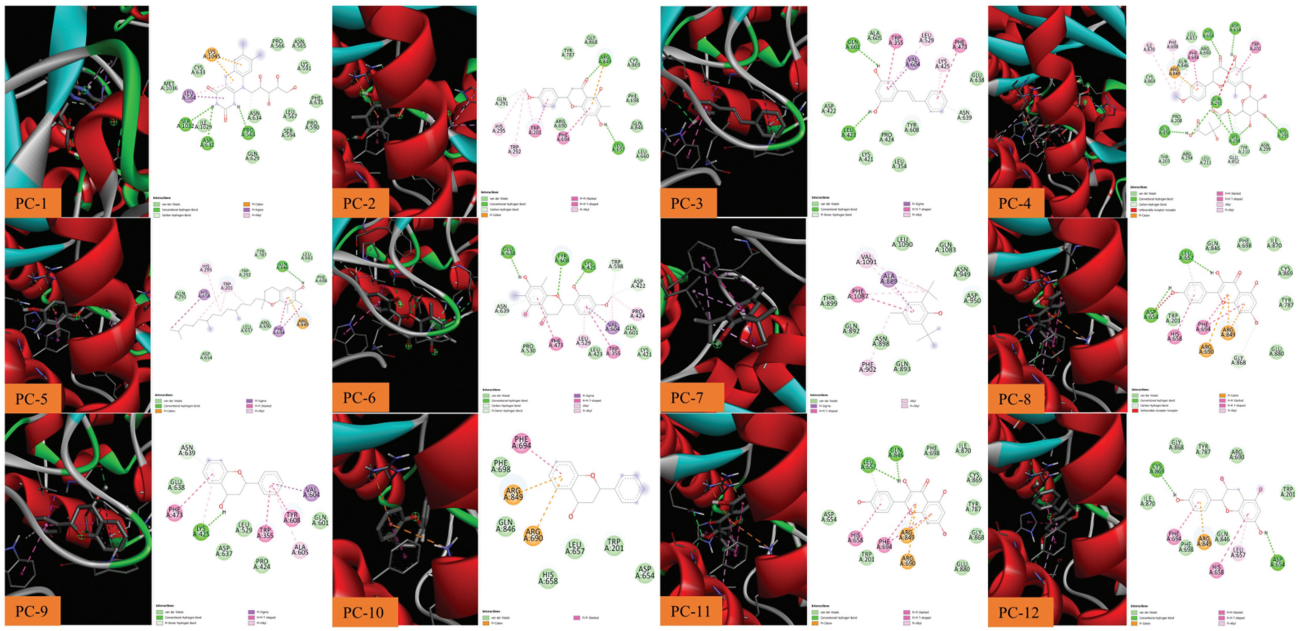

Fig. 2 Amino acid interactions and binding pose of phytoconstituents (PC-1 to PC-12) with PI3K pathway (PDB ID: 3OAW).

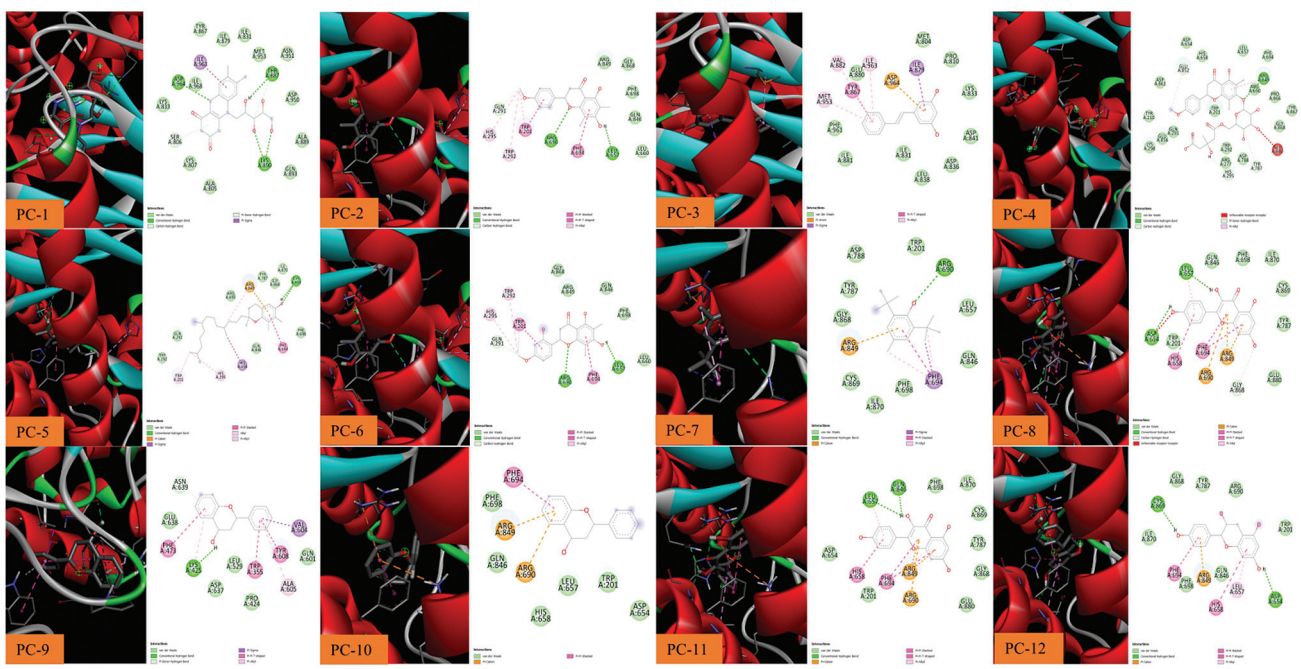

Fig. 3 Amino acid interactions and binding pose of phytoconstituents (PC-1 to PC-12) with PI3K pathway (PDB ID: 5QO4)

are presented in ►**Table 1** for both the target proteins. These interactions are vital for maintaining the structural integrity of proteins, as they can stabilize folded states through electrostatic attractions. The result of the study promotes future research on various pathways of cancer including in vitro and in vivo analyses (►**Tables 2**–**5**).

Conclusion

The PI3K pathway plays an important role in uncontrolled cell growth and cell proliferation, which cause cancer.[16] Out of 40 bioactive constituents from four different pteridophytes including *M. struthiopteris*, *C. contaminans*, *C. phalerata*, and *A. penangiana*, several have shown potential as an anticancer agent. Among them, 12 molecules showed relative binding affinity with both the proteins (PDB ID: 5OQ4 and PDB ID: 3OAW) of PI3K signaling, whereas 4 molecules revealed greater binding score toward PDB ID:5OQ4 proteins and 5 molecules revealed greater binding score toward PDB ID: 3OAW protein as compared to reference compounds. Three molecules named as PC-2 (Matteucinol), PC-4 (Matteuorienate-A), and PC-9 (flavan-4-ol) have higher binding affinity as compared to both the reference compounds revealing their potential for

Table 2 Physicochemical parameters of bioactive compounds

Molecules	Formula	MW	Heavy atoms	Aromatic heavy atoms	Rotatable bonds	H-bond acceptors	H-bond donors	MR	TPSA
PC-1	$C_{17}H_{20}N_4O_6$	376.36	27	14	5	8	5	96.99	161.56
PC-2	$C_{18}H_{18}O_5$	314.33	23	12	2	5	2	85.97	75.99
PC-3	$C_{14}H_{12}O_2$	212.24	16	12	2	2	2	65.86	40.46
PC-4	$C_{30}H_{36}O_{14}$	620.6	44	12	11	14	6	150.03	218.74
PC-5	$C_{28}H_{48}O_2$	416.68	30	6	12	2	1	134.31	29.46
PC-6	$C_{18}H_{18}O_6$	330.33	24	12	2	6	3	87.99	96.22
PC-7	$C_{15}H_{24}NaO$	243.34	17	6	2	1	1	71.97	20.23
PC-8	$C_{15}H_{10}O_6$	286.24	21	16	1	6	4	76.01	111.13
PC-9	$C_{15}H_{14}O_2$	226.27	17	12	1	2	1	66.24	29.46
PC-10	$C_{15}H_{14}O_2$	226.27	17	12	1	2	1	66.24	29.46
PC-11	$C_{15}H_{10}O_6$	286.24	21	16	1	6	4	76.01	111.13
PC-12	$C_{15}H_{14}O_5$	274.27	20	12	1	5	4	72.31	90.15

Abbreviations: MR, molar refractivity; MW, molecular weight; and TPSA, topological polar surface area.

Table 3 Drug-likeness parameters of bioactive compounds

Molecule	Lipinski violations	Ghose violations	Veber violations	Egan violations	Muegge violations
PC-1	0	1	1	1	1
PC-2	0	0	0	0	0
PC-3	0	0	0	0	0
PC-4	3	3	2	1	4
PC-5	1	3	1	1	1
PC-6	0	0	0	0	0
PC-7	0	0	0	0	2
PC-8	0	0	0	0	0
PC-9	0	0	0	0	0
PC-10	0	0	0	0	0
PC-11	0	0	0	0	0
PC-12	0	0	0	0	0

Table 4 Pharmacokinetic parameters of bioactive compounds

Molecule	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log Kp (cm/s)
PC-1	Low	No	No	No	No	No	No	No	−9.63
PC-2	High	Yes	No	Yes	Yes	Yes	Yes	Yes	−5.77
PC-3	High	Yes	No	Yes	No	Yes	No	No	−5.12
PC-4	Low	No	Yes	No	No	No	No	No	−9.62
PC-5	Low	No	Yes	No	No	No	No	No	−1.51
PC-6	High	No	Yes	Yes	No	Yes	Yes	Yes	−6.12
PC-7	High	Yes	Yes	No	No	No	No	No	−4.16
PC-8	High	No	No	Yes	No	No	Yes	Yes	−6.7
PC-9	High	Yes	Yes	No	No	No	Yes	No	−5.76
PC-10	High	Yes	No	No	No	No	Yes	No	−5.66

Table 4 (*Continued*)

Molecule	GI absorption	BBB permeant	Pgp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log Kp (cm/s)
PC-11	High	No	No	Yes	No	No	Yes	Yes	–6.7
PC-12	High	No	Yes	No	No	No	No	No	–7.46

Abbreviations: BBB, blood–brain barrier; GI, gastrointestinal; Pgp, P-glycoprotein.

Table 5 Toxicity prediction of bioactive compounds

Molecule	Hepatotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity
PC-1	0.93(–)	0.75(–)	0.94(–)	0.72(–)	0.75(–)
PC-2	0.69(–)	0.68(–)	0.74(+)	0.82(–)	0.84(–)
PC-3	0.79(–)	0.74(–)	0.92(–)	0.93(–)	0.97(–)
PC-4	0.82(–)	0.8(–)	0.89(+)	0.69(–)	0.7(–)
PC-5	0.93(–)	0.79(–)	0.79(–)	0.95(–)	0.89(–)
PC-6	0.69(–)	0.68(–)	0.97(+)	0.82(–)	0.84(–)
PC-7	0.83(–)	0.71(–)	0.97(–)	0.96(–)	0.92(–)
PC-8	0.68(–)	0.72(–)	0.96(–)	0.52(–)	0.98(–)
PC-9	0.66(–)	0.52(–)	0.99(–)	0.52(+)	0.55(–)
PC-10	0.64(–)	0.54(–)	0.99(–)	0.53(–)	0.71(–)
PC-11	0.68(–)	0.72(–)	0.96(–)	0.52(–)	0.98(–)
PC-12	0.71(–)	0.7(–)	0.98(–)	0.56(–)	0.84(–)

Note: +: active, –: inactive.

promising molecules for cancer therapeutics. ADMET studies revealed their pharmacokinetic and physiochemical profiles. Molecular docking studies frequently examine the effect of particular acid residues on binding affinity, providing information about how mutations may affect protein function. Examining these interactions helps researchers better understand molecular recognition mechanisms and the significance of acid residues in maintaining protein–ligand complexes. Further investigations are warranted to confirm their potentials through various in silico, in vitro, and in vivo approaches. These compounds could contribute significantly in cancer research and in therapeutic uses.

Authors' Contributions

A.K. contributed to planning, structure, compilation, and finalization of the manuscript. M.S. and P.B. contributed equally and were involved in writing, data generation, and completion of the manuscript. S.S. and S.G. were involved in writing, data generation, and completion of the manuscript. S.P. and D.K. were involved in rechecking of data and completion of the manuscript.

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Conflict of Interest

None declared.

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