Evaluation of *Berberis vulgaris* Phytochemicals for Targeting PIM1 Kinase in Prostate Cancer: An *In silico* Approach

Mudassir Alam [a*], Kashif Abbas [a], Mohd Tanjeem Raza [a], Hameim Yahya [a], Mohd Faizan Saifi [a] and Shakir Kamal [b]

[a] Department of Zoology, Aligarh Muslim University, Aligarh, (202002), India.
[b] Department of Biotechnology, Aligarh Muslim University, Aligarh, (202002), India.

Authors' contributions

Article Information

Original Research Article

ABSTRACT

Background: PIM1 kinase is a serine/threonine kinase known for its excessive production in various human cancers, particularly prostate cancer. This enzyme promotes prostate cancer development by adding phosphate groups to cellular components, preventing programmed cell death (apoptosis), and facilitating cell cycle progression. Thus, PIM1 kinase could serve as a therapeutic target for the treatment of prostate cancer. Phytochemicals present in *Berberis vulgaris* possess anti-cancerous properties. Current study investigated the phytochemicals present in *Berberis* which could inhibit PIM1 kinase, thus serving as a drug candidate.
Methods: In this study, various computational tools were employed to assess the potential of

_____

*Corresponding author: E-mail: syedalamalig@gmail.com;

phytochemicals present in the root extract of *B. vulgaris*. The work employed computational tools-molecular docking, pharmacokinetics, ADME, toxicity, and biological activity prediction to elucidate top potent phytochemicals.

Results: The computational analysis revealed promising potential in the phytochemicals found in *B. vulgaris*, particularly berberine, columbamine, isocorydine, and oxyberberine, as inhibitors of PIM1 kinases. This suggests that these root extract compounds of *B. vulgaris* may serve as an effective anti-cancer agent by inhibiting PIM1 kinase activity.

Conclusion: The identified compounds, berberine, columbamine, isocorydine, and oxyberberine, show promising candidates for further research and development of anti-cancer therapies targeting PIM1. They showed good docking scores and drug-likeness properties and exhibited biological activity of anticarcinogenic, antineoplastic, Pim1 kinase inhibitor, and Prostate cancer treatment.

1. INTRODUCTION

Prostate cancer (PCa) is a highly prevalent cancer in males, making it one of the most frequently diagnosed cancers, with approximately 1.1 million cases reported annually on a global scale [1]. The PIM family comprises closely related serine/threonine kinases: PIM1, PIM2, and PIM3. PIM1 exists in two isoforms (33 and 44 kDa), while PIM2 has three isoforms (34, 37, and 40 kDa), and PIM3 has one isoform [2]. The functional distinctions between the longer isoform (44 kDa) and the shorter isoform (33 kDa) of PIM1 are noteworthy. PIM1L, the 44 kDa variant, is predominantly situated on the cell's outer membrane, whereas PIM1S, the 33 kDa variant, is mainly located within the nucleus. An intriguing observation is that PIM1L interacts with the SH3 (SRC homology 3) domain of the Etk tyrosine kinase. This interaction has been linked to chemotherapeutic drug resistance in models of PCa cells [3]. Elevated levels of PIM-1 are the direct result of oncogenic fusion proteins and active signal transduction pathways and can contribute to genomic instability and facilitate the development of cancerous growth. PIM-1 kinase phosphorylates multiple cellular substrates to inhibit apoptosis and promote cell cycle progression. It can also phosphorylate the androgen receptor (AR), thereby regulating AR degradation and function, indicating its involvement in castration-resistant PCa [4]. In many instances, the advancement of PCa is relentless, resulting in increasing levels of prostate-specific antigen (PSA) in blood, even when serum testosterone is reduced to castration levels (<50 ng/dL). This condition is referred to as castration-resistant prostate cancer (CRPC) [5]. The significant increase in MYC protein levels has previously been shown to correlate with elevated PIM1 protein levels during androgen ablation therapy. Moreover, when examining the mouse xenograft model of human

PCa, the PIM1 has been noted to improve the tumorigenic effects produced by MYC. In addition, the coexpression of PIM1 and MYC in human PCa with higher Gleason scores has been associated suggesting that these oncoproteins collaborate to promote the progression of advanced PCa [6]. PIM1 kinase has emerged as a promising therapeutic target for treating this disease. Inhibitors of PIM1 kinase have been developed, and early-phase clinical trials have shown the potential of using these inhibitors as therapeutic agents for PCa; these inhibitors are designed to target PIM1 and specifically minimize off-target effects on other kinases [7]. Among the various species of *Berberis*, *B. vulgaris* and *B. stata* have received the most extensive research attention. *Berberis* plants contain a significant group of compounds known as alkaloids, constituting a diverse array of secondary metabolites with potent biological activities such as anti-inflammatory [8], antioxidant [9], and anti-cancer [10]. Studies have indicated that berberine, an isoquinoline alkaloid isolated from the roots and bark of the *Berberis* plant, hinder the movement and penetration of chondrosarcoma cells in humans by reducing the expression of the αvβ3 integrin through the modulation of protein kinase C (PKC δ), c-Src, and AP-1 [11]. It also suppresses migration and invasion of PCa cells through the suppression of epithelial–mesenchymal transition (EMT)-related genes [12]. Phytochemicals in B. vulgaris can induce apoptosis, inhibit cell proliferation, and modulate the immune system, which is crucial for managing PCa [13]. The research seeks to assess the potential of phytochemicals as inhibitors of PIM1 kinase against the 6MT0 structure (Crystal structure of human Pim-1 kinase in complex with a

quinazolinone-pyrrolodihydropyrrolone inhibitor). Various computational methodologies, such as molecular docking and analysis of physicochemical properties, pharmacokinetics, absorption, distribution, metabolism, as well as toxicological and biological activity predictions, were employed to elucidate and evaluate the effectiveness of these phytochemicals.

2. MATERIALS AND METHODS

2.1 Protein Preparation

The study utilized a Database of proteins (https://www.rcsb.org/) to access the PDB file structure of human Pim-1 kinase, identified by its unique PDB ID: 6MT0. The Protein Data Bank (PDB) is a comprehensive repository housing data on experimental proteins and nucleic acid structures. Removing water molecules from protein preparation was effectively carried out using PyMOL [14]. PyMOL is an open-source software tool that generates molecular visuals, making it an excellent choice for this docking preparation.

2.2 Ligand Retrieval and Preparation

The molecular structures of B. vulgaris compounds were retrieved from the PubChem database in sdf format. PubChem database is a valuable resource that provides detailed information about chemical compounds, including their structures, formulas, and molecular weights. In this study, OpenBabel [15] tool from PyRx 0.8 [16] was used to prepare the ligands for further analysis. OpenBabel is a software tool commonly used for ligand preparation in molecular docking studies. The ligand energy was minimized using the mmff94 force field to achieve stable and reliable structures for the ligands. The ligands in sdf file format were converted to pdbqt format, which made them executable and ready for docking simulations and other computational analyses. This conversion step ensured compatibility and facilitated the subsequent molecular modelling and ligand-receptor interaction studies.

2.3 Molecular Docking

Molecular docking analysis focused on the interaction between *Berberis* compounds as ligands and Pim-1 kinase as the target macromolecule. Present study employed the

AutoDock Vina [17], available in PyRx 0.8, to carry out molecular docking simulations for this investigation. This allowed them to explore the potential binding interactions between the ligands and the macromolecule and gain insights into their binding affinities and orientations.

2.4 Visualization of Docking Results

Following molecular docking, study identified the protein-ligand complex with the most favourable negative score, indicating a strong affinity. This optimal binding pose was selected for further analysis using Discovery Studio 4.5 [18]. This facilitated visualization and exploration of binding mode, allowing scrutiny of ligand-receptor interactions. This in-depth analysis elucidates crucial molecular interactions governing the ligand's high binding affinity to the Pim-1 kinase protein.

2.5 Physiochemical Properties Prediction

Physiochemical attributes of all compounds were assessed using the DruLito program [19]. This evaluation encompassed the determination of multiple parameters essential for characterizing the drug-likeness of a compound. Additionally, instances where the compounds violated Lipinski's rule 5 [20] were identified. Lipinski's rule 5 outlines the crucial criteria that orally active drugs must adhere to to demonstrate their pharmacological effectiveness.

2.6 Absorption, Metabolism, and Distribution

The absorption, distribution, and metabolism predictions for the chosen compound were assessed through the application of admetSAR [21]. An online tool accessible at http://lmmd.ecust.edu.cn/admetsar2/ analysed a diverse set of parameters. These parameters played a crucial role in the prediction process, contributing to a comprehensive understanding of the compound's absorption, distribution, and metabolism characteristics.

2.7 Prediction of Toxicity

The toxicity assessment of the selected compounds was carried out using ProTox-II (https://tox-new.charite.de/protox_II/index.php?site=compound_input) [22]. This web-based platform serves as a virtual toxicity laboratory, enabling the prediction of various toxicological outcomes associated with a chemical's structure. The system employs computational models trained

on real-world data (from in vitro or in vivo experiments) to anticipate the hazards posed by existing substances.

2.8 Biological Activity of the Compound

The PASS web server (http://www.pharmaexpert.ru/passonline) [23] was employed to predict the biological activity of the chosen phytochemicals. It uses a ligand-based approach to analyze the structure-activity relationships and provides an estimated biological activity profile as an output. Utilizing complex atom neighbour descriptors, the PASS analysis aids in comprehending a drug's effects through its molecular formula, indicating that its biological function is purely determined by its chemical arrangement.

3. RESULTS AND DISCUSSION

3.1 Docking Score of the Compounds

The docking study involved utilizing the 3D crystal structure of pim-1 kinase, identified by PDB ID: 6MT0. Autodock Vina, accessed through PyRx 0.8, served as the tool for analysis. To prepare both the protein and the ligand for docking, UCSF Chimaera's Dockprep feature was employed. The protein was transformed into a macromolecule, and the chosen compounds underwent initial minimization using the mmff94 forcefield. Subsequently, the compounds were converted to pdbqt format using OpenBabel within PyRx. For the docking procedure, a grid box with dimensions of 48.92 Å × 55.66 Å × 46.56 Å was employed, centred at coordinates (-39.18, -13.23, -0.41). The exhaustiveness level was set to the default value of 8. Specific details regarding the ligands or compounds and their respective docking scores are provided in Table 1. The most favourable docking poses and their interactions with the target protein are visually represented in Fig. 1(a-h). Notably, each of the chosen compounds from the *Berberis* extract demonstrated promising docking scores, indicating their potential efficacy in binding to the pim-1 kinase.

Table 1. Molecular weights, PubChem IDs, and docking scores (kcal/mol) of ligands Aromoline, Berbamine, Berberine, Columbamine, Isocorydine, Oxyberberine, Palmatine, and Tejedine

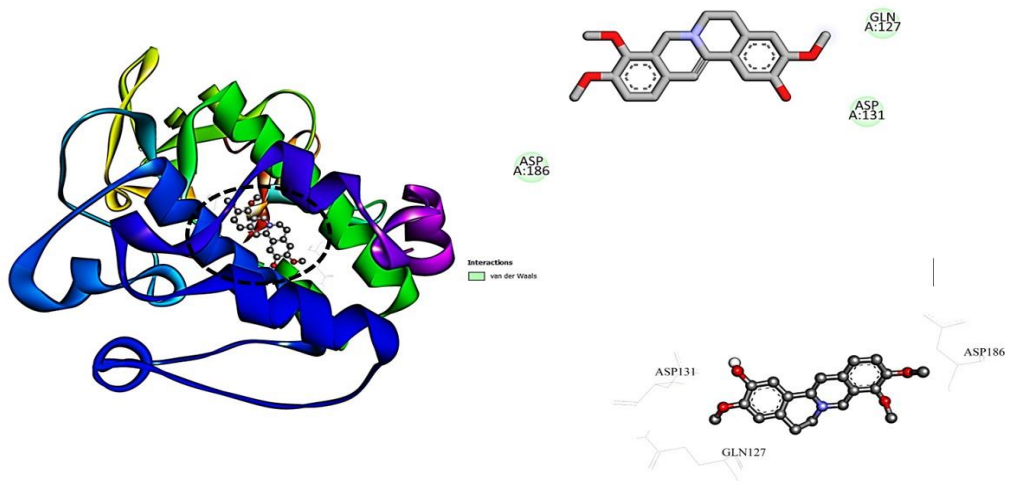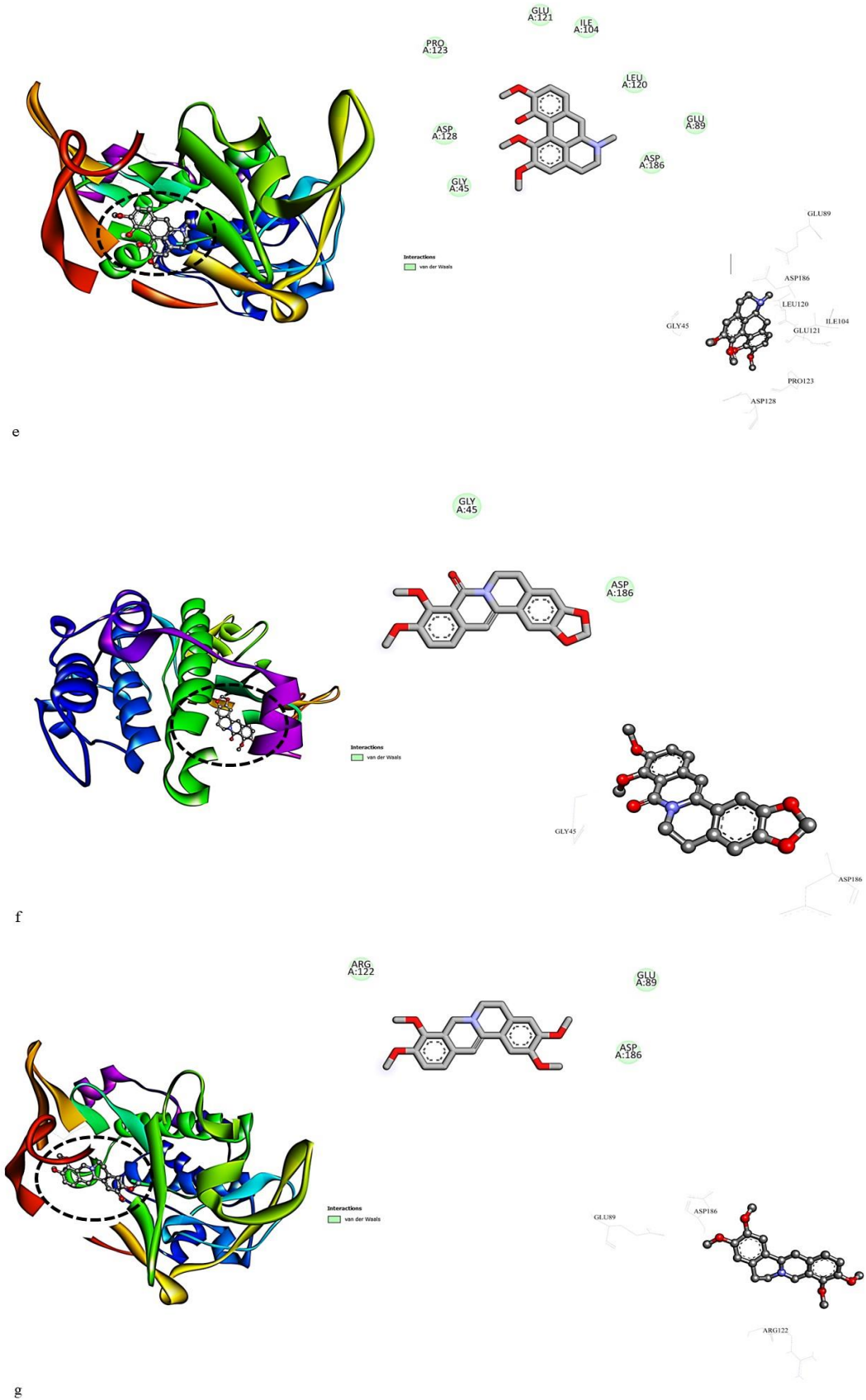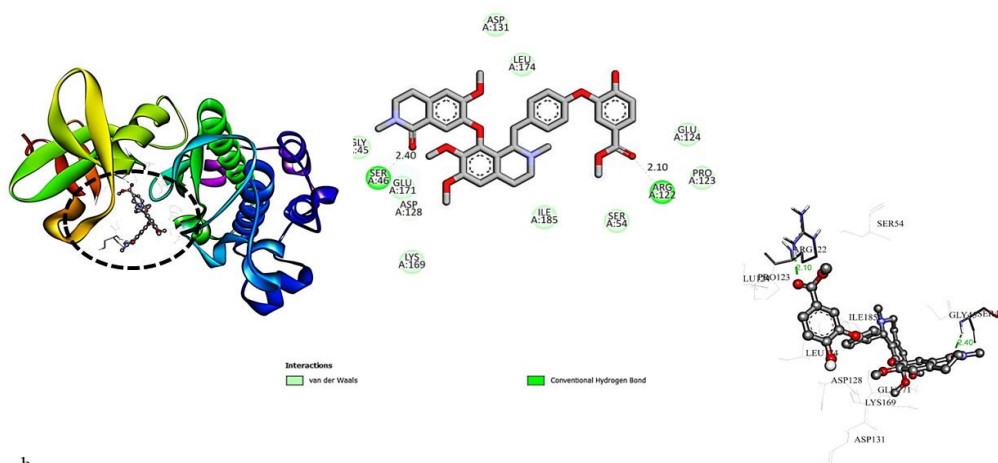| Ligands	Molecular weight	PubChem ID	Docking score (kcal/mol)
Aromoline	594	362574	-9.0
Berbamine	608	275182	-8.6
Berberine	336	2353	-9.2
Columbamine	338	72310	-8.3
Isocorydine	341	10143	-9.1
Oxyberberine	351	11066	-9.3
Palmatine	352	19009	-8.0
Tejedine	668	72795147	-8.4

a

b

c

d

e

f

g

h
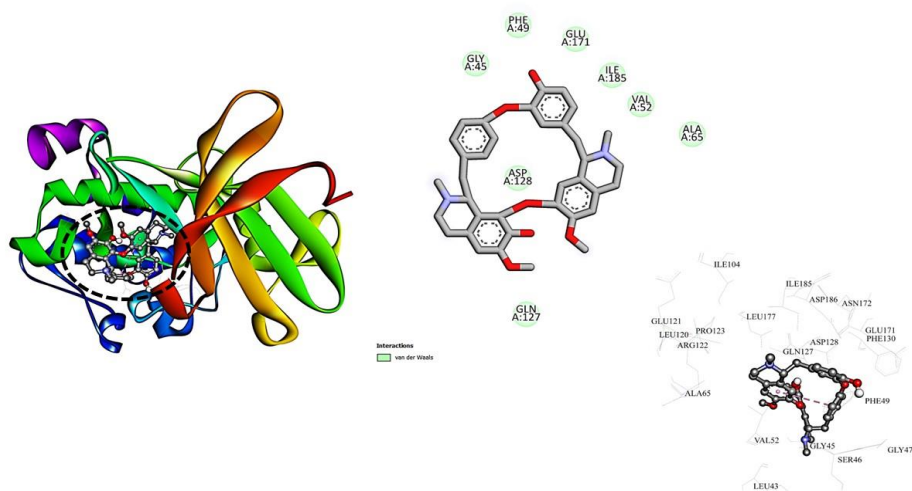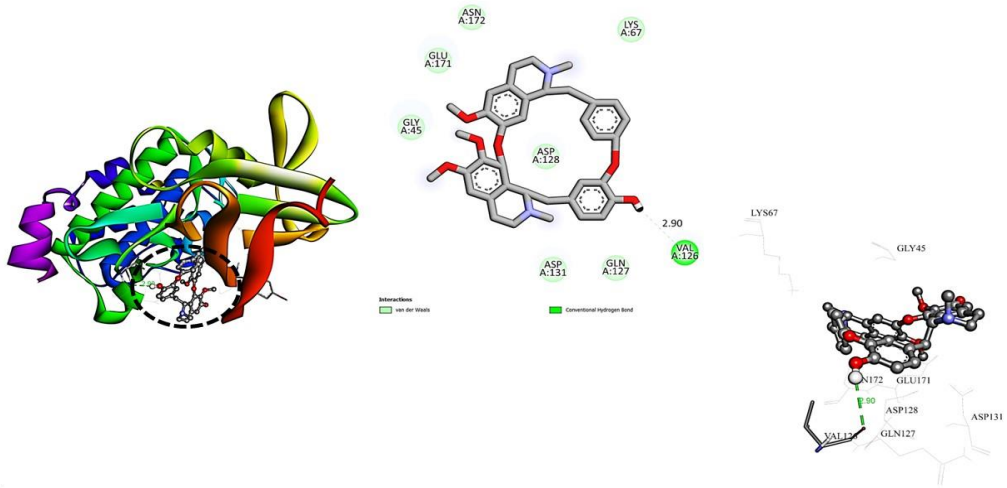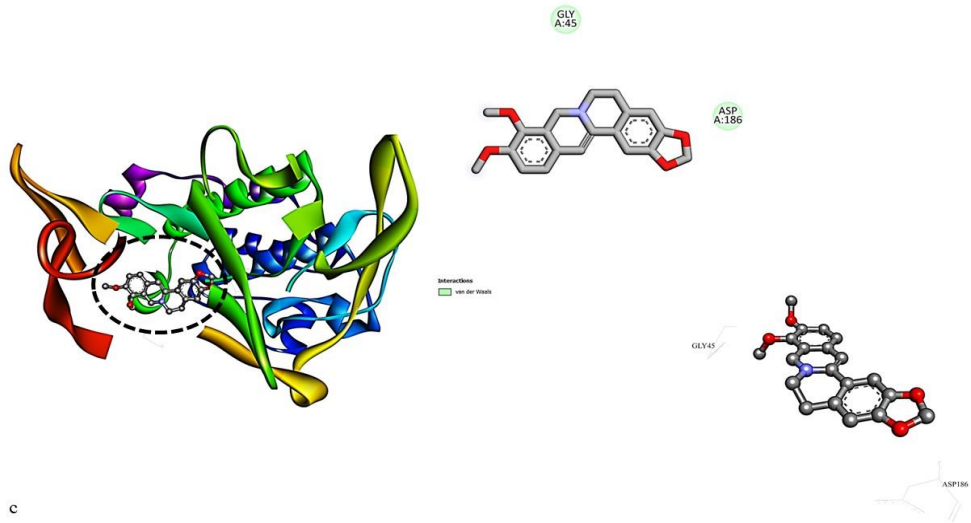
Fig. 1. (a-h): Protein-ligand interaction: (a) Aromoline (b) Berbamine (c) Berberine (d) Columbamine (e) Isocorydine (f) Oxyberberine (g) Palmatine (h) Tejedine

3.2 Protein-Ligand Interaction

The interactions between the protein and ligands were governed by van der Waals forces and hydrogen bonding, both of which played pivotal roles. A succinct summary of these interactions is presented in Table 2. For instance, in the case of the aromoline molecule, van der Waals interactions were identified with Gly45, Phe49, Val55, Ala65, Gln127, Asp128, Glu171, and Ile185. Berbamine demonstrated van der Waals interactions with Gly45, Lys67, Gln127, Asp128, Asp131, Gln171, and Asn172, accompanied by the establishment of a hydrogen bond with Val126, characterized by a bond length of 2.90 Å. Conversely, berberine participated in van der Waals interactions with Gly45 and Asp186, while no hydrogen bonds were formed with amino acids. Columbamine manifested van der Waals interactions with Gln127, Asp131, and Asp186. Isocorydine's van der Waals interactions were evident with Gly45, Glu89, Ile104, Leu120, Gln121, Pro123, Asp128, and Asp186. Oxyberberine engaged in van der Waals interactions with Gly45 and Asp186. Meanwhile, palmatine exhibited van der Waals interactions with Glu89, Arg122, and Asp186. Lastly, tejedine displayed van der Waals interactions with Gly45, Ser54, Pro123, Gln124, Asp128, Asp131, Lys169, Gly171, Leu174, and Ile185. It also formed hydrogen bonds with Ser461 (2.40 Å) and Arg122 (2.10 Å).

Table 2. Interactions and bond lengths (Å) observed between the ligands and their respective interacting residues, including van der Waals interactions and hydrogen bonding

Ligands	Van der Waals interaction	H- bonding	Bond length (Å)
Aromoline	Gly45, Phe49, Val55, Ala65, Gln127, Asp128, Glu171, Ile185	--	--
Berbamine	Gly45, Lys67, Gln127, Asp128, Asp131, Gln171, Asn172	Val126	2.90
Berberine	Gly45, Asp186	--	--
Columbamine	Gln127, Asp131, Asp186	--	--
Isocorydine	Gly45, Glu89, Ile104, Leu120, Gln121, Pro123, Asp128, Asp186	--	--
Oxyberberine	Gly45, Asp186	--	--
Palmatine	Glu89, Arg122, Asp186,	--	--
Tejedine	Gly45, Ser54, Pro123, Gln124, Asp128, Asp131, Lys169, Gly171, Leu174, Ile185	Ser461 Arg122	2.40 2.10

3.3 Evaluation of Pharmacological and Toxicological Properties

The assessment of drug-likeness in phytochemicals derived from *Berberis* root extract involved a thorough analysis of ADME/T properties using the DruLito program. This encompassed the application of drug similarity rules, including Lipinski's rule, to discern suitable compounds. The summarized outcomes are presented in Tables 3 and 4, with the latter offering insights into the anticipated absorption, distribution, and metabolism via the admetSAR server. The pivotal criteria influencing a compound's potential as a drug candidate, encompassing topological polar surface area (TPSA), molecular weight (MW), sp3 hybridization, logS (solubility), and xlog3 value,

were considered. A comparative representation of observed compound values against standard

benchmarks is visually depicted in Fig. 2. Aromoline and Berbamine share characteristics of high molecular weight, hydrophobicity, and a violation of Lipinski's Rule of Five. In contrast, Berberine exhibits a lower molecular weight, reduced hydrophobicity, and adherence to Lipinski's Rule of Five. Columbamine aligns with Berberine in terms of molecular weight and compliance with Lipinski's Rule of Five. Isocorydine and Oxyberberine display moderate molecular weight, lower hydrophobicity, and adherence to Lipinski's Rule of Five. Palmatine, akin to Berberine, exhibits a moderate molecular weight and compliance with Lipinski's Rule of Five. Tejedine stands apart due to its higher molecular weight, increased hydrogen bond acceptors, low bioavailability, and a violation of Lipinski's Rule of Five. Consequently, only compounds meeting standardized criteria underwent further analysis.
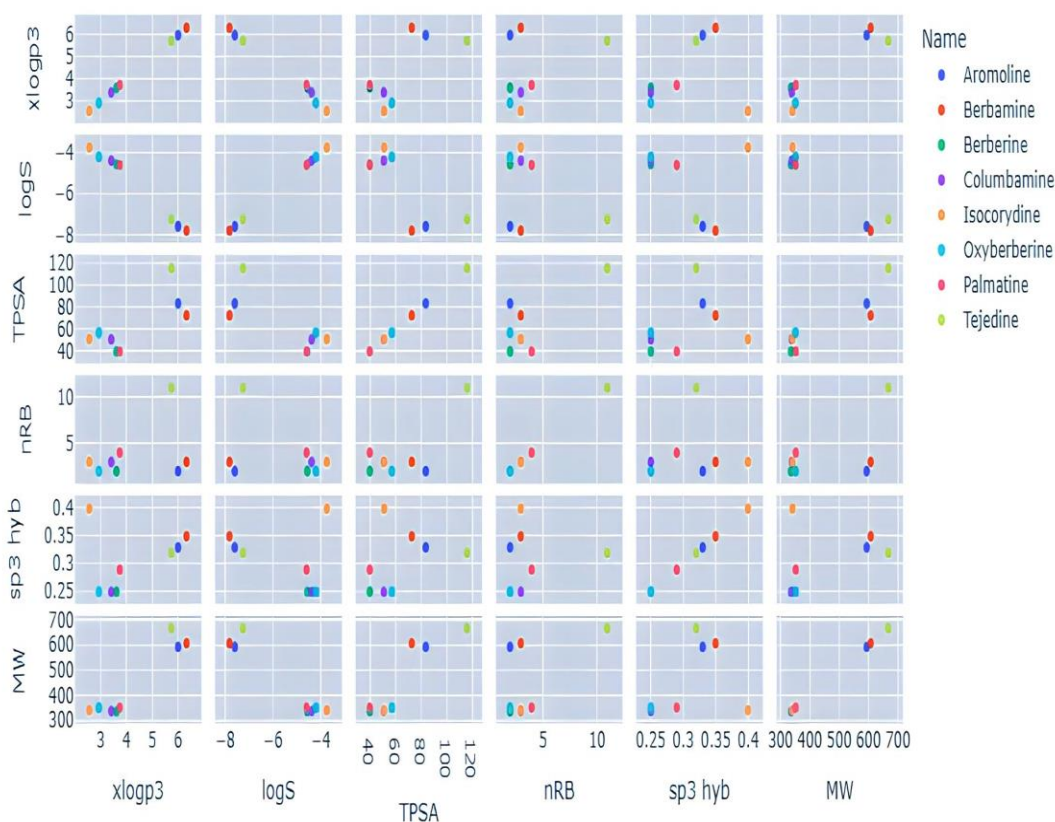

Fig. 2. Comparative representation of observed values for topological polar surface area (TPSA), molecular weight (MW), sp3 hybridization, logS (solubility), xlogP3, and nRB in compounds, juxtaposed against standardized benchmarks. The specified benchmarks are as follows: TPSA (20-130 Å2), logS (<6), sp3 hybridization (>0.25), MW (<500), nRB (<9), and xlogP3 (-0.7 to +5.0)

Table 3. Assessment of pharmacological properties of compounds assessed using DruLito

Ligands	PUBCHEM ID	MW	xlogp3	logS	HBA	HBD	TPSA	nRB	SP3 HYB	GI AB.	DL
Aromoline	362574	594.27	6.01	-7.59	8	2	83.86	2	0.33	HIGH	NO
Berbamine	275182	608.29	6.34	-7.81	8	1	72.86	3	0.35	HIGH	NO
Berberine	2353	336.12	3.62	-4.55	4	0	39.93	2	0.25	HIGH	YES
Columbamine	72310	338.14	3.42	-4.37	4	1	50.93	3	0.25	HIGH	YES
Isocorydine	10143	341.16	2.57	-3.73	5	1	51.16	3	0.4	HIGH	YES
Oxyberberine	11066	351.11	2.94	-4.19	6	0	57.23	2	0.25	HIGH	YES
Palmatine	19009	352.15	3.75	-4.58	4	0	39.93	4	0.29	HIGH	YES
Tejedine	72795147	668.27	5.75	-7.25	11	1	116.23	11	0.32	LOW	NO

MW: molecular weight; xlogp3: lipophilicity; logS: solubility; HBA: Hydrogen bond acceptor; HBD: Hydrogen bond donor; TPSA: topological polar surface area; nRB: number of rotatable bonds; SP3 HYB: Sp3 hybridization; GI AB.: Gastrointestinal absorption; DL: Drug-likeness

Table 4. Absorption, distribution and metabolism profiles of the selected compounds. Parameters include absorption characteristics such as blood-brain barrier permeability and human intestinal absorption, distribution focusing on subcellular localization, and metabolism involving cytochrome P450 (CYP) enzyme interactions

Parameters	Berberine	Columbamine	Isocorydine	Oxyberberine	Palmatine
ABSORPTION					
BB-barrier	+	-	+	+	-
Human intestinal absorption	+	+	+	+	+
P-glycoprotein substrate	-	-	-	-	-
P-glycoprotein inhibitor	+	-	-	+	+
DISTRIBUTION					
Subcellular localization	Mitochondria	Mitochondria	Mitochondria	Mitochondria	Mitochondria
METABOLISM					
CYP2C9 substrate	Non-substrate	Non-substrate	Substrate	Non-substrate	Non-substrate
CYP2D6 substrate	Non-substrate	Substrate	Substrate	Non-substrate	Substrate
CYP3A4 substrate	Non-substrate	Non-substrate	Non-substrate	Substrate	Substrate
CYP1A2 inhibition	Inhibitor	Non-inhibitor	Inhibitor	Inhibitor	Non-inhibitor
CYP2C9 inhibition	Non-inhibitor	Non-inhibitor	Non-inhibitor	Inhibitor	Non-inhibitor
CYP2D6 inhibition	Inhibitor	Inhibitor	Inhibitor	Non-inhibitor	Inhibitor
CYP2C19 inhibition	Non-inhibitor	Non-inhibitor	Non-inhibitor	Inhibitor	Non-inhibitor

The toxicity of compounds, including Berberine, Columbamine, Isocorydine, Oxyberberine, and Palmatine, was assessed using the ProTox-II server. The results, summarized in Table 5, indicate that these compounds are considered inactive or have weak/low effects across various parameters, suggesting a relatively low level of concern regarding carcinogenicity, mutagenicity, cytotoxicity, immunotoxicity, and androgen receptor activity. This in silico approach provided valuable insights for the safety evaluation of chemical compounds.

Table 5. Toxicological assessment of compounds using the PROTOX-II server, parameters include carcinogenicity, mutagenicity, cytotoxicity, immunotoxicity and androgen receptor activities

Parameters	Berberine	Columbamine	Isocorydine	Oxyberberine	Palmatine
Carcinogenicity	Not present	Not present	Not present	Not present	Not present
Mutagenicity	Not present	Not present	Not present	Not present	Not present
Cytotoxicity	Not present	Not present	Not present	Not present	Not present
Immunotoxicity	Weak/low	Weak/low	Weak/low	Weak/low	Weak/low
Androgen receptor	Not present	Not present	Not present	Not present	Not present

Table 6. Biological activity prediction of compounds (Pa = probability to be active; Pi = probability to be inactive)

Ligand names	Biological action	Pa	Pi
Berberine	Anticarcinogenic	0.192	0.129
	Antineoplastic	0.781	0.014
	Pim1 kinase inhibitor	0.154	0.075
	Prostate cancer treatment	0.237	0.060
Columbamine	Anticarcinogenic	0.300	0.058
	Antineoplastic	0.785	0.014
	Pim1 kinase inhibitor	0.138	0.104
	Prostate cancer treatment	0.186	0.082
Isocorydine	Anticarcinogenic	0.170	0.158
	Antineoplastic	0.234	0.198
	Pim1 kinase inhibitor	0.279	0.172
	Prostate cancer treatment	----	----
Oxyberberine	Anticarcinogenic	0.210	0.109
	Antineoplastic	0.509	0.069
	Pim1 kinase inhibitor	0.143	0.093
	Prostate cancer treatment	0.383	0.024
Palmatine	Anticarcinogenic	0.229	0.095
	Antineoplastic	0.800	0.012
	Pim1 kinase inhibitor	--	--
	Prostate cancer treatment	0.169	0.097

3.4 Compounds Biological Activity Predictions

PASS webserver was utilized to validate the anticipated biological effects. The investigation demonstrated that compounds within the range of series 1–5 exhibit properties that combat carcinogenesis and counteract neoplastic growth. All compounds except molecule 5 can inhibit PIM1 kinase, with the added benefit of prostate cancer treatment for all except molecule 5. The Pa values, ranging from 0.170 to 0.300 for anticarcinogenic and 0.234 to 0.800 for antineoplastic properties, indicate the likelihood of these effects. Similarly, for PIM1 kinase inhibition, the Pa values range from 0.000 to 0.279, while for prostate cancer treatment, the range is between 0.000 and 0.383. When the Pa value surpasses the Pi value, it indicates the probable presence of specified biological activity. The summarized outcomes are presented in Table 6.

4. DISCUSSION

The docking study on the pim-1 kinase using Autodock Vina and PyRx 0.8 provided valuable insights into the interactions between selected compounds from *Berberis* root extract and the target protein. The chosen compounds, including Aromoline, Berbamine, Berberine, Columbamine, Isocorydine, Oxyberberine, Palmatine, and Tejedine, demonstrated promising docking scores, suggesting their potential efficacy in binding to the pim-1 kinase. The study revealed that van der Waals interactions and hydrogen bonding played crucial roles in binding the compounds to the pim-1 kinase. The specific interactions with amino acid residues, such as Gly45, Phe49, Val55, Ala65, Gln127, Asp128, Glu171, and Ile185, highlighted the molecular details of the binding mode for each compound. Notably, hydrogen bonding interactions were observed in some compounds, further contributing to stabilizing the protein-ligand complexes. Assessment of the drug-likeness of the phytochemicals was done using the DruLito program. The evaluation included TPSA, MW, sp3 hybridization, logS, and xlog3 values. The results indicated that while some compounds exhibited high molecular weight and hydrophobicity characteristics, adherence to Lipinski's Rule of Five varied among the compounds. The phytochemicals which exhibited drug-likeness were further tested to ensure the safety and suitability of the compounds. Toxicity predictions were made using the Protox II server. The results suggested that all selected compounds, including Berberine, Columbamine, Isocorydine, Oxyberberine, and Palmatine, were considered inactive or had weak/low effects across various toxicity parameters, indicating a relatively low level of concern regarding carcinogenicity, mutagenicity, cytotoxicity,

immunotoxicity, and androgen receptor activity. The biological effects of the compounds were validated using the PASS web server, which demonstrated that the compounds, namely berberine, columbamine, Isocorydine, Oxyberberine, and palmatine, exhibited properties that combat carcinogenesis and counteract neoplastic growth. Most compounds showed the ability to inhibit PIM1 kinase, with the additional benefit of prostate cancer treatment for all except one molecule.

5. CONCLUSION

PIM1 kinase, prominently expressed in various cancers such as prostate cancer, necessitates a meticulous examination of its underlying cellular mechanisms. Its role in survival pathways and unregulated proliferation compels a thorough investigation. Such scrutiny provides a promising avenue for therapeutic exploration, holding the potential to impede the progression of prostate cancer. *B. vulgaris*, a botanical repository rich in diverse natural compounds, emerges as a noteworthy candidate. Many potential phytochemicals with anticancer properties are identified within its root extract. In conclusion, a comprehensive analysis integrating molecular docking, drug-likeness assessment, toxicity prediction, and validation of biological effects suggests that compounds derived from *Berberis* root extract, including Berberine, Columbamine, Isocorydine, Oxyberberine, and Palmatine, exhibit promise as potential inhibitors of PIM1 kinase, thereby possessing anticarcinogenic and antineoplastic properties. Nevertheless, further experimental validation and in vitro and in vivo studies are strongly suggested to affirm their therapeutic potential in the domain of prostate cancer drug development.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Rawla P. Epidemiology of Prostate Cancer. World J Oncol. 2019;10(2):63-89.

2. Luszczak S, Kumar C, Sathyadevan VK, Simpson BS, Gately KA, Whitaker HC, Heavey S. PIM kinase inhibition: co-targeted therapeutic approaches in prostate cancer. Signal Transduct Target Ther. 2020;5(1):7

3. Nock S, Karim E, Unsworth AJ. Pim Kinases: Important Regulators of Cardiovascular Disease. Int J Mol Sci. 2023;24(14):11582.

4. Markou A, Tzanikou E, Strati A, Zavridou M, Mastoraki S, Bournakis E, Lianidou E. PIM-1 Is Overexpressed at a High Frequency in Circulating Tumor Cells from Metastatic Castration-Resistant Prostate Cancer Patients. Cancers (Basel). 2020;12(5):1188.

5. Pantel K, Hille C, Scher HI. Circulating Tumor Cells in Prostate Cancer: From Discovery to Clinical Utility. Clin Chem. 2019;65(1):87-99.

6. Eerola SK, Kohvakka A, Tammela TLJ, Koskinen PJ, Latonen L, Visakorpi T. Expression and ERG regulation of PIM kinases in prostate cancer. Cancer Med. 2021;10(10):3427-3436.

7. Jeyapal GP, Chandrasekar MJN, Krishnasamy R, Selvaraj J, Mohammad M, Nanjan MJ. Potential Pharmacological Inhibitors of Pim Kinase Under Clinical Trials. Anticancer Agents Med Chem. 2018;(8):1100-1114.

8. Jahan F, Alvi SS, Islam MH. Berberis aristata and its secondary metabolites: Insights into nutraceutical and therapeutical applications. Pharmacological Research - Modern Chinese Medicine. 2022;5:100184.

9. Neag MA, Mocan A, Echeverría J, Pop RM, Bocsan CI, Crişan G, Buzoianu AD. Berberine: Botanical Occurrence, Traditional Uses, Extraction Methods, and Relevance in Cardiovascular, Metabolic, Hepatic, and Renal Disorders. Front Pharmacol. 2018;9:557.

10. Mustafa K, Mohamed H, Shah AM, Yu S, Akhlaq M, Xiao H, Li S, Naz T, Nosheen S, Bai X, Song Y. In Vitro Anticancer Potential of Berberis lycium Royle Extracts against Human Hepatocarcinoma (HepG2) Cells. Biomed Res Int. 2020 Oct;2020:8256809.

11. Koutova D, Kulhava M, Havelek R, Majorosova M, Královec K, Habartova K, Hošťálková A, Opletal L, Cahlikova L, Řezáčová M. Bersavine: A Novel Bisbenzylisoquinoline Alkaloidwith Cytotoxic, Antiproliferative and Apoptosis-

Inducing Effects on Human Leukemic Cells. Molecules. 2020;25(4):964.

12. Samadi P, Sarvarian P, Gholipour E, Asenjan KS, Aghebati-Maleki L, Motavalli R, Hojjat-Farsangi M, Yousefi M. Berberine: A novel therapeutic strategy for cancer. IUBMB Life. 2020 Oct;(10):2065-2079.

13. Paudel S, Mishra N, Agarwal R. Phytochemicals as Immunomodulatory Molecules in Cancer Therapeutics. Pharmaceuticals (Basel). 2023;16(12): 1652.

14. Schrödinger L, DeLano W. PyMOL. 2020. Available from:http://www.pymol.org/pymol.

15. O'Boyle NM, Banck M, James CA, Morley C, Vandermeersch T, Hutchison GR. Open Babel: An open chemical toolbox. J Cheminform. 2011;3(1):1-4.

16. Dallakyan S, Olson AJ. Small-molecule library screening by docking with PyRx. Chem Biol Methods Protoc. 2015:243-50.

17. Trott O, Olson AJ. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. J Comput Chem. 2010;31(2):455-61.

18. Discovery Studio Modeling Environment, Release 4.5. BIOVIA, Dassault Systèmes, San Diego; 2021.

19. Geete A., Damre M., Kokkula A. Drug Likeness Tool (DruLiTo) Chemistry Development Kit (CDK), Department of Pharmacoinformatics NIPER, Mohali. [(accessed on 22 July 2021)]; Available online: http://www.niper.gov.in

20. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings 1PII of original particle: S0169-409X(96)00423-1. Adv Drug Deliv Rev. 2001;46(1-3): 3-26.

21. Cheng F, Li W, Zhou Y, et al. AdMetSAR: a comprehensive source and free tool for assessment of chemical ADMET properties. J Chem Inf Model. 2012;52 (11):3099-3105.

22. Banerjee P, Eckert A, Schrey AK, Preißner R. ProTox-II: a webserver for the prediction of toxicity of chemicals. Nucleic Acids Res. 2018;46(W1):W257-W263.

23. Filimonov DA, Lagunin AA, Gloriozova TA, Rudik AV, Druzhilovskii DS, Pogodin PV, Poroikov VV. Prediction of the biological activity spectra of organic compounds using the PASS online web resource. Chem Heterocycl Compd. 2014;50: 444-57.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/113485