Original Research Article

Lead Anticancer Agents of Crinine Alkaloids: Cytotoxic, Caspase-3, and Anti-angiogenic Exploration

ABSTRACT

Several alkaloids with anticancer activities have been reported among the *Crinum* species. In this study, an *in silico* screening of crinine alkaloids was carried out to identify potential Caspase-3 activators and anti-angiogenic compounds. Thirty-one (31) crinine alkaloids were assessed for drug-likeness using the SwissADME online Web server. Nine (9) alkaloids, satisfying Lipinski's rules for drug-likeness were selected and screened *in silico* for cytotoxic properties against cancer and normal cell lines using the Cell Line Cytotoxity Predictor (CLC-Pred). The alkaloids possessing drug-like properties and showing good selectivity towards cancer cell lines were evaluated for Caspase-3 activating and anti-angiogenic activities by docking with the Caspase-3 and VEGFR2 proteins, respectively. The binding energy of the compounds was compared with those of the standard drugs. Powelline, augustine, and undulatine possess drug-like properties and demonstrated good selectivity against lung cancer (A549) and oligodendroglioma (Hs683) cell lines. Among these three compounds, powelline had the best potential as a Caspase-3 stimulant and anti-angiogenic agent. Powelline, augustine, and undulatine are potential lead anticancer agents against human lung cancer and oligodendroglioma.

Keywords: Anti-angiogenic, Cancer, Caspase-3, Crinine, Cytotoxic

1.0 INTRODUCTION

Cancer is associated with high mortality, despite the different therapeutic interventions available for its treatment (Lin et al., 2019). Globally, about one in every six deaths is due to cancer, approximating about 10 million deaths per year (WHO, 2023). Plant-based medicines have been used to treat various illnesses in various parts of the world for ages, and their therapeutic effectiveness has made them the subject of investigation by researchers. Several phytoconstituents of pharmaceutical importance have been isolated and characterized from plants. Compounds isolated from plants have served as important sources of lead molecules for chemotherapeutic drug investigations. Examples of anticancer agents of plant origin include vincristine, taxol, vinblastine, irinotecan, topotecan, and etoposide (Calderón-Montaño et al., 2021). Several reports have shown that alkaloids, flavonoids, and terpenoids isolated from plants have significant anticancer properties by modulating pathways that alter the migration, proliferation, and apoptosis of cancerous cells using various biological mechanisms (George et al., 2021). About 80 % of drugs approved by the Food and drug administration (FDA), USA for use in cancer therapy are natural products or their derivatives (Bishayee.and Sethi, 2016).

Cancer alters several physiological processes including disruption of the balance between apoptotic and non-apoptotic proteins, suppression of caspase functions (thereby evading apoptosis), and inhibition of death receptor signaling. Apoptosis (programmed cell death) helps to eliminate old, defective, and unneeded cells. Therapeutic strategies based on apoptosis modulation have been applied to treat inflammation, neurodegenerative diseases, and cancer (Pfeffer and Singh, 2018). Caspases are apoptosis regulators made up of initiator caspases and executioner caspases. The initiator caspases are caspase-2, caspase-8, caspase-9 and caspase-10. Executioner caspases include caspase-3, caspase-6, and caspase-7. Caspase-3 plays a key role in apoptosis and is an attractive therapeutic target for human diseases associated with apoptosis (McIlwain et al., 2015).

Angiogenesis plays a vital role in aiding normal and abnormal cell proliferation. Angiogenesis constructs new capillary blood vessels from pre-existing ones to ensure a sufficient supply of oxygen, nutrients, and other essentials to the proliferating cells. In addition, angiogenesis provides a channel through which cellular wastes are removed. Therefore, angiogenesis plays a significant role in maintaining cell viability, development, and proliferation (Aguilar-Cazares et al., 2019). The proliferation of tumor cells depends predominantly on angiogenesis since tumors remain benign and subsequently die from necrosis when they lack sufficient blood vessels to transport oxygen and other essentials for cell proliferation. Angiogenesis provides the abnormal cells with a network to carry out metastasis and corresponding secondary infection (Lugano et al., 2020). Angiogenesis is controlled by some protein kinases: Vascular endothelial growth factor receptors (VEGFRs), Fibroblast growth factor receptors (FGFRs), and Epidermal growth factor receptors (EGFRs). Among the activators of angiogenesis, vascular endothelial growth factors (VEGFs) signal proteins that stimulate new blood vessel formation by vasculogenesis and angiogenesis. Anti-angiogenic drugs are now being employed in the fight against cancer. VEGFRs and their specific agonist (VEGF) are over-expressed in many human tumours, therefore, VEGFRs are considered to be very important regulators of angiogenesis and tumour growth (Guo et al., 2010). The VEGFRs family can be classified into three subtypes: VEGFR-1, VEGFR-2, and VEGFR-3 (Stuttfeld and Ballmer-Hofer, 2009). VEGFR-2 is the most important target for anti-angiogenic therapy, and its blocking is a creative approach for the discovery of novel drugs against angiogenesis–dependent malignancies (Holmes et al., 2007).

The genera, *Crinum*, consisting of about 130 species are perennial bulbous herbs (Reefat et al., 2012), are known to possess a broad range of biological activities including antineoplastic, antimicrobial, antiviral, and analgesic properties (Fennell and Staden, 2001). *Crinum* species are extremely rich in alkaloids. Many alkaloids isolated from these plants demonstrated anticancer activity in several *in vitro* studies (Abebe et al., 2020).

In this study, selected crinine-type alkaloids were accessed for drug-likeness. Furthermore, the cytotoxic, Caspase-3 activating, and anti-angiogenic potentials of the compounds were evaluated. The structures of the compounds being investigated are in Figure 1

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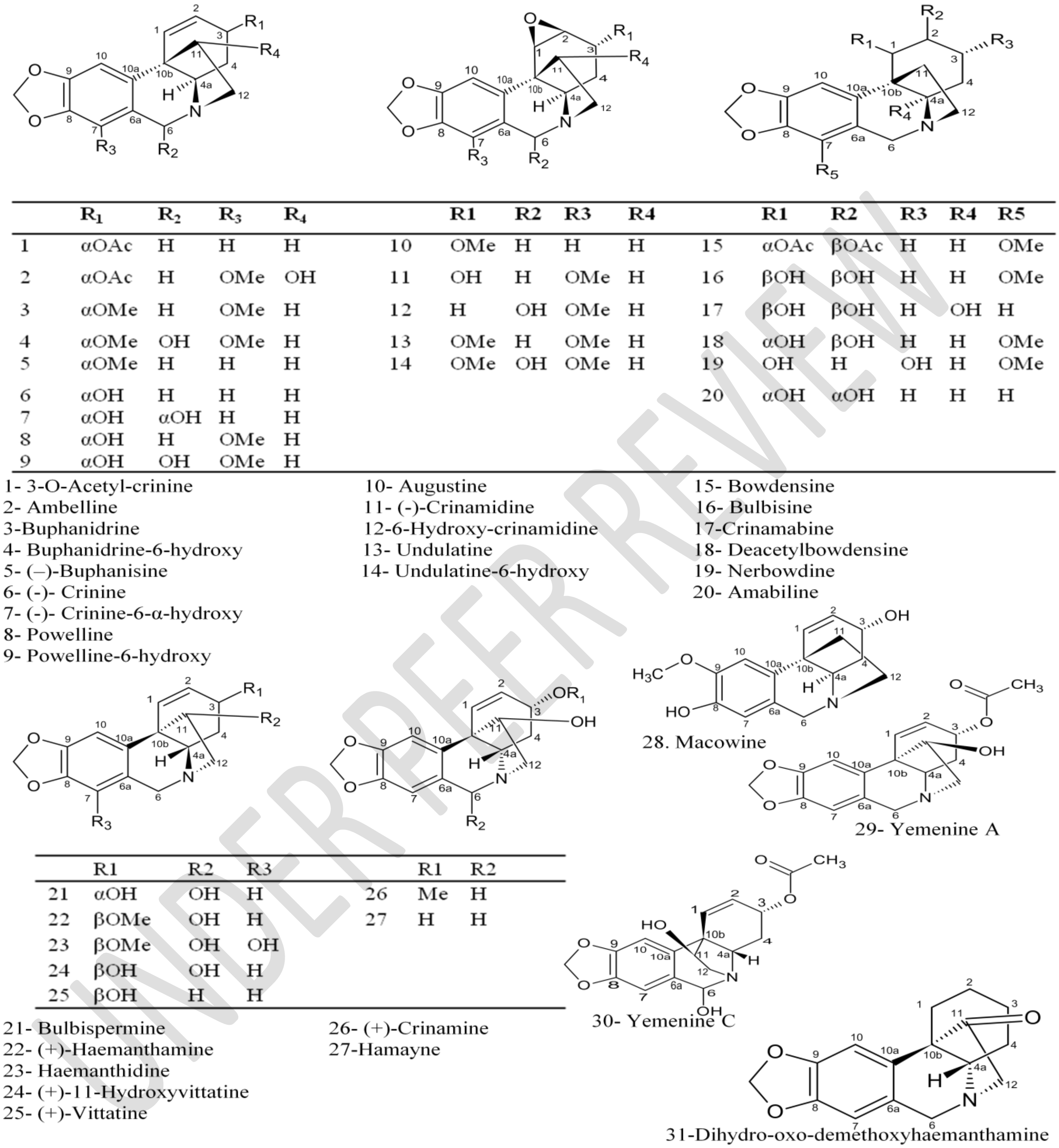

	R1	R2	R3	R4
1	αOAc	H	H	H
2	αOAc	H	OMe	OH
3	αOMe	H	OMe	H
4	αOMe	OH	OMe	H
5	αOMe	H	H	H
6	αOH	H	H	H
7	αOH	αOH	H	H
8	αOH	H	OMe	H
9	αOH	OH	OMe	H

	R1	R2	R3	R4
10	OMe	H	H	H
11	OH	H	OMe	H
12	H	OH	OMe	H
13	OMe	H	OMe	H
14	OMe	OH	OMe	H

	R1	R2	R3	R4	R5
15	αOAc	βOAc	H	H	OMe
16	βOH	βOH	H	H	OMe
17	βOH	βOH	H	OH	H
18	αOH	βOH	H	H	OMe
19	OH	H	OH	H	OMe
20	αOH	αOH	H	H	H

1- 3-O-Acetyl-crinine
2- Ambelline
3-Buphanidrine
4- Buphanidrine-6-hydroxy
5- (–)-Buphanisine
6- (-)- Crinine
7- (-)- Crinine-6-α-hydroxy
8- Powelline
9- Powelline-6-hydroxy

10- Augustine
11- (-)-Crinamidine
12-6-Hydroxy-crinamidine
13- Undulatine
14- Undulatine-6-hydroxy

15- Bowdensine
16- Bulbisine
17-Crinamabine
18- Deacetylbowdensine
19- Nerbowdine
20- Amabiline

28. Macowine

29- Yemenine A

	R1	R2	R3
21	αOH	OH	H
22	βOMe	OH	H
23	βOMe	OH	OH
24	βOH	OH	H
25	βOH	H	H

	R1	R2
26	Me	H
27	H	H

21- Bulbispermine
22- (+)-Haemanthamine
23- Haemanthidine
24- (+)-11-Hydroxyvittatine
25- (+)-Vittatine

26- (+)-Crinamine
27-Hamayne

30- Yemenine C

31-Dihydro-oxo-demethoxyhaemanthamine

Figure 1: Structures of Crinine alkaloids under investigation

2.0 MATERIALS AND METHODS

2.1 Prediction of Drug-Likeness and other Physicochemical Properties of Compounds

The drug-likeness of the selected crinine-type alkaloids was predicted by pasting their SMILE formats in the SwissADME online Web server (https://www.swissadme.ch). The parameters investigated are molecular weight, lipophilicity log (log P), hydrogen bond acceptor (HBA), hydrogen bond donor (HBD), and topological polar surface area (TPSA). The cutoff values for the drug-like properties were set using Lipinski's rule of five (ROF).

2.2Prediction of Cytotoxicity of Compounds

In silico cytotoxicity prediction on the compounds was carried out using Cell Line Cytotoxity Predictor (CLC-Pred), an online web service tool (http://www.way2drug.com/cell-line/) that predicts cytotoxic effects of chemical compounds in non-transformed and cancer cell lines based on their structural formula. The cytotoxicity of the crinine alkaloids was determined by pasting their SMILE formats into the online web server; cytotoxicity against the different cell lines was predicted as Pa and Pi values. An alkaloid has a high probability of action against a particular cell line if Pa > 0.5; Pi indicates the likelihood that the compound would be inactive (Lagunin et al., 2018).

2.3 Assessment of Compounds as Potential Caspase-3 Stimulants

In silico analysis of compounds for Caspase-3 activating properties were assessed using the online website (http://www.way2drug.com/passonline/predict.php). The SMILES format for each Crinine alkaloid was pasted on the online web server. Using the search tool, the potentials of the compounds to act as stimulants for Caspase-3 were assessed from the parameters Pa and Pi. An alkaloid with Pa values > 0.5 has good potential as Caspase-3 activator. Pi values measure the likelihood that the compound is not a Caspase activator (Desai and Joshi, 2019).

2.4 Molecular Docking Analysis

Based on the results of the cytotoxicity studies, some of the compounds were selected for further investigation as possible Caspase-3 activators and VEGFR inhibitors (Chaudhary et al., 2023). The two target proteins – a Caspase-3 (PDB ID: 1NMS) and a Vascular Endothelial Growth Factor Receptor 2 (PDB ID:3VHE) selected for the current study were obtained from the Protein Data Bank. The binding properties of the selected alkaloids were compared with those of the standard drugs, Procaspase-activating compound-1

(PAC-1) and Sorafenib (a potent VEGFR2 inhibitor (Wilhelm et al., 2006). The structures of the alkaloids and the standard drugs (PAC-1 and Sorafenib) were obtained from the PubChem database and saved in the SDF format. The structures were converted into the mol2 format using the Open Babel software prior to docking (O'Boyle et al., 2011). Molecular docking was carried out using the SwissDock Server (http://www.swissdock.ch/) (Grosdidier et al., 2011). The ligands (in the mol2 format) and the proteins (in the PDB format) were uploaded through the portals provided on the server. At the termination of the docking, the system sends a link containing the results to the email of the user. The SwissDock generates all the possible binding modes for each ligand and generates information such as the binding free energy, cluster rank, and the fullfitness score, among others. The most favourable binding model is one with the least energy. After docking, the interactions between the ligands and the proteins were visualized using Chimera. The specific atoms of the amino acids interacting with the ligands, and the nature of the interactions were identified (Wafa and Mohamed, 2020).

3.0 RESULTS

All the compounds satisfied Lipinski's rule of five conditions for drug-likeness. In addition, all the compounds possess high gastrointestinal absorption. Further analysis of the other physicochemical properties of the compounds show that only nine (9) of the compounds do not act as substrates for PgP and could penetrate the blood brain barrier. These compounds are: 3-O-Acetyl-crinine (1), Buphanidrine (3), Buphanidrine-6-hydroxy (4), (–)-Buphanisine (5), powelline (8), augustine (10) and undulatine (13), (+)-Haemanthamine (22), and (+)-Crinamine (26). The results on the drug-likeness and other physicochemical properties of these nine (9) compounds are presented in Table 1. These nine compounds are retained for further studies.

Table 1: Drug-Likeness and other Physicochemical Properties of Compounds

Compd	M.W.	TPSA	iLogP	HBA	HBD	WLOGP	GI	BBB	PgP	Druglikeness (Lipinski)	Bioavailability	MLOGP
1.	313.35	48.00	2.92	5	0	1.60	High	Yes	No	Yes	0.55	2.28
3	315.36	40.16	3.36	5	0	1.69	High	Yes	No	Yes	0.55	1.83
4	331.36	60.39	2.97	6	1	1.01	High	Yes	No	Yes	0.55	1.69
5	285.34	30.93	3.11	4	0	1.68	High	Yes	No	Yes	0.55	2.15
8	301.34	51.16	2.91	5	1	1.04	High	Yes	No	Yes	0.55	1.59
10	301.34	43.46	3.15	5	0	0.89	High	Yes	No	Yes	0.55	1.41
13	331.36	52.69	3.42	6	0	0.90	High	Yes	No	Yes	0.55	1.10
22	301.34	51.16	2.93	5	1	0.65	High	Yes	No	Yes	0.55	1.32
26	301.34	51.16	2.79	5	1	0.65	High	Yes	No	Yes	0.55	1.321

M.W- Molecular weight; TPSA – Total Polar Surface Area; iLogP – n-octanol/water partition coefficient ; HBA – Hydrogen Bond Acceptors; HBD – Hydrogen Bond Donors; WLogP - Wildman octanol-water partition coefficient ; GI – Gastrointestinal absorption; BBB- Blood-Brain Barrier; PgP- Permeability glycoprotein ; MLogP- Moriguchi octanol-water partition coefficient

The predictions of the cytotoxic properties of the nine compounds are shown in Table 2. Pa is an indicator of the probability that the compound would be active. This probability is based on the degree of similarities of the structures of the molecules under investigation with those most typical in a subset of actives in the PASS training set. Pi, on the other hand, estimates the probability that the compound being studied is inactive. The results showed that the compounds would likely be active against a broad range of cancer cell lines (Table 2). From the Pa values obtained, the selected crinine alkaloids would likely show the best activity against Lung carcinoma (A549) and Oligodendroglioma (Hs683). However, 3-O-Acetyl-crinine (1), Buphanidrine (3), Buphanidrine-6-hydroxy (4), (–)-Buphanisine (5), (+)-Haemanthamine (22), and (+)-Crinamine (26) also showed high potential for activity against a normal cell line Foreskin fibroblast BJ (at Pa> 0.5) and are therefore not suitable anticancer drug candidates. Therefore, only powelline (8), augustine (10) and undulatine (13) were screened for activity as potential Caspase-3 stimulants and VEGF-2 inhibitors.

Table 2: Prediction of Cytotoxicity of Compounds on Cancer Cell Lines (at Pa > 0.5)

Compound		Cancer Cell Lines										Normal Cell Line
		A549	PC-6	DMS-114	PC-9	SK-MEL	Hs683	MCF7	HL-60	HepG2	G-361	BJ
1	Pa	0.796	0.578	-	-	-	0.740	0.511	-	-	-	0.538
	Pi	0.011	0.018	-	-	-	0.007	0.049	-	-	-	0.004
3	Pa	0.874	0.542	0.522	-	-	0.732	0.523	-	-	-	0.520
	Pi	0.005	0.021	0.030	-	-	0.007	0.047	-	-	-	0.004
4	Pa	0.840	-	-	-	0.727	0.587	-	-	-	-	0.509
	Pi	0.008	-	-	-	0.001	0.029	-	-	-	-	0.004
5	Pa	0.841	0.569	-	0.514	-	0.803	0.509	-	-	-	0.556
	Pi	0.008	0.019	-	0.014	-	0.004	0.050	-	-	-	0.004
8	Pa	0.830	0.554	0.520	0.503	-	0.796	-	-	-	-	-
	Pi	0.009	0.020	0.031	0.016	-	0.004	-	-	-	-	-
10	Pa	0.763	0.581	-	0.503	-	0.781	-	-	-	-	-
	Pi	0.014	0.018	-	0.016	-	0.005	-	-	-	-	-
13	Pa	0.807	0.554	0.522	-	-	0.705	-	-	-	-	-
	Pi	0.011	0.020	0.030	-	-	0.009	-	-	-	-	-
22	Pa	0.976	-	-	-	0.969	0.776	0.631	0.632	0.508	0.506	0.934
	Pi	0.004	-	-	-	0.001	0.005	0.028	0.014	0.022	0.003	0.001
26	Pa	0.976	-	-	-	0.969	0.776	0.631	0.632	0.508	0.506	0.934
	Pi	0.004	-	-	-	0.001	0.005	0.028	0.014	0.022	0.003	0.001

A549-Lung carcinoma; PC-6 – Small cell lung carcinoma; DMS-114 – Lung carcinoma; PC-9 –Lung adenocarcinoma; SK-MEL-Melanoma; Hs683- Oligodendroglioma; MCF7 - Breast carcinoma; HL-60 - Promyeloblast leukemia; HepG2 – Hepatoblastoma; G-361- Melanoma; BJ- Foreskin fibroblast; Pa- Probability to be active; Pi- probability to be inactive

The results obtained on screening the compounds as potential Caspase-3 stimulants are shown in Table 3. Among the three compounds investigated, Powelline (Pa = 0.423) showed the best potential as Caspase-3 stimulant. None of the compounds exhibited a potential as high as that of the standard drug, PAC-1(Pa = 0.772) as a Caspase – 3 stimulant.

Table 3: Assessment of Compounds as Potential Caspase-3 Stimulants

Compounds	Caspase-3 Stimulant	
	Pa	Pi

Powelline	0.423	0.043
Augustine	0.324	0.099
Undulatine	0.293	0.143
PAC-1	0.772	0.007

Pa- Probability to be active; Pi- probability to be inactive; PAC-1 - Procaspase-activating compound-1

The potential of the Powelline (8), Augustine (10) and Undulatine (13) as Caspase-3 activators was further investigated by docking them against the Caspase-3 protein (PDB ID: 1NMS). The results are shown in Table 4. Among the three compounds investigated, powelline (with a binding energy of -6.97 kcal mol^{-1}) had the closest binding energy to that of the standard drug, PAC-1 (with a binding energy of -7.46 kcal mol^{-1}). Figure 2 shows the binding orientations of Powelline (8), Augustine (10), Undulatine (13) and PAC-1 within the binding pockets of the protein, 1NMS.

Table 4:Docking results of Caspase-3 Protein (PDB ID: 1NMS) with selected Phytoconstituents

Compound	**Binding Affinity (kcal/mol)**	**Fullfitness**	**H-bonding interractions (Ligand…Protein residue)**	**Length (A^{o})**
Augustine	-6.64	-1802.0172	O3…HN THR62	7.123
			O2…HN TRP214	7.748
			O1…HN ARG207	5.704
			O…HN SER209	3.281
			O…HN LYS210	5.792
			O…HN ASP 211	7.527
Powelline	-6.97	-2028.124	O3…HN THR62	7.297
			O1…HN SER65	6.672
			O2…HN TRP214	7.376
			O…HN PHE250	4.433
			O…HN LYS259	7.738
			O…HN ALA258	7.445

			H13…O ASP253	6.974
Undulatine	-6.73	-1795.1301	O3…HN THR62	7.312
			O1…HN ARG207	4.163
			O3…HN SER205	7.832
PAC-1	-7.46	-1940.5931	H27…O ASP253	7.692
			O…HN SER205	6.704
			O…HN ARG207	5.066
			N1…O SER65	6.996
			N1…O GLY212	7.774

THR – Threonine; TRP – Tryptophan; ARG – Arginine; SER – Serine; LYS – Lysine; ASP- Aspartic acid; PHE- Phenylalanine; ALA – Alanine; GLY - Glycine

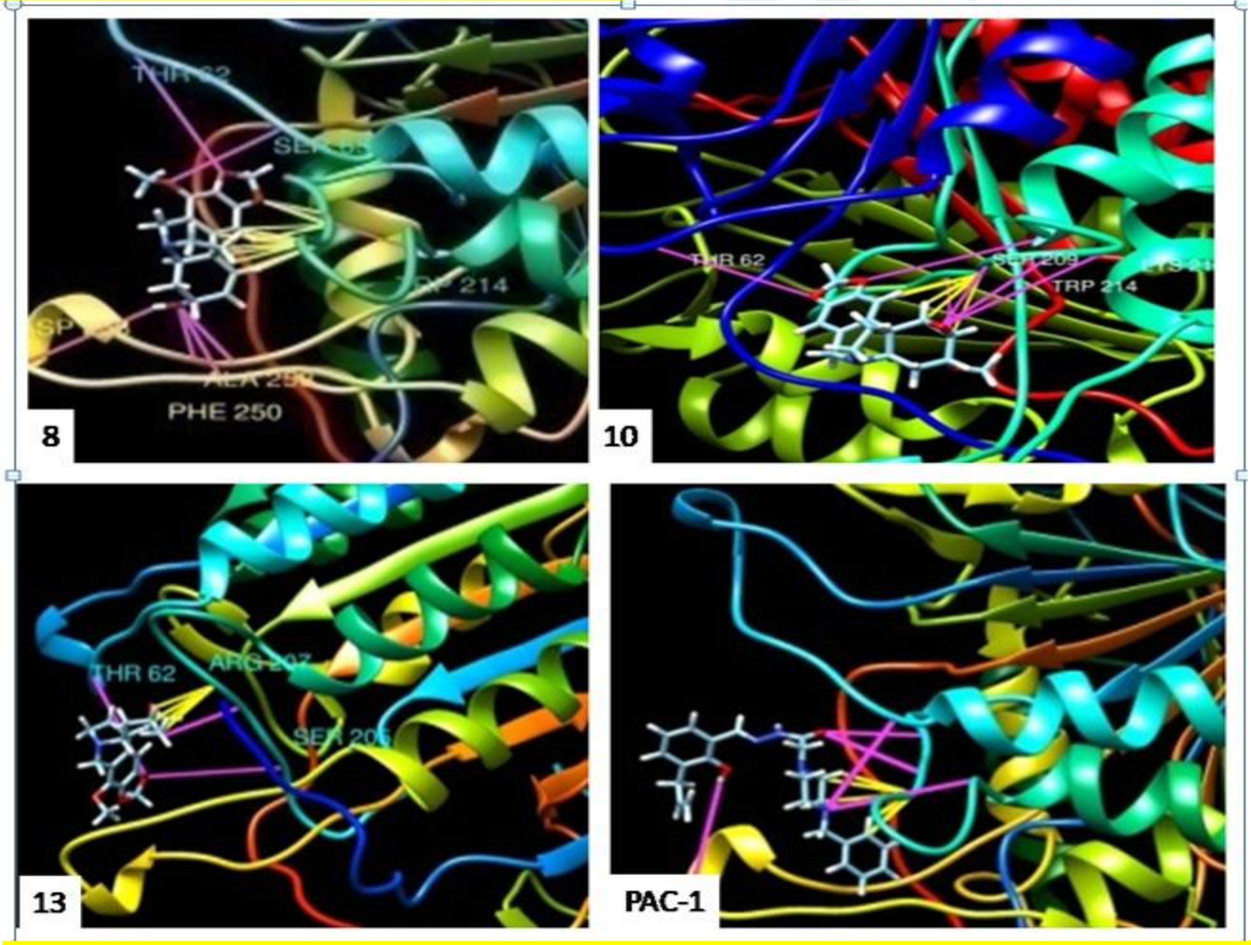

Figure 2: Docking poses of Powlline (8), Augustine (10), undulatine (13) and Procaspase-activating compound-1 (PAC-1) against 1NMS

Molecular docking (MD) was performed to assess the binding mode of the compounds with the VEGFR2. The binding energy obtained for augustine, powelline and undulatine are −6.99, -7.04, and -6.54 kcal mol^{-1}, respectively. The standard drug, Sorafenib had a binding energy of - 7.39 kcal mol^{-1}. Further details on the hydrogen bonding interactions between the ligands and the protein are provided in Table 5. Figure 3 shows the different orientations of Powelline (8), Augustine (10), Undulatine (13) and Sorafenib within the binding pockets of the protein, 3VHE.

Table 5: Docking results of Vascular Endothelial Growth Factor Receptor 2 (VEGFR2), 3VHE with selected Phytoconstituents

Compound	**Binding Affinity (kcalmol-^{1})**	**Fullfitness**	**Hydrogen Bonding Interactions (Ligand…Protein)**	**Length (A^{o})**
Augustine	-6.99	-1432.0152	N…O PHE845	6.468
Powelline	-7.04	-1455.5247	O1…HN ALA874	6.443
			N…O ALA874	4.740
			N…O PHE845	6.664
			N…O THR875	6.448
			H13…O PHE845	6.632
			H13…O LYS871	6.074
			O…HN LEU882	7.483
			O…HN LEU912	3.011
Undulatine	-6.54	-1222.1562	O1…HN LEU896	7.019
			O2…HN VAL1042	8.043
			N…O VAL1042	7.488
			N…O TYR 1008	7.974
			N…O CYS1007	5.557

			N…O ASN1040	5.926
Sorafenib	-7.39	-1483.3163	H3…O PHE918	8.136

THR – Threonine; TRP – Tryptophan; ARG – Arginine; SER – Serine; LYS – Lysine; ASP- Aspartic acid; PHE- Phenylalanine; ALA – Alanine; LEU- Leucine; Val – Valine; TYR – Tyrosine; CYS- Cysteine; ASN - Asparagine

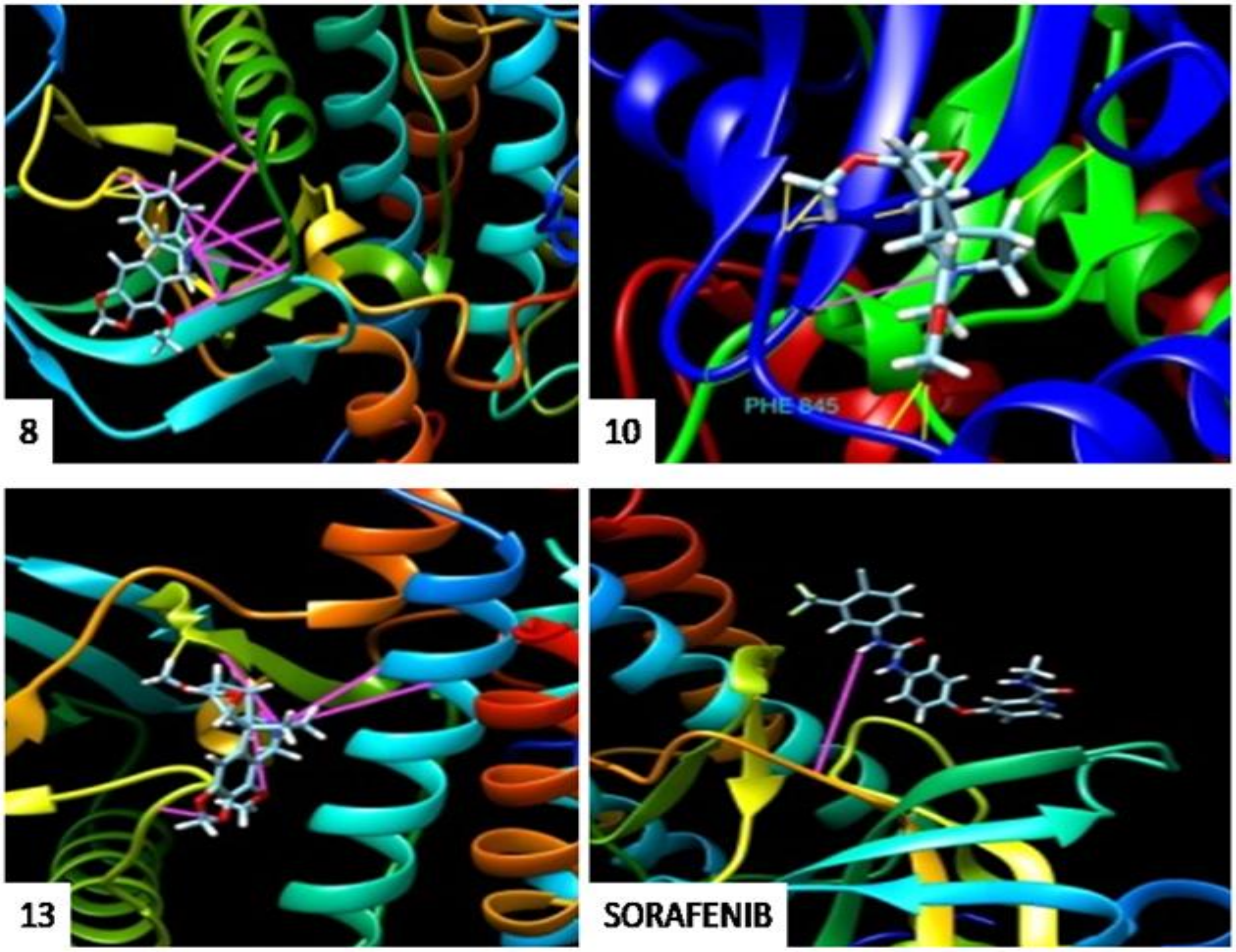

Figure 3: Docking poses of Powlline (8), Augustine (10), undulatine (13) and Procaspase-activating compound-1 (PAC-1) against 3VHE

4.0 DISCUSSION

The drug-likeness of the crinine alkaloids has been predicted *in silico*, following Lipinski's rule of 5, which gives properties to a compound must possess to have potential as a drug candidate (Lipinski et al., 2012). All the compounds satisfied Lipinski's rules for drug-likeness. Potential drug candidates with a PSA value less than 140 A^2, possess excellent intestinal absorption properties; those with a PSA value less than $70A^2$ can pass through the blood-brain barrier (Muchmore et al., 2010). The blood-brain barrier (due to the anatomical structure of the capillary network in the brain) protects the brain tissues from invasion by foreign substances. To successfully penetrate the brain, a drug candidate must be relatively small or lipid soluble or must be picked up by the carrier-mediated transport mechanism of the Central Nervous System (CNS) (Pandev et al., 2015). A drug must be able to cross the blood-brain barrier to exert therapeutic actions on the brain. The nine crinine alkaloids shown in Table 1 could penetrate the blood-brain barrier and are poor substrates for Permeability glycoprotein (Pgp). Pgp conveys drugs away from the cell membrane and cytoplasm, resulting in therapeutic failure when drug concentration reduces. An optimal drug candidate possesses high gastrointestinal permeability and low Pgp efflux liability (Geldenhuys et al., 2015).

The nine (9) crinine alkaloids selected for cytotoxicity studies (based on the criteria above) showed potential for activity against several cancer cell lines (at Pa > 0.5). Literature reports have shown that several crinine alkaloids demonstrate antiproliferative properties in several cancer cell lines (Trujillo et al., 2023). In the current study, the alkaloids demonstrated the best activity against lung carcinoma (A549) and Oligodendroglioma (Hs683) cancer cell lines. Lung cancer ranks among the leading causes of cancer mortality (Thandra, 2021). The A549 is the human non-small cell lung cancer cell line (NSCLC) is responsible for up to 85% of lung cancers. Despite advances in the treatment of NSCLC using chemotherapy, radiotherapy, and surgery, it still has a poor prognosis with a median survival time of less than one year and less than a 2-year survival rate of less than 20% (Urvay et al., 2016). The compounds in this study showed high potential as anticancer agents for treating NSCLC. Oligodendroglioma is a diffusely infiltrating glioma constituting approximately 5% of primary intracranial tumors (Ostrom et al., 2017) and an incidence of 0.2 per 100,000 people comprising 5% of all primary CNS tumors (Wesseling et al., 2015). The treatment methods for Oligodendroglioma consist of surgical, chemotherapy, and radiation therapy. However, six (6) of the compounds (1, 3, 4, 5, 22, and 26) demonstrated poor selectivity towards the cancer cell lines (since they possess high likelihood of activity against the normal Foreskin fibroblast (BJ) cell line). A good drug candidate should have high selectivity toward its target (Calderón-Montaño et al., 2021). Only augustine, powelline, and undulatine showed good selectivity towards the cancer cell lines and they are potential lead anticancer compounds for treating lung carcinoma (A549) and Oligodendroglioma (Hs683). Among these three (3) compounds, powelline showed the best potential as a Caspase-3 stimulant and an anti-angiogenic agent. Literature reports indicate that powelline had antitumor and anticancer activity in *in vitro* models (Sebola et al., 2020; Trujillo et al., 2023).

5.0 CONCLUSION

Augustine, powelline, and undulatine possess drug-like properties and good selectivity towards different cancer cell lines, especially the lung carcinoma (A549) and Oligodendroglioma (Hs683). Powelline showed the best potential as a Caspase-3 stimulant and an anti-angiogenic agent. Powelline, Augustine and undulatine are potential lead compounds for the treatment human lung cancer and oligodendroglioma. The results obtained from this study have laid a basis for further investigation of the compounds *in vitro* and *in vivo* studies to establish the predicted activity.

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