Natural Compounds Targeting VEGFRs in Kidney Cancer: An *In silico* Prediction

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ABSTRACT: Vascular endothelial growth factor receptor-tyrosine kinase inhibitors (VEGFR-TKIs), which target angiogenesis by blocking VEGF signaling, are used in the treatment of many cancers including kidney cancer. Despite their efficacy in cancer, serious adverse effects such as hypertension and cardiovascular toxicities remain a clinical challenge. Natural non-toxic compounds targeting VEGFRs might be an alternative to VEGFR-TKIs. In the current study, we screened databases and literature which recommend natural compounds for kidney cancer and found approximately five hundred natural compounds. After screening for toxicity and drug-likeliness properties, fifteen of these compounds remained. Subsequently, we performed molecular docking studies against VEGFR-1 and VEGFR-2 with Lenvatinib, reported to be the most toxic of TKIs, and the fifteen natural compounds. As a result, Polydatin and Plakortide M gave the closest results to Lenvatinib in the interactions of the compounds with VEGFR-1 and VEGFR-2, respectively.

Keywords: VEGFR-TKIs, natural compounds, kidney cancer, VEGFR-1 and VEGFR-2, ADMET, *in silico* analysis

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INTRODUCTION

Worldwide, kidney or renal cancer (including renal pelvis) ranked 16th among all cancers with 431288 new cases (2.2% of all sites) and 14th with 179368 new deaths (1.8% of all sites) according to GLOBOCAN 2020 data (Sung et al., 2021). There are several types of kidney cancer including renal cell carcinoma (RCC; the most common type with 85%), urothelial carcinoma, sarcoma, Wilms tumor (the most common type in children), and lymphoma. The treatment of kidney cancers varies according to the type and grade of cancer as with other cancers. One of these treatment options is targeting vascular endothelial growth factor receptors (VEGFRs), types of tyrosine kinase, that belong to the receptor tyrosine kinase family.

There are three VEGFRs in humans including VEGFR-1, VEGFR-2, and VEGFR-3 and they bind vascular endothelial growth factors [(VEGFs; VEGF-A, VEGF-B, VEGF-C, VEGF-D, and PIGF (placental growth factor)] (Table 1). They play a role in many biological processes such as angiogenesis, cell survival and migration, cancer cell invasion, macrophage function, chemotaxis, and differentiation (Jia et al., 2004; Lesslie et al., 2006; Simons et al., 2016; Vural, 2018).

Table 1. VEGFRs in Humans

Protein Name	Approved Gene Symbol and Name	Ligands for VEGFRs
VEGFR-1	FLT1 (fms related receptor tyrosine kinase 1)	VEGFA, VEGFB, and PGF
VEGFR-2	KDR (kinase insert domain receptor)	VEGFA, VEGFC and VEGFD
VEGFR-3	FLT4 (fms related receptor tyrosine kinase 4)	VEGFC and VEGFD

The anti-angiogenic treatment is an important option in many tumors including RCC; therefore, the VEGFRs, especially VEGFR-1 and VEGFR-2, are important drug targets for cancer therapy because they are highly expressed in many tumors (Yan et al, 2015; Vural, 2018; Lian et al, 2019; Fogli et al, 2020; Kinget et al., 2021). As of April 2022, there are a total of ten approved VEGFR-tyrosine kinase inhibitors (VEGFR-TKIs) in clinical use for various cancer, and seven of these are approved by FDA for kidney cancers (Table 2).

Table 2. FDA approved VEGFR-TKIs for Kidney Cancers (Jeong et al., 2013; Roskoski, 2022)

VEGFR-TKIs	Approved for kidney cancers	Years of approval by FDA for kidney cancers
Lenvatinib	RCC (in combination with Everolimus)	2016
Axitinib	Advanced RCC	2012
Cabozantinib	RCC	2016
Pazopanib	RCC	2009
Sorafenib	RCC	2005
Sunitinib	RCC	2006
Tivozanib	Advanced RCC	2021

RCC: Renal Cell Carcinoma

VEGFR-TKIs block VEGFR activation (mediated by VEGFs) and thus they inhibit angiogenesis and tumor cell growth. Although good results have been obtained in the treatment of RCC and other tumors with VEGFR-TKIs, adverse effects caused by them such as hypertension and cardiovascular damage and the development of drug resistance remain serious clinical problems (Pandey et al., 2018; Erman et al., 2021; Hou et al., 2021; Sharma et al., 2021). Hou et al (2021) reported that the degree of cardiotoxic risk differed between VEGFR-TKIs, and Lenvatinib has been associated with the highest probability of producing all degrees of cardiovascular injury and hypertension. Natural non-toxic compounds targeting VEGFRs might be an alternative to VEGFR-TKIs to reduce such adverse effects.

In the current study, we aimed to find non-toxic natural compounds that target VEGFR-1 and VEGFR-2, which are prognostic biomarkers in kidney cancer. For this purpose, we searched natural compounds for kidney cancer from both various databases and the literature. Afterward, we conducted *in silico* studies with the compounds remaining after being eliminated according to their toxicity profiles and drug-likeliness properties.

MATERIALS AND METHODS

Screening and selection of natural compounds for kidney cancer

After two of the three VEGFRs (VEGFR-1 and VEGFR-2) were found to be prominent targets for VEGFR-TKIs in kidney cancer, the natural compounds as an alternative to these inhibitors were screened.

The compounds recommended for kidney cancer were searched both in some databases such as NPACT (Naturally occurring Plant-based Anticancerous Compound-Activity-Target DataBase), CTD (The Comparative Toxicogenomics Database), and in the literature (Haque et al., 2017; Prša et al., 2020; Kang et al., 2021; Molaei et al., 2021; Wang et al., 2021). From the search, about five hundred natural compounds were found against kidney damage and cancer. The selection of compounds for *in silico* studies was done according to their drug-likeliness and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties.

The SwissADME (http://www.swissadme.ch), ADMETLab 2.0 (Xiong et al., 2021), and pkCSM (Pires et al., 2015) web servers were used to evaluate the drug-likeness parameters (Lipinski's rule of five, Ghose, Veber, Egan and Muegge filters) and ADMET values [Absorption parameters: Caco-2 and MDCK permeability, P-glycoprotein substrate or inhibitor, Human Intestinal Absorption (HIA). Distribution parameters: Plasma protein binding, Steady-state volume of distribution (VDss), blood-brain barrier (BBB) penetration, Fraction unbound (Fu). Metabolism parameters: CYP inhibitor or substrate Excretion parameters: Total clearance (Total C), renal OCT2 substrate, half-life (T1/2). Toxicity parameters: Human Maximum Tolerated Dose (HMTD), hERG I and II inhibitor, Hepatotoxicity, Carcinogenicity, Respiratory Toxicity] of the candidate compounds. The SMILE of each natural compound was obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov).

Molecular docking studies with human VEGFR-1 and VEGFR-2

Molecular docking studies were conducted using AutoDock 4.2 software to identify the interactions of fifteen natural compounds and Lenvatinib with VEGFR-1 and VEGFR-2. Crystal structures of human VEGFR-1 (PDB ID:3HNG) and VEGFR-2 (PDB ID:2XIR) were obtained from the RCSB Protein Data Bank (www.rcsb.org). The molecular structure of the compounds was drawn using Gaussview 5.0 and then optimized using the DFT method with the help of the Gaussian 03 package based on the theoretical level of the B3LYP method and the 6–31G basis set.

To find potential binding sites between VEGFRs of the optimized molecular structures, active sites were determined from the interaction map of the ligands, which the enzymes made complexes in the crystal structure and docking studies were performed for the identified active regions.

In the molecular docking studies, the cluster RMSD (Root-Mean-Square Deviation) value was calculated for the validation of the targeted active site of both VEGFR-1 and VEGFR-2. For the docking studies to be valid, this value is required to be in the range of 0-2 A°.

In the validation of molecular docking of VEGFR-1; N-(4-Chlorophenyl)-2-((pyridin-4-ylmethyl) amino)benzamide co-ligand with PDB ID: 3HNG code obtained from the protein data bank. The re-docking was done in the grid box created for the target region. It was determined that the cluster RMSD value of the ligand molecule, which was tested with 8 different conformations, was 1.15 A°. For VEGFR-2 validation, PF-00337210 (N,2-dimethyl-6-(7-(2-morpholinoethoxy) quinolin-4-yloxy)

benzofuran-3-carboxamide) co-ligand with PDB ID: 2XIR code obtained from the protein data bank and the re-docking was done in the grid box created for the target region. The cluster RMSD value of the ligand molecule, which was tested with 10 different conformations, was determined as 1.69 A°. It was found that the ligand compounds docked for the determined target region of both targets had compatible RMSD values. The clustering histogram and RMSD tables were added to supplementary information (Suppl. Table 1 and 2).

In docking studies x: 7.217; y: 21.488; z: 30.462 for VEGFR-1, and x: 21.22; y: 25.101; z: 40.255 for VEGFR-2 were determined as coordinate centers. Then, using a grid box with 50×50×50 points at the center of the predicted locations and a grid point spacing of 0.375 Å, the lowest placed conformations were selected for further studies. Water molecules were removed with AutoDock tools and subsequently, polar hydrogen atoms, Gasteiger partial charges, and Kollman charges were added to the targets. Additionally, the rotatable bonds of the compounds were adjusted. Lamarckian genetic algorithm approach was applied in both simulations. The interactions of VEGFR-1 and VEGFR-2 with the compounds were analyzed using the Discovery Studio Client 4.1 program.

RESULTS AND DISCUSSION

The non-toxic and drug-likeliness natural hit compounds for kidney cancer

The compounds with zero violations with drug-likeliness and toxicity were considered for *in silico* studies. Skin sensitization and eye irritation were excluded for these compounds in the toxicity screenings.

After selection according to drug-likeliness and ADMET criteria, fifteen hit compounds remained out of the five hundred natural compounds. The PubChem IDs and synonyms of these fifteen compounds and the control (Lenvatinib) were given in Table 3.

**Table 3.** The hit compounds after drug-likeliness and ADMET results

The Compounds	Synonyms	PubChem IDs
Lenvatinib	Lenvima	9823820
(+)-3-Carene	Isodiprene	443156
1,2,4-Nonadecanetriol	1,2,4-trihydroxynonadecane	10567452
Avocadene	heptadec-16-ene-1,2,4-triol	158573
Beta-Caryophyllene	L-Caryophyllene	5281515
Beta-Elemene	Levo-beta-elemene	6918391
Chlorogenic acid	Heriguard	1794427
D-Pinitol	Methylinositol	164619
Embelin	Embelic acid, Emberine	3218
Ethyl gallate	Phyllemblin	13250
Honokiol	5,3'-Diallyl-2,4'-dihydroxybiphenyl	72303
Linalool	Linalol, Linalyl alcohol	6549
Paeonol	Peonol	11092
Plakortide M	-	11724719
Polydatin	Piceid	5281718
Schisandrin	Schizandrol A, Schizandrin	23915

The docking results with VEGFR-1 and VEGFR-2 of the hit compounds

Results for docking studies of the fifteen compounds and Lenvatinib against human VEGFR-1 are shown in Table 4. According to the results, the natural compounds closest to Lenvatinib are Polydatin > Beta-Caryophyllene > Plakortide M. The results indicated that Polydatin has the highest binding affinity for VEGFR-1 after Lenvatinib. The 3D and 2D interactions of Lenvatinib and Polydatin with the VEGFR-1 active site are shown in figures 1 and 2, respectively.

Table 4. The docking scores of the hit compounds against human VEGFR-1

The Compounds	Binding Energy (kcal/mol)	Ligand Efficiency	Inhibitory Conc. (µM)
Lenvatinib	**-9.22**	**-0.31**	**0.175**
(+)-3-Carene	-5.33	-0.53	124.2
1,2,4-Nonadecanetriol	-5.00	-0.23	217.8
Avocadene	-4.62	-0.23	412.1
Beta-Caryophyllene	**-7.88**	**-0.53**	**1.69**
Beta-Elemene	-7.39	-0.49	3.81
Chlorogenic acid	-6.98	-0.28	7.62
D-Pinitol	-3.79	-0.29	1660
Embelin	-6.35	-0.30	22.3
Ethyl gallate	-5.32	-0.38	125.6
Honokiol	-7.06	-0.35	6.72
Linalool	-5.20	-0.47	155.4
Paeonol	-5.36	-0.45	116.98
Plakortide M	**-7.68**	**-0.32**	**2.34**
Polydatin	**-8.56**	**-0.31**	**0.528**
Schisandrin	-6.44	-0.21	19.18
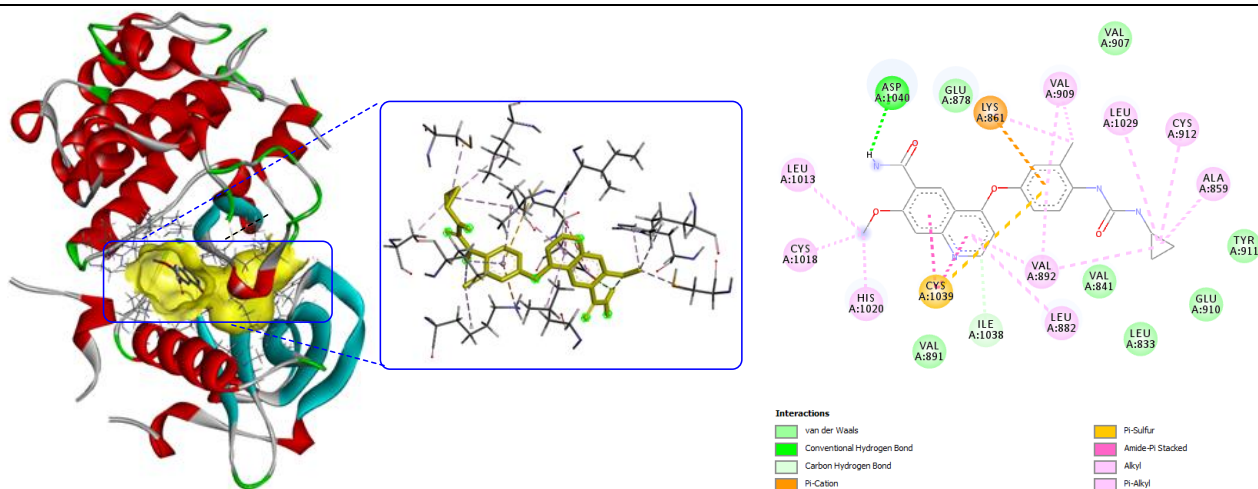
Figure 1. 3D and 2D ligand-protein interactions of VEGFR-1 active site with Lenvatinib
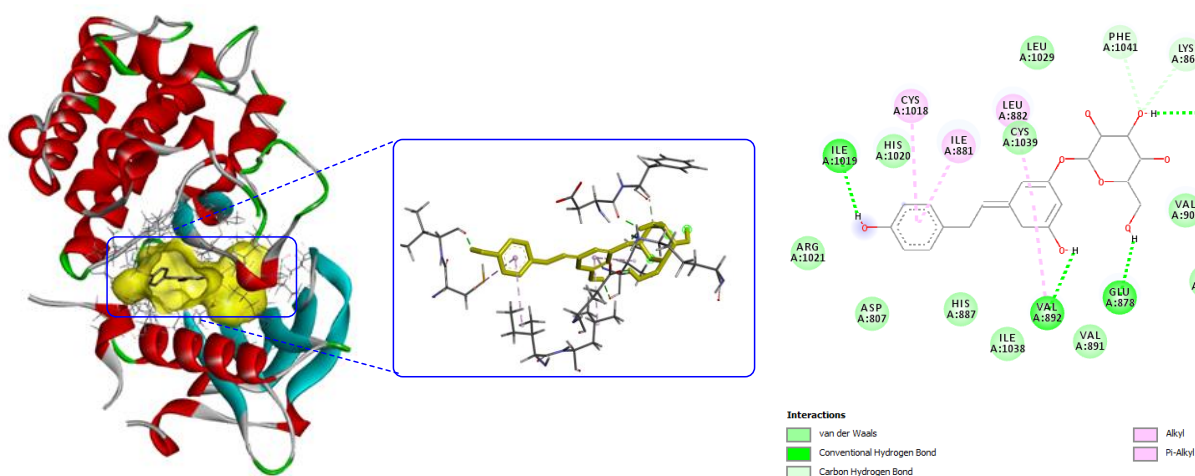
Figure 2. 3D and 2D ligand-protein interactions of VEGFR-1 active site with Polydatin

In addition, the 2D interaction of the compounds with the active site in the targets was analyzed to elucidate their interactions. The hydrogen bonding and other non-covalent interactions of the most potent compounds with VEGFR-1 were shown in Table 5. Lenvatinib interacted with ASP1040 and ILE1038 in the VEGFR-1 to form hydrogen bonds. Similarly, Polydatin formed H-bonds with ASP1040 and also

interacted non-covalently with CYS1018 and VAL892 in common with Lenvatinib. The other compounds (Beta-Caryophyllene and Plakortide M) did not establish H-bond interactions in the target region, but it was observed that they have high docking scores by establishing other non-covalent interactions similar to the interactions of Lenvatinib.

Table 5. The docking interactions of the most potent compounds with human VEGFR-1

Compounds	VEGFR-1 (PDB ID : 3HNG)	
	H-bonding	**Other non-covalent interactions**
Lenvatinib	ASP1040, ILE1038	LEU1013, CYS1018, HIS1020, CYS1039, LYS861, LEU882, VAL909, VAL892
Polydatin	ILE1019, VAL892, GLU878, **ASP1040**	**CYS1018,** ILE881, **VAL892**, ILE881, PHE1041
Beta-Caryophyllene	None	**LEU882**, **CYS1039**, VAL841, **LYS861**, ALA861, **VAL909**, ALA859, VAL907
Plakortide M	ARG1021, ILE1019	**CYS1018, VAL909, CYS1039**, **VAL892**, **LEU882, LEU1013,** ILE881, **HIS1020**

Lenvatinib and Polydatin targeting VEGFR-1 were also examined for Structure-Activity Relationship (SAR). The structure of Lenvatinib can be divided into four regions for VEGFR-1 interaction, including an H bond and a lipophilic tail, a trisubstituted benzene ring, an ether bridge, and a cyclopropyl-substituted urea structure. In the structure of Polydatin, the regions corresponding with these four parts in Lenvatinib are the saccharide group capable of H bond and lipophilic interaction, a trisubstituted benzene ring, an ether bridge, and a conjugated phenol structure (Figure 3). It was already stated above that Polydatin can form hydrogen bonding and non-covalent interactions similar to those of Lenvatinib (Table 5). The structural similarity of Polydatin with Lenvatinib can be explained as the reason for having a higher docking score compared to other natural compounds by interacting with the amino acids responsible for the activity.
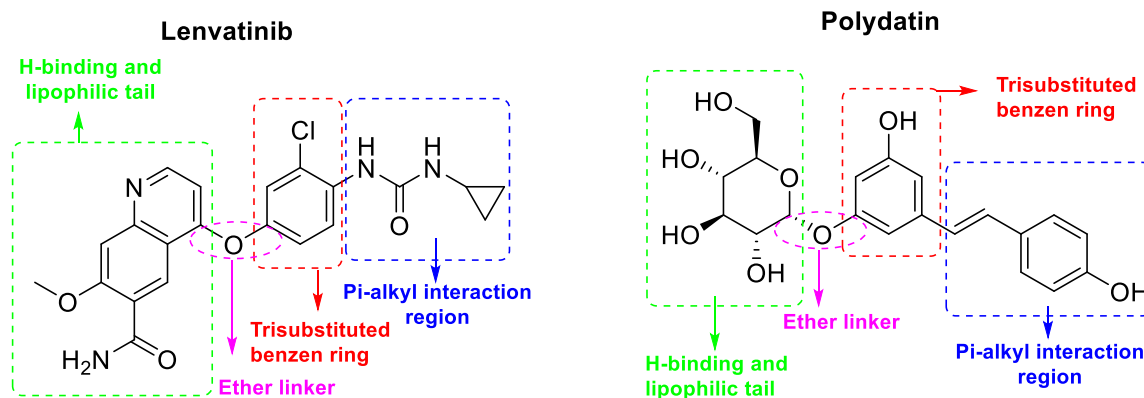

Figure 3. Structure-Activity Relationship of Lenvatinib and Polydatin for VEGFR-1

Polydatin, which was determined as the most potent *in silico* inhibitor for VEGFR-1 after Lenvatinib, is a monocrystalline compound found in the root and rhizome of Polygonum cuspidatum Sieb. et Zucc. It was also detected in grape, peanut, hop cones and pellets, cocoa-containing products, and many daily diets (Du et al., 2013). Apart from its protective role against sepsis-induced acute kidney injury (Gao et al., 2020), many in vitro and in vivo studies were suggested that Polydatin is hepatoprotective (Wu et al., 2012; Zhang et al., 2012), neuroprotective (Rivière et al., 2010; Ji et al., 2012), and lung-protective (Shiyu et al., 2011). It was also reported to have anti-inflammatory activity (Lanzilli et al., 2012), anti-tumor activity (Liu et al., 2011), and antioxidant properties (Wang et al., 2015). In addition, Polydatin showed a protective effect for cardiomyocytes after myocardial infarction model in mice (Zhang et al., 2017).

According to our *in silico* ADMET results, Polydatin did not cardiotoxic (not hERG inhibitor), hepatotoxic, carcinogenic, or respiratory toxicant (Table 8). Its HMTD was 0.569 log(mg/kg/day), thus it can only produce toxicity in large doses (the threshold toxic dose is considered high in pkCSM if the HMTD is greater than 0.477) and its theoretical inhibition concentration for VEGFR-1 was 0.528 μM (Table 4). In addition, Polydatin was Caco-2 impermeable (- 0.077; low permeability if < 0.9) however, it can be sufficiently absorbed (51.1%) from the human intestine (less than 30% is considered to be poorly absorbed). Log VDss of Polydatin was relatively high (0.125) which means that it can leave the plasma and distribute to other tissue compartments (VDss is considered low if log VDss < -0.15 and high if > 0.45), except brain (LogBB: -1.029; a logBB < -1 considered to be poorly distributed to the brain) (Table 8).

The docking results of VEGFR-2 with the hit compounds and Lenvatinib were shown in Table 6. The compounds that gave results close to Lenvatinib were Plakortide M > Honokiol > Polydatin. The results indicated that Plakortide M has the highest binding affinity for VEGFR-2 after Lenvatinib. The 3D and 2D interactions of Lenvatinib and Plakortide M with the VEGFR-2 active site were shown in figures 4 and 5, respectively.

Table 6. The docking scores of the hit compounds against human VEGFR-2

| The Compounds	Binding Energy (kcal/mol)	Ligand Efficiency	Inhibitory Conc. (μM)
Lenvatinib	**-10.86**	**-0.36**	**0.11**
(+)-3-Carene	-5.19	-0.52	156.66
1,2,4-Nonadecanetriol	-5.11	-0.23	180.03
Avocadene	-5.28	-0.26	134.13
Beta-Caryophyllene	-7.44	-0.50	3.54
Beta-Elemene	-7.47	-0.50	3.36
Chlorogenic acid	-7.42	-0.30	3.64
D-Pinitol	-3.41	-0.26	3.17
Embelin	-7.23	-0.34	5.02
Ethyl gallate	-5.07	-0.36	192.78
Honokiol	**-8.03**	**-0.40**	**1.31**
Linalool	-5.15	-0.47	166.94
Paeonol	-5.37	-0.45	116.29
Plakortide M	**-8.07**	**-0.34**	**1.22**
Polydatin	**-7.87**	**-0.28**	**1.7**
Schisandrin	-4.50	-0.15	503.81
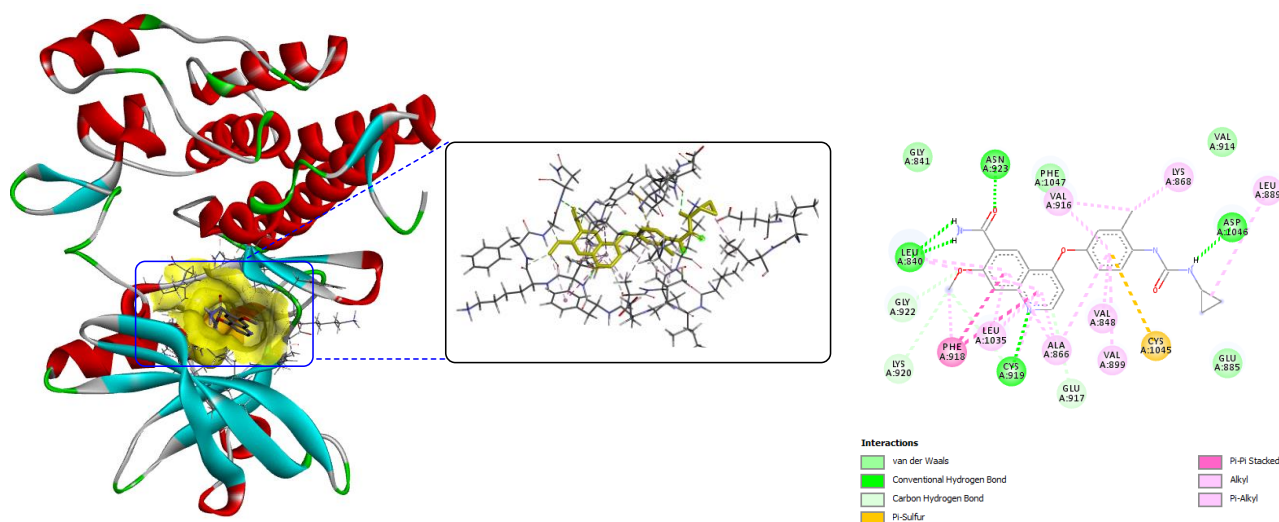
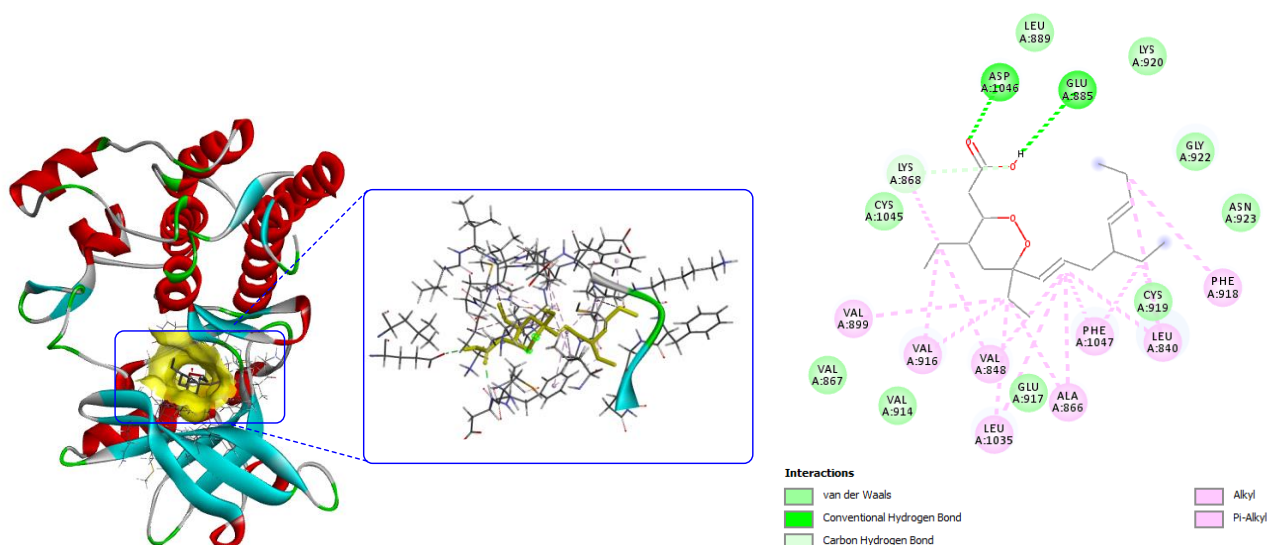**Figure 4.** 3D and 2D ligand-protein interactions of VEGFR-2 active site with Lenvatinib

Figure 5. 3D and 2D ligand-protein interactions of VEGFR-2 active site with Plakortide M

In addition, the docking interactions of the compounds with VEGFR-2 were given in Table 7. Plakortide M, the most potent *in silico* inhibitor for the VEGFR-2 after Lenvatinib, formed H-bond interaction with ASP1046 as with Lenvatinib and interacted non-covalently with VAL899, VAL916, VAL848, ALA866, and LYS868. Honokiol, which had the second strongest binding energy for VEGFR-2, did not form H-bonds similar to those of Lenvatinib, however it interacted non-covalently with VAL848, ALA866, and VAL916. Polydatin had closed docking scores to Plakortide M and Honokiol. It was formed three hydrogen bonds responsible for the activity such as CYS919, LEU840, and ASN923 and also established a similar non-covalent interaction with the residues that Lenvatinib interacted with the active site.

In the SAR analysis with docking interactions found for VEGFR-2, it can be said that the Lenvatinib and Plakortide M structures consist of an H-bond group, a cyclic group for non-covalent interactions, and a tail that provides pi-alkyl interaction (Figure 6). The structural similarity of Plakortide M to Lenvatinib can be explained as the reason why it has a higher docking score for VEGFR-2 compared to other natural compounds by interacting with the amino acids responsible for the activity.

Table 7. The docking interactions of the most potent compounds with human VEGFR-2

Compounds	VEGFR-2 (PDB ID : 2XIR)	
	H-bonding	**Other non-covalent interactions**
Lenvatinib	LEU840, ASN923, CYS919, ASP1046	PHE918, CYS1045, ALA866, VAL848, LYS868, VAL916, LEU889, VAL899
Plakortide M	**ASP1046**, GLU885	**VAL899**, **VAL916**, **VAL848**, LEU1035, **ALA866**, PHE918, LEU840, **LYS868**
Honokiol	GLU917	LEU840, PHE918, CYS1045, **VAL848**, **ALA866**, **VAL916**, LEU1035
Polydatin	**CYS919**, **LEU840**, **ASN923**, GLU885	**VAL848**, **ALA866**, **VAL899**, **LYS868**, **VAL916**, GLY922, LEU1035, **CYS1045**

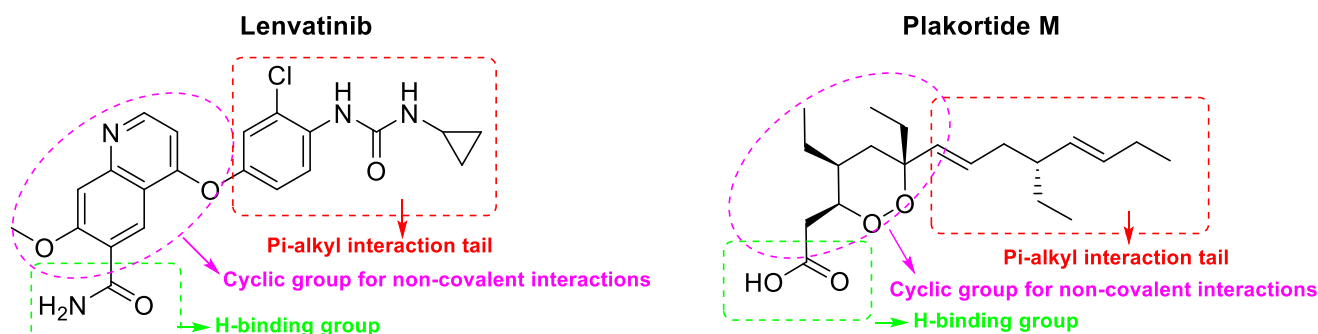**Lenvatinib**　　　　　　　　　　　　　　　　　　**Plakortide M**

Figure 6. Structure-Activity Relationship of Lenvatinib and Plakortide M for VEGFR-2

Plakortide M, which was determined as the most potent *in silico* inhibitor for VEGFR-2 after Lenvatinib, is a bioactive product found in a marine sponge *Plakortis halichondrioides* Wilson, 1902. There is only one study in the literature on Plakortide M and it was reported that Plakortide M showed cytotoxic activity against central nervous system tumor cells, but its activity was lower than Plakortide N (del Sol Jiménez et al., 2003). On the other hand, according to our *in silico* ADMET results, Plakortide M did not cardiotoxic (not hERG inhibitor), hepatotoxic, carcinogenic, or respiratory toxicant (Table 8). Its HMTD was 0.46 log(mg/kg/day) thus it can produce toxicity in small doses (the threshold toxic dose is considered low in pkCSM if the HMTD is less than or equal to 0.477) and its theoretical inhibition concentration for VEGFR-2 was 1.22 µM (Table 6). In addition, Plakortide M was Caco-2 permeable (high permeability if > 0.9) and highly absorbed from the intestine (90.9%). Log VDss of Plakortide M was low (-0.33) which means that it has a propensity to remain in the plasma (VDss is considered low if log VDss < -0.15). A lower dose of Plakortide M is required to achieve a given plasma concentration when considering that it can be used as a medicine and it can readily cross the blood-brain barrier (LogBB: 0.36. a logBB > 0.3 considered to readily cross the barrier).
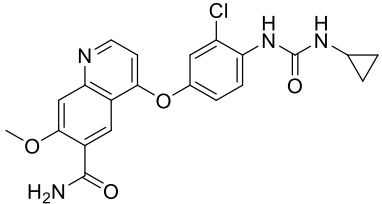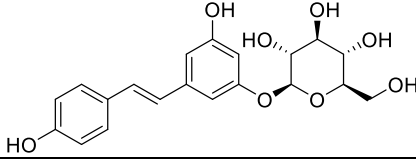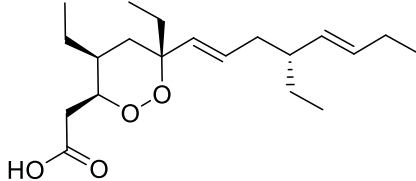
Table 8. ADMET results for Lenvatinib, Polydatin, and Plakortide M

Compounds	Important ADME Parameters						Important Toxicity Parameters				
	Caco-2 perm.	Human Intest. Abs. (%)	Log VDss	Log BBB perm.	CYP substrate or inhibitor	Total C (log ml/min/kg)	HMTD (log mg/kg/ day).	hERG I-II inhibitor	Hepato-toxicity	Carcino-gencity	Respiratory toxicity
Lenvatinib	0.031	88.9	0.304	-1.342	S: CYP3A4 I: CYP2C9 I: CYP3A4	0.213	0.426	No-Yes	Yes	+	- -
Polydatin	-0.077	51.1	0.125	-1.029	No	0.057	0.569	No	No	-	- - -
Plakortide M	1.561	90.9	-0.33	0.36	No	1.91	0.46	No	No	- -	-

Substrate (S) of which CYPs: CYP2D6, CYP3A4. Inhibitor (I) of which CYPs: CYP2D6, CYP3A4, CYP1A2, CYP2C9, CYP2C19. The classification of toxicity endpoints : 0-0.1 (- - -), 0.1-0.3 (- -), 0.3-0.5 (-), 0.5-0.7 (+). The output value is the probability of being toxic, within the range of 0 to 1 (0 = non-toxic, 1 = toxic).

The physicochemical properties of Lenvatinib, Polydatin, and Plakortide M were indicated in Table 9. Lenvatinib and Plakortide M have a high Log P value, while Polydatin is very low at 0.447. However, it can be interpreted that the hydroxyl groups in the compound interact with the residues in the active site of the enzyme as acceptor and donor and cause an increase in the inhibitory activity. In addition, the hydroxyl groups in Polydatin caused the polar surface area to expand. This shows that the potent *in silico* inhibitory activities of Polydatin and Plakortide M, which are determined as lead compounds, are related to their properties with LogP, Rotatable Bonds, Hydrogen bond acceptor and donor, and polar surface area.

Table 9. Molecular properties and depictions of Lenvatinib, Polydatin, and Plakortide M

Compounds	Molecular weight	LogP	Rotatable Bonds	Acceptors	Donors	Surface Area	Depictions
Lenvatinib	426.86	4.072	6	5	3	176.867	
Polydatin	390.388	0.447	5	8	6	160.705	
Plakortide M	338.488	5.295	10	3	1	146.4	

In conclusion, while Lenvatinib was reported to have the most potential adverse effects such as cardiotoxicity and hypertension among VEGFR-TKIs (Hou et al., 2021), neither Polydatin nor Plakortide M showed toxicity according to our results. Supporting the results, the cardioprotective effect (Zhang et al., 2017) and many other pharmacological effects of Polydatin were reported in the literature (Rivière et al., 2010; Shiyu et al., 2011; Liu et al., 2011; Lanzilli et al., 2012; Ji et al., 2012; Wu et al., 2012; Zhang et al., 2012; Wang et al., 2015; Gao et al., 2020), but only one study stated that Plakortide M has antitumor activity (del Sol Jiménez et al., 2003). The results suggested that Polydatin and Plakortide M can act like Lenvatinib at the active site of VEGFR-1 and VEGFR-2, respectively and they may be potential inhibitors for these targets.

CONCLUSION

Due to the serious toxicity of VEGFR-TKIs, mainly Lenvatinib, used in cancer therapy, the search for natural and non-toxic compounds targeting VEGFRs continues. The present study identified Polydatin and Plakortide M as *in silico* inhibitors of VEGFR-1 and VEGFR-2, respectively which are important drug targets in kidney cancer. Also, the designated compounds do not show toxicity according to both our results and the literature. *In vitro* and *in vivo* studies are needed to find the inhibitory potential and toxicity profiles of Polydatin and Plakortide M against VEGFRs.

Conflict of Interest

The article authors declare that there is no conflict of interest between them.

Author's Contributions

The authors declare that they have contributed equally to the article.

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