



# In Silico Molecular Docking of Bioactive Molecules Isolated from *Raphia taedigera* Seed Oil as Potential Anti-cancer Agents Targeting Vascular Endothelial Growth Factor Receptor-2

Haruna Isiyaku Umar<sup>1</sup> · Isaac Olatunde Awonyemi<sup>2</sup> · Segun Micheal Abegunde<sup>3</sup> · Festus O. Igbe<sup>2</sup> · Bushra Siraj<sup>4</sup>

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## Abstract

The role of angiogenesis in cancer pathophysiology cannot be over emphasized as this process aids tumor metastasis via nourishment of nutrient deprived tumors with oxygen and nutrients. Thus, it is pertinent to inhibit this process via the vascular endothelial growth factor receptor 2 (VEGFR-2). Most available anticancer drugs that targets VEGFR-2 exerts promising angiogenic effects but they bare several adverse effects. Hence, the need to uncover novel compounds from plants with less or no toxicity that have high efficacy targeting angiogenesis. In this present work, in silico docking studies was employed to reveal the potentials of bioactive compounds isolated from *Raphia taedigera* seed oil against VEGFR-2 using axitinib and sorafenib as control. The crystal structure of VEGFR-2 and the compounds were retrieved from protein database and pubchem servers respectively. The compounds were subjected to drug likeness and ADMET screening using Discovery studio 2016 and AdmetSAR server respectively. The docking between the compounds and VEGFR-2 was carried out with the aid of AutoDock Vina and visualization of the molecular interactions were done using PyMOL, LigPlot<sup>+</sup> and Protein–ligand interactions profiler's server. The results showed that 3-Methoxy-2,3-dimethylundec-1-ene scaled through the drug likeness screening. All the compounds show good binding affinities with 4,4,6a,6b,8a,11,11,14b-Octamethyl-1,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,14,14a,14b-octadecahydro-2H-picen-3-one having the best binding affinity of -8.9 kcal/mol. The ADMET prediction shows that these compounds are safer than the controls. Conclusively, the in silico study suggests that these compounds could prove to be probable anti-cancer agents but a further study is needed.

**Keywords** Anti-cancer · *Raffia taedigera* · Anxinib · Sorafenib

## 1 Introduction

Cancer is defined as the uncontrolled propagation and abnormal proliferation of the body's specific cells and world health organization established cancer as the second

leading cause of death worldwide, about 9.6 million deaths was reported in 2018 [1].

The process of generating new capillary blood vessels is termed angiogenesis which play important roles in organ development and differentiation during embryogenesis, wound healing and at a certain stage of female reproduction cycle [2, 3]. In spite of this, angiogenesis is implicated in a number of disorders such as tumor growth and metastasis, cancers, ischemic diseases, atherosclerosis, chronic inflammatory disorders, rheumatoid arthritis, and eye disease [3, 4]. Angiogenesis remains a hallmark of cancer by aiding tumor metastasis through nourishment of nutrient deprived tumors with oxygen and nutrients [5, 6].

Recently, the need to restrain the growth and metastasis of cancerous cells, angiogenesis blockade becomes an effective measure [7] because of the several signaling pathways engaged by this process, development of resistance towards anti-cancer agents where observed leading to inefficiency

✉ Haruna Isiyaku Umar  
uhumar@futa.edu.ng

<sup>1</sup> Central Research Laboratory, The Federal University of Technology, Akure, Nigeria

<sup>2</sup> Department of Biochemistry, The Federal University of Technology, Akure, Nigeria

<sup>3</sup> Department of Science Technology, The Federal Polytechnic, Ado-Ekiti, Ekiti State, Nigeria

<sup>4</sup> Dr. Zafar H.Zaidi Centre for Proteomics, University of Karachi, Karachi, Pakistan

of antiangiogenics. There are inhibitors/drugs designed to target tyrosine kinases (TKs), as they exhibit effectiveness by binding to the ATP binding sites of TKs' receptors consequently overcoming the challenge of drug resistance in cancer treatment [8, 9]. The TKs' receptors are; vascular endothelial growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR) and platelet derived growth factor receptor (PDGFR), of which VEGFR-2, an isoforms of VEGFR, plays a critical role in angiogenesis by activating several downstream signaling pathway upon binding of VEGF molecule [9].

According to previous studies, VEGF molecule, as a key controller of vascularization, is hyper expressed in cancerous cells due to over-activation of oncogenes that leads to pragmatic increase of VEGFR-2 auto-phosphorylation which results in the activation of several downstream signaling molecules heading to vascular permeability, cell migration, and cell survival followed by angiogenesis [9–11]. There are several VEGFR-2 inhibitors such as axitinib, regorafenib, sorafenib, and sunitinib, approved for various types of cancer of which sorafenib is the first TKI to exert promising antiangiogenics effect against VEGFR-2. However, these available drugs bare several adverse effects such as diarrhea, fatigue, hypothyroidism, myelosuppression, hypertension, thrombosis, and proteinuria [6, 7, 12]. In other to overcome this challenges, there is a need to uncover novel compounds especially from plants with less or no toxicity with high efficacy, targeting angiogenesis in tumor cells. In quest for this activities, we found out that *Raphia taedigera*, an underutilized tree which usually grows in the tropical, sub-tropical ecosystem and belongs to the family of Aracacea consists of sixteen (16) bioactive compounds of medicinal importance [13]. *R.taedigera* seed oil is rich in phytochemicals, antioxidants and other secondary plants metabolites [13]. This makes it a good choice for this research work.

## 2 Materials and Methods

### 2.1 Protein Target Selection and Preparation

The three-dimensional (3D) crystal structures of Vascular endothelial growth factor receptor 2, VEGFR-2 (PDB ID: 2oh4) was retrieved from the Protein Data Bank (PDB) ([www.pdb.org/pdb](http://www.pdb.org/pdb)). PDB is a database that contains the data of experimental structures of proteins and nucleic acids. The protein was then prepared and refined for docking using Chimera© (version 1.13) software tool (<http://www.cgl.ucsf.edu/chimera>). This was done by removing the co-crystallized ligand and additional water molecules to make it as

a nascent receptor, after which hydrogen and charges were added to the protein.

### 2.2 Ligand Selections and Preparations

Three dimensional (3D) structures of the molecules were obtained in Simple Data File from PubChem server (<https://www.ncbi.nlm.nih.gov/pccompound>) and were converted to mole files using MarvinSketch© (ver. 15.11.30). The molecules were optimized using the Merck molecular force field (MMFF94) in Avogadro (ver. 1.10). A total of sixteen compounds (16) from *Raphia taedigera* seed oil were selected for the study, while axitinib and sorafenib were adopted as the control drugs (Table 1).

### 2.3 Drug Likelihood Screening

The compounds were screened for drug likelihood as described by Lipinski et al. [14]. The compounds were screened employing Discovery studio (Version 16) software to calculate their logP, molecular weight, hydrogen bond donors and acceptors values. The Lipinski's rule of five was applied to screen for the probable molecules that can serve as oral drugs [15].

### 2.4 Validation of Molecular Docking Protocol

Validation of the docking protocol was carried out to ensure accuracy and enhance the reliability of the docking results according to Gregory et al. [16]. The idea is to accurately regenerate both the binding pose and the molecular interaction of the co-crystallized ligand of the experimentally-crystallized protein structure. Consequently, the ligand found at the binding site of the protein crystal was separated from the protein and then modified by adding charges using add charge tool from Chimera. The ligand was then docked back into VEGFR-2 active site using AutoDock Vina in PyRx suite, while its binding poses and molecular interactions were compared to that of the x-ray diffraction crystal structure using Ligplot<sup>+</sup> software.

### 2.5 Molecular Docking

The docking was executed using flexible docking protocol as described by Trott and Olson, 2005 [17] with slight modifications by Sekar et al.[18]. In brief; Python Prescription 0.8, a suite comprising of automated molecular docking tools called Auto Dock Vina was deployed for the molecular docking of the selected ligands with VEGFR-2 used as active site. The protein data bank, partial charge, and atom

**Table 1** lipinski's rule of five of the bioactive compounds isolated from *Raphia taedigera* seed oil

S/N	Compound name	PubChem ID	Molecular weight	AlogP	No. of HBD	No. of HBA	Violations
1	Hexadecanoic acid, methyl ester	8181	270.26	5.64	0	2	1
2	<i>n</i> -Hexadecanoic acid	985	256.24	5.55	1	1	1
3	Trans-13-octadecenoic acid, methyl ester	5,364,506	296.27	6.20	0	2	1
4	Oleic Acid	445,639	282.26	6.11	1	1	1
5	Octadecanoic acid	5281	284.27	6.33	1	1	1
6	<i>Cis</i> -13-Octadecenoic acid	5,312,441	282.26	6.11	1	1	1
7	6-Octadecenoic acid	11,634	282.26	6.11	1	1	1
8	<i>Cis</i> -Vaccenic acid	5,282,761	282.26	6.11	1	1	1
9	Palmitoyl chloride	8206	274.21	6.23	0	1	1
10	Trans-13-Octadecenoic acid	6,161,490	282.26	6.11	1	1	1
11	9,12-Octadecadienoic acid (Z,Z)	3931	280.24	5.88	1	1	1
12	4,4,6a,6b,8a,11,11,14b-Octamethyl-1,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,14,14a,14b-octadecahydro-2H-picen-3-one	612,782	424.37	8.38	0	1	1
13	3-Methoxymethoxy-2,3-dimethylundec-1-ene	542,549	242.23	4.69	0	2	0
14	Cyclohexanecarboxylic acid, undecyl ester	582,157	282.26	5.64	0	2	1
15	Beta-Amyrin	73,145	426.39	8.02	1	1	1
16	Lup-20(29)-en-3-one	12,359,010	426.37	8.02	1	1	1
17	Sorafenib	216,239	464.83	5.55	3	4	1
18	Axitinib	6,450,551	386.48	4.64	2	4	0

AlogP = lipophilicity, HBD = hydrogen bond donor, HBA = hydrogen bond acceptor

type a file (PDBQT) of the protein was generated from PDB files earlier created as inputs). The specific target site of the enzyme was set with the help of grid box. The X, Y and Z dimensions were set to  $3.849 \times 32.4702 \times 15.8499$ , the X, Y and Z centers were adjusted based on the active site of the receptor. After the docking runs for all the compounds, 10 configurations for each protein–ligand complex were generated for all the phytocompounds along with the text files of dock scoring results were produced for the purpose of manual comparative analysis.

## 2.6 Data Analysis and Visualization

The protein–ligand complexes as well as the molecular interaction were all visualized using PyMOL© Molecular Graphics (version 1.3, 2010, Shrodinger LLC). LigPlot<sup>+</sup> © Roman Lakoskwi (version 2.1.) and Protein–Ligand interaction Profiler's web server (<https://projects.biotec.tu-dresden.de/plip-web/plip>) [19] were further deployed to retrieve molecular interactions that occur between the Compounds and VEGFR-2.

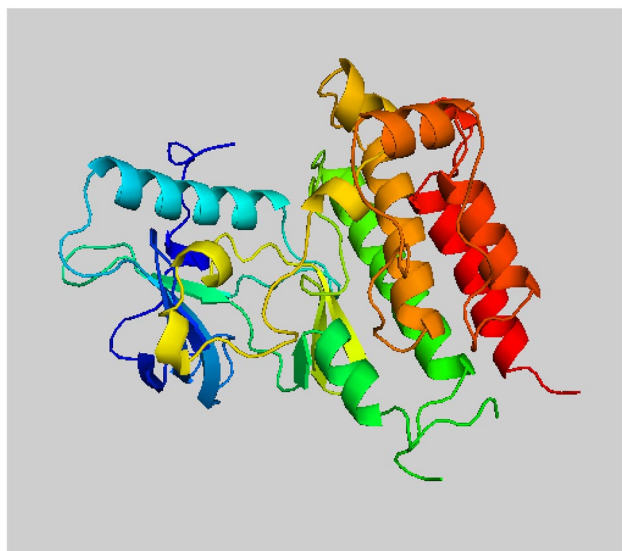
## 2.7 ADME/T Prediction

Absorption, distribution, metabolism, excretion, and toxicity (ADMET) of compounds are their pharmacokinetic properties and are needed to be evaluated to determine their activity

inside the body. The ADMET properties of the ligands were analyzed using admetSAR, an online ADMET prediction tool (<http://lmmd.ecust.edu.cn:8000/>) as described in [20] with some slight modification.

## 3 Results and Discussions

Lipinski's rule of five for all the molecules was listed in Table 1. These molecules must possess following properties to be considered oral drug-like. They are: molecular weight < 500, number of hydrogen bond donors < 5, number of hydrogen bond acceptors < 10, ALogP < 5, and violation with no more than 1. These drug-like molecules also satisfy ADME properties. All the remaining compounds violated one rule (AlogP i.e. lipophilicity) except for 3-Methoxy-2,3dimethylundec-1-ene and axitinib violated no rule. The violation noticed from this study was mainly lipophilicity. Lipophilicity is one of the important properties to predict oral bioavailability of drug molecule as this affects the absorption, hydrophobic drug-receptor interactions, metabolism of molecules as well as their toxicity in the body; as higher ALogP is linked to lower absorption and vice versa [4, 21, 22] hence, the need to enhance these bioactive compounds in a way that will improve their overall physicochemical properties. Thus, all bioactive compounds that violated one rule were further considered for molecular docking analysis (Figs. 1, 2).



**Fig. 1** Vascular endothelial growth factor receptor-2 (VEGFR-2) 3D crystal structure

In the process of activating VEGFR-2 kinase, ATP is consumed. The catalytic domain of VEGFR-2 is located between the N-terminal lobe and C-terminal lobe, which housed the ATP binding site where many kinase inhibitors act as ATP mimetics and compete with the cellular ATP for binding with the ATP binding site; consequently suppressing the receptor auto phosphorylation [2, 6]. As previously reported, the ATP binding site of VEGFR-2 constitute residues such as Leu838, Gly839, Ala864, Lys866, Leu868, Glu883, Lys885, Leu887, Val914, Glu915, Phe916, Cys917, Lys918, Phe919, Gly920, Asn921, Leu926, Arg927, Leu1033, Ser1035, Cys1043, Asp1044, Phe1045, Arg1049 and Lys1053 [2, 4].

Docking is the process that identifies the best binding conformation or pose for a ligand, within the active site of a protein receptor with known structure [23, 24]. Best binding conformations does not manifest as a very low binding energy values alone but the type of molecular interactions such as hydrogen bond, hydrophobic and electrostatic interactions, with essential amino acid residues in the binding pocket of our receptor [25]. Before docking the bioactive compounds with our target protein, few steps were taking to validate the docking procedure deployed in this present study as to provide answer to the question of how trustworthy the protocols and docking tools were in generating correct binding signatures and quality interaction between protein and the bioactive compounds under study. The validation procedure yields a successful regeneration of the

ligand binding pose in an analogous way to the experimental results (Fig. 3).

The bioactive molecules that scaled through drug likeness screening were docked successfully with VEGFR-2. Those bioactive molecules that had the lowest binding energy were considered the best ligand molecules in inhibiting VEGFR-2 since lower binding energy (Kcal/mol) corresponds to higher binding affinity indicating inhibition [26]; consequently predict that these bioactive compounds isolated from *R. taedigera* possess anti-angiogenic ability. Table 3 and Fig. 3a–p shows the results of molecular docking between the assessed active compounds with VEGFR-2. The docking results indicate that all bioactive compounds from the *R. taedigera* seed oil show better binding positions with VEGFR-2 except for 6-Octadecanoic acid and 3-Methoxy-2,3-dimethylundec-1-ene by having a relatively higher binding energy values of  $-4.1$  and  $-5.4$  kcal/mol respectively, while all other bioactive compounds had binding energy value between  $-6.1$  and  $-8.9$ . Among the bioactive compounds with the best binding positions, compound 12 as listed on Table 2 had the best binding position with a binding energy value of  $8.9$  kcal/mol. This bioactive compound established hydrophobic interactions with Arg1025, Asp1026, Arg1030, Asn1031, Asp1044, Ala1048, Arg1049, Asp1050, Ile1051, Arg1064 and Tyr1080 in the ATP binding site of VEGFR-2. The interactions between this bioactive compound and these above listed hydrophobic amino acids indicates that the compound penetrated deeply into the ATP binding gouge (see Fig. 4p) might be why it had the lowest binding energy as well may to the inhibition of the role of VEGFR-2 in angiogenesis.

Summarily, seven bioactive compounds from the seed oil formed hydrogen bonds with Asn921 and Arg1049; two bioactive compounds formed hydrogen bond with Asp1044; two compounds formed hydrogen bond with Asn921; one compound formed hydrogen bond with Phe843 and Gly1046; and one compound formed hydrogen bond with Lys866. Similarly, all bioactive compounds established hydrophobic interaction with several amino acids residues (Table 2 and Fig. 4). Arg1049 and Lys866 were found to form salt bridge with the carboxylate group of nine bioactive compounds with Arg1049 having the larger number (8) through the protein–ligand interaction profiler server (<https://projects.biotec.tu-dresden.de/plip-web/plip>). Deductively, bioactive compounds of *R. taedigera* oil seed uphold excellent non-covalent interactions with the surrounding amino acids in the ATP binding gouge as consequence yield greater protein–ligand complexes (Fig. 4a–p). The non-covalent

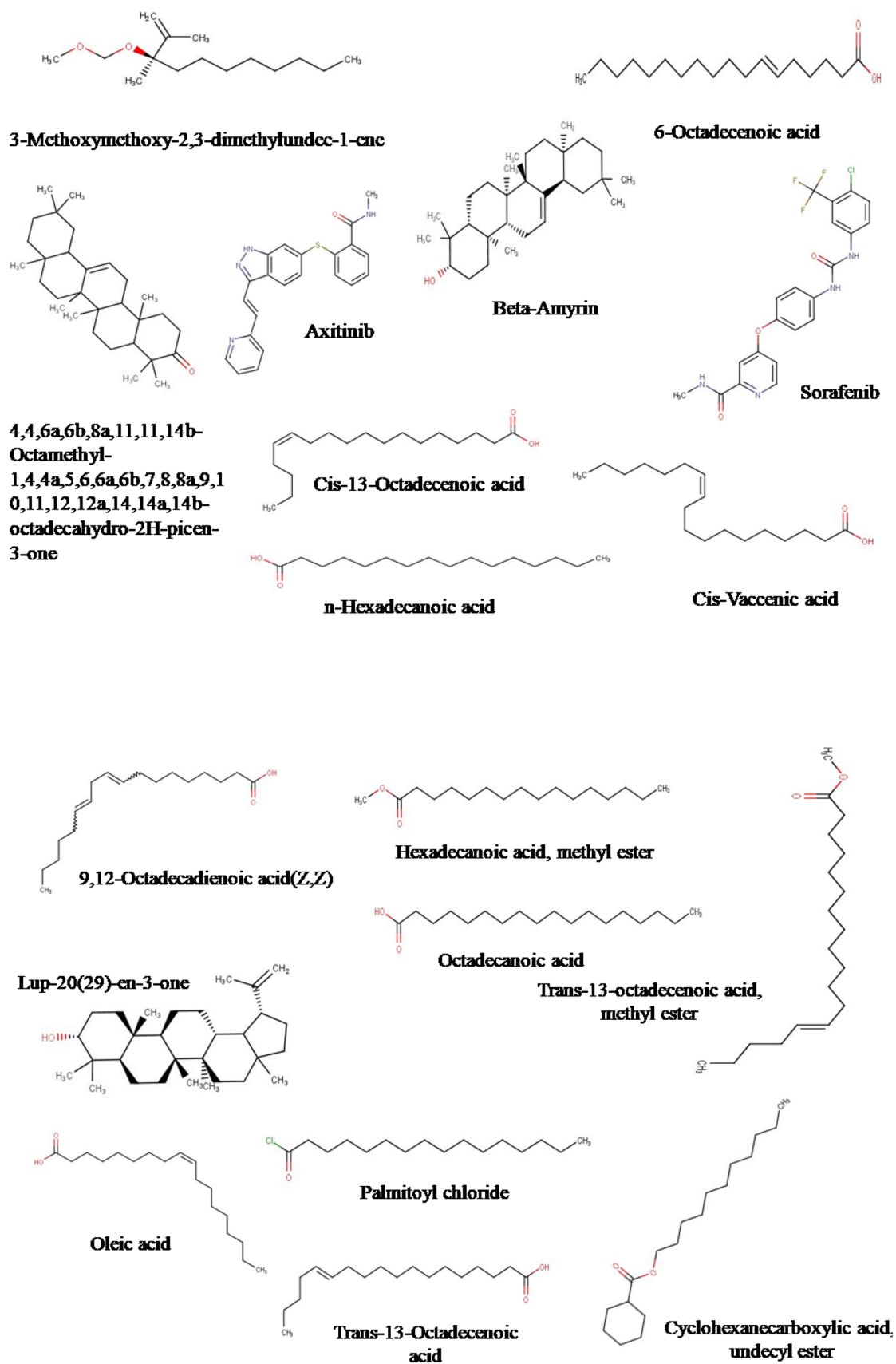
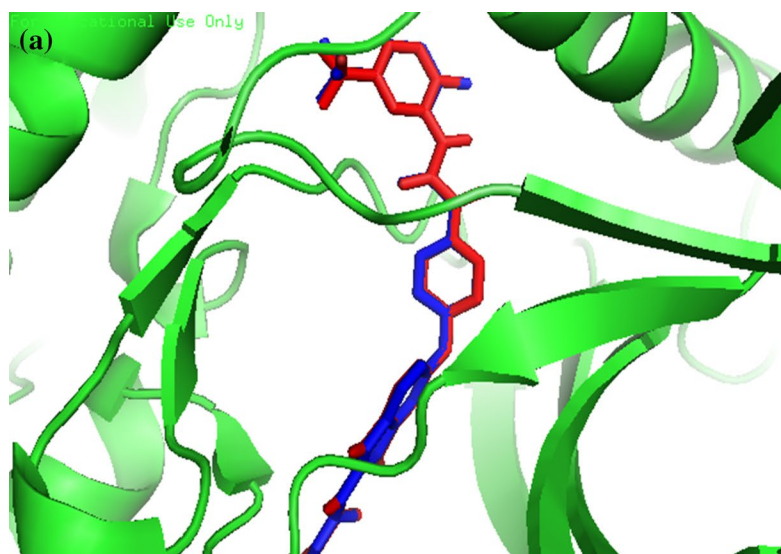
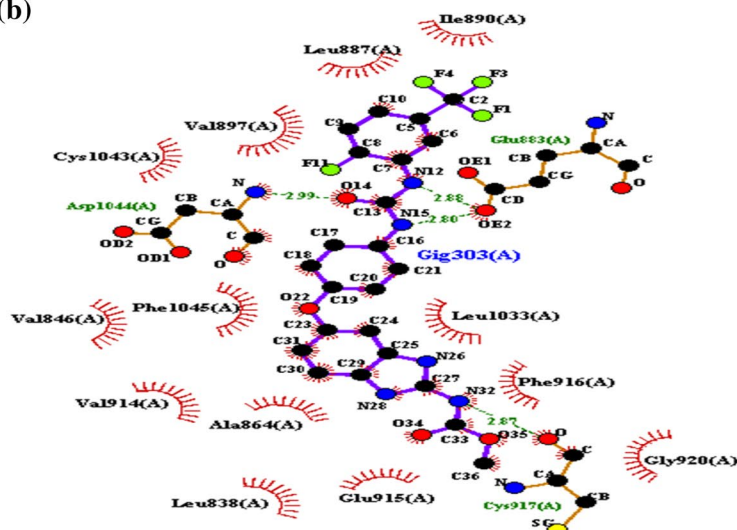


Fig. 2 Structures of bioactive compounds from *Raphia taedigera* seed oil, axitinib and sorafenib

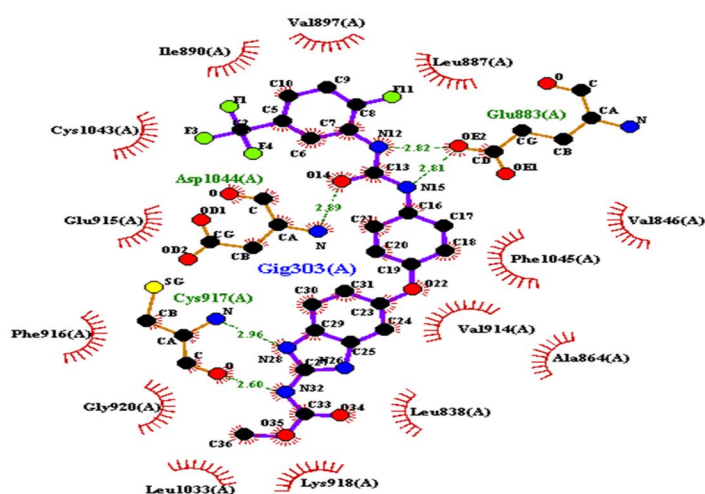
**Fig. 3** Verification of docking protocol. This vital process can enhance the accuracy and reliability of a molecular docking experiment. **a** Comparison of binding modes for co-crystallised ligand (blue) vs. re-docked ligand (red) shown as stick representation. Molecular docking protocol accurately regenerated the binding configuration of crystallographically determined protein–ligand complex. **b** Molecular interaction showing the essential hydrogen bonds (green dotted lines) and hydrophobic interactions with amino acid residues (red curves) for re-docked ligand. **c** Molecular interaction generated by LigPlus for co-crystallized ligand with VEGFR-2 active site (see online version for colours)



(b)



(c)



**Table 2** The results of molecular docking study between the bioactive compounds isolated from *Raphia taedigera* seed oil and VEGFR-2

S/N	Compound name	Binding energy (Kcal/mol)	Number of H-bond formed	Residues involved in H-bond formation	Distance (Å)	Residues involved in Hydrophobic interaction	Residues involved in Salt bridge
1	Hexadecanoic acid, methyl ester	- 6.1	1	Asp1044	3.06	Leu838, Val846, Ala864, Lys866, Glu883, Leu887, Val897, Val914, Phe916, Leu1033, Cys1043, Asp1044 and Phe1045	Arg1049 with carboxylate group at a distance of 4.89 Å
2	<i>n</i> -Hexadecanoic acid	- 6.2	3	Asn921 and Arg1049	3.04 (3.04) and 3.00	Leu838, Val846, Ala864, Lys866, Val897, Val914, Gly920, Asn921, Leu1033, Cys1043, Asp1044, Phe1045 and Arg1049	Arg1049 with carboxylate group at a distance of 4.80 Å
3	Trans-13-octadecenoic acid, methyl ester	- 6.1	2	Asn921	2.94 and 2.98	Leu838, Val846, Ala864, Lys866, Phe916, Cys917, Gly920, Asn921, Leu1033, Phe1045 and Arg1049	-
4	Oleic Acid	- 6.4	3	Asn921 and Arg1049	3.28 (2.85) and 3.06	Val846, Ala864, Lys866, Glu883, Val897, Val914, Phe916, Cys917, Gly920, Asn921, Leu1033, Cys1043, Asp1044, Phe1045 and Arg1049	Arg1049 the carboxylate group at a distance of 4.81 Å
5	Octadecanoic acid	- 6.1	2	Asn921 and Arg1049	3.03 and 3.20	Leu838, Val846, Ala864, Lys866, Glu883, Val897, Val914, Gly920, Asn921, Leu1033, Cys1043 and Phe1045	Arg1049 the carboxylate group at a distance of 4.89 Å
6	<i>Cis</i> -13-Octadecenoic acid	- 6.3	3	Asn921 and Arg1049	3.22 (2.97) and 3.10	Leu838, Val846, Ala864, Lys866, Val914, Cys917, Gly920, Asn921, Leu1033, Cys1043, Asp1044 and Phe1045	Arg1049 the carboxylate group at a distance of 4.87 Å
7	6-Octadecenoic acid	- 4.1	-	-	-	Leu838, Val846, Ala864, Lys866, Val914, Phe916, Lys918 and Gly920	Lys866 with carboxylate group at a distance of 4.84 Å
8	<i>Cis</i> -Vaccenic acid	- 6.6	3	Asn921 and Arg1049	3.20 (2.95) and 3.04	Leu838, Val846, Lys866, Glu883, Val914, Phe916, Cys917, Gly920, Asn921, Leu1033, Cys1043, Asp1044, Phe1045 and Arg1049	Arg1049 with carboxylate group at a distance of 4.87 Å

Table 2 (continued)

S/N	Compound name	Binding energy (Kcal/mol)	Number of H-bond formed	Residues involved in H-bond formation	Distance (Å)	Residues involved in Hydrophobic interaction	Residues involved in Salt bridge
9	Palmitoyl chloride	- 6.1	2	Asn921	3.00 and 3.11	Leu838, Val846, Lys866, Val897, Val914, Cys920, Asn921, Leu1033, Cys1043 and Phe1045	-
10	Trans-13-Octadecenoic acid	- 6.2	3	Asn921 and Arg1049	3.05 (2.92) and 2.97	Leu838, Val846, Ala864, Lys866, Glu883, Val897, Val914, Cys917, Gly920, Asn921, Leu1033, Asp1044, Phe1045 and Arg1049	Arg1049 with carboxylate group at a distance of 4.95 Å
11	9,12-Octadecadienoic acid(Z,Z)	- 6.7	2	Asp921 and Arg1049	2.93 and 3.05	Leu838, Val846, Ala864, Lys866, Glu883, Leu887, Val897, Val914, Glu915, Phe916, Gly920, Asn921, Leu1033, Cys1043, Asp1044, Phe1045 and Arg1049	Arg1049 with carboxylate group at a distance of 4.94 Å
12	4,4,6a,6b,8a,11,11,14b-Octamethyl-1,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,14,14a,14b-octadecahydro-2H-picen-3-one	- 8.9	-	-	-	Arg1025, Asp1026, Arg1030, Asn1031, Asp1044, Ala1048, Arg1049, Asp1050, Ile1051, Arg1064 and Tyr1080	-
13	3-Methoxymethoxy-2,3-dimethylundec-1-ene	- 5.4	-	-	-	Leu838, Val846, Lys866, Glu883, Val912, Val914, Cys917, Lys918, Gly920, Asn921, Leu1033 and Phe1045	-
14	Cyclohexanecarboxylic acid, undecyl ester	- 7	1	Asp1044	3.11	Leu838, Val846, Ala864, Lys866, Glu883, Leu887, Ile890, Val897, Val914, Leu1017, His1024, Leu1033, Cys1043, Asp1044 and Phe1045	-
15	Beta-Amyrin	- 7.9	1	Lys866	3.07	Phe843, Lys866, Ala879, Glu883, Ile886, Leu887, Ile890, Asp1044 and Gly1046	-
16	Lup-20(29)-en-3-one	- 8.1	2	Phe843 and Gly1046	3.15 and 2.70	Phe843, Ala879, Glu883, Ile886, Leu887, Asp1044 and Gly1046	-



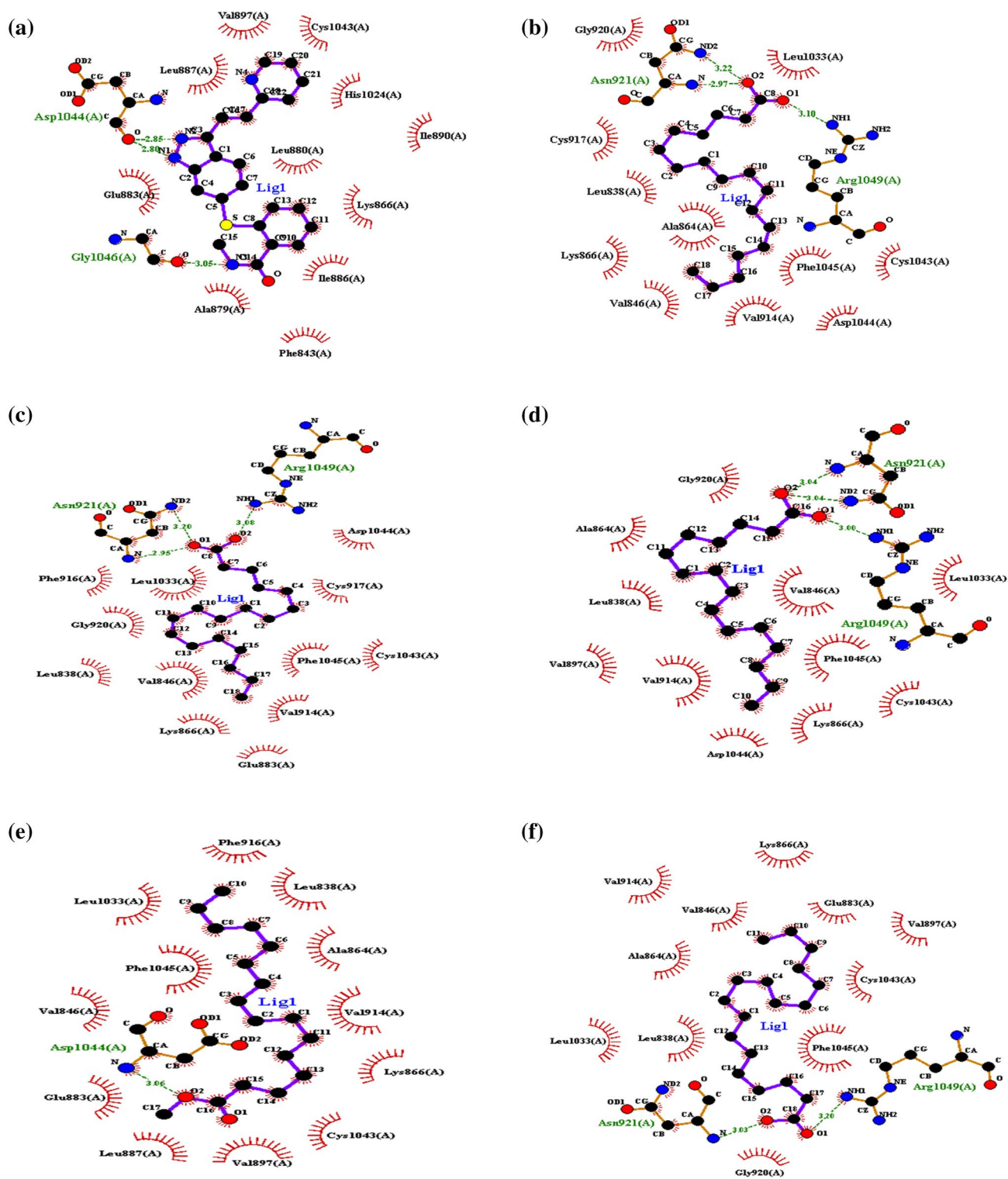
Table 2 (continued)

S/N	Compound name	Binding energy (Kcal/mol)	Number of H-bond formed	Residues involved in H-bond formation	Distance (Å)	Residues involved in Hydrophobic interaction	Residues involved in Salt bridge
17	Sorafenib	- 7.4	5	Arg1030, Arg1049, Asp1050 and Tyr1080	3.03 (3.14), 2.98, 2.91 and 3.05	Arg1025, Asp1026, Arg1030, Asp1044, Ala1048, Arg1049, Asp1050, Pro1066 and Tyr1080	-
18	Axitinib	- 8.4	3	Asp1044 and Gly1046	2.85 (2.80) and 3.05	Phe843, Lys866, Ala879, Leu880, Glu883, Ile886, Leu887, Ile890, Val897, His1024, Cys1043, Asp1044 and Gly1046	-

The docking was carried out using AutoDock Vina-Python prescription Suite 0.8

interactions reported in this present in silico study viz; hydrogen bond, hydrophobic interaction and salt bridge formations, were earlier reported [27–29] to provide stability to the protein–ligand complexes and also influence the binding energy values of the ligand in complex with a protein.

The rationale behind conducting Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) tests of any chemical compound within human body is to determine the pharmacological and pharmacodynamic properties of a candidate drug molecule within a biological system. ADMET properties were predicted using pharmacokinetic parameters of ADMETSAR server for 14 candidate molecules with 2 control drugs (Axitinib and Sorafenib) after successful docking. All the molecules can absorb in intestine using Caco-2 permeability and Human Intestinal Absorption (HIA) except Axitinib and Sorafenib (control drugs) in case of Caco-2 permeability listed in Table 3. All the molecules also exhibit property for BBB penetration. These molecules have high plasma protein binding rate. Most of them (9) reside in mitochondria and rests of them (6) are localized in the plasma membrane. Only one is found to be localized in lysosomes. Among drug metabolism, none of the molecules would be metabolize by CYP2D6, but beta-amyrin, lup-20(29)-en-3-one and sorafenib would act as substrate for CYP3A4 while axitinib would inhibit CYP3A4. No single molecule is found to be involved in toxicity from AMES test. *Salmonella typhimurium* reverse mutation assay (AMES) toxicity is a preliminary drug screening test to analyze whether the drug causes any mutation in bacteria *Salmonella typhimurium*. Two candidates among all are predicted to be cancer-causing molecules. Axitinib and Sorafenib were predicted to cause human hepatocytes toxicity (Human HT) since human liver is the main site of various drugs and xenobiotic agents' metabolism which is extremely vulnerable to their harmful effects. Human-HT involves any type of injury done to the liver that may lead to organ failure and even death [20]. Acute toxicity in rats from LD50 value was also estimated [20] where the control drugs had a higher value than the bioactive compounds. The in silico ADMET result of this research shows that bioactive compounds presents in *R.taedigera* might be safer than axitinib and sorafenib. We recommend other control aside axitinib and sorafenib be used in the future research and further study using molecular dynamics simulation of at least 100 ns also recommended.



**Fig. 4** Molecular interactions of bioactive compounds isolated from *Raphia taedigera* seed oil, axitinib and sorafenib within the active site of VEGFR-2 (a) axitinib (b) *cis*-13-octadecenoic acid (c) *cis*-vaccenic acid (d) *n*-hexadecanoic acid (e) hexadecanoic acid, methyl ester (f) octadecanoic acid (g) oleic acid (h) palmitoyl chloride (i) sorafenib (j) *trans*-13-octadecenoic acid, methyl ester (k) *trans*-13-octadecenoic acid (l) Cyclohexanecarboxylic acid, undecyl ester (m) 9,12-octa-

decadienoic acid (*Z, Z*) (n) *b*-amyryn (o) lup-20(29)-en-3-one (p) 4,4,6a,6b,8a,11,11,14b-Octamethyl-1,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,14,14a,14b-octadecahydro-2H-picen-3-one (**compound 12**) as obtained from molecular docking using Autodock Vina. 2D interaction analysis shows hydrogen bond (green dashed lines) and hydrophobic interaction (Red curved lines) using LigPlot

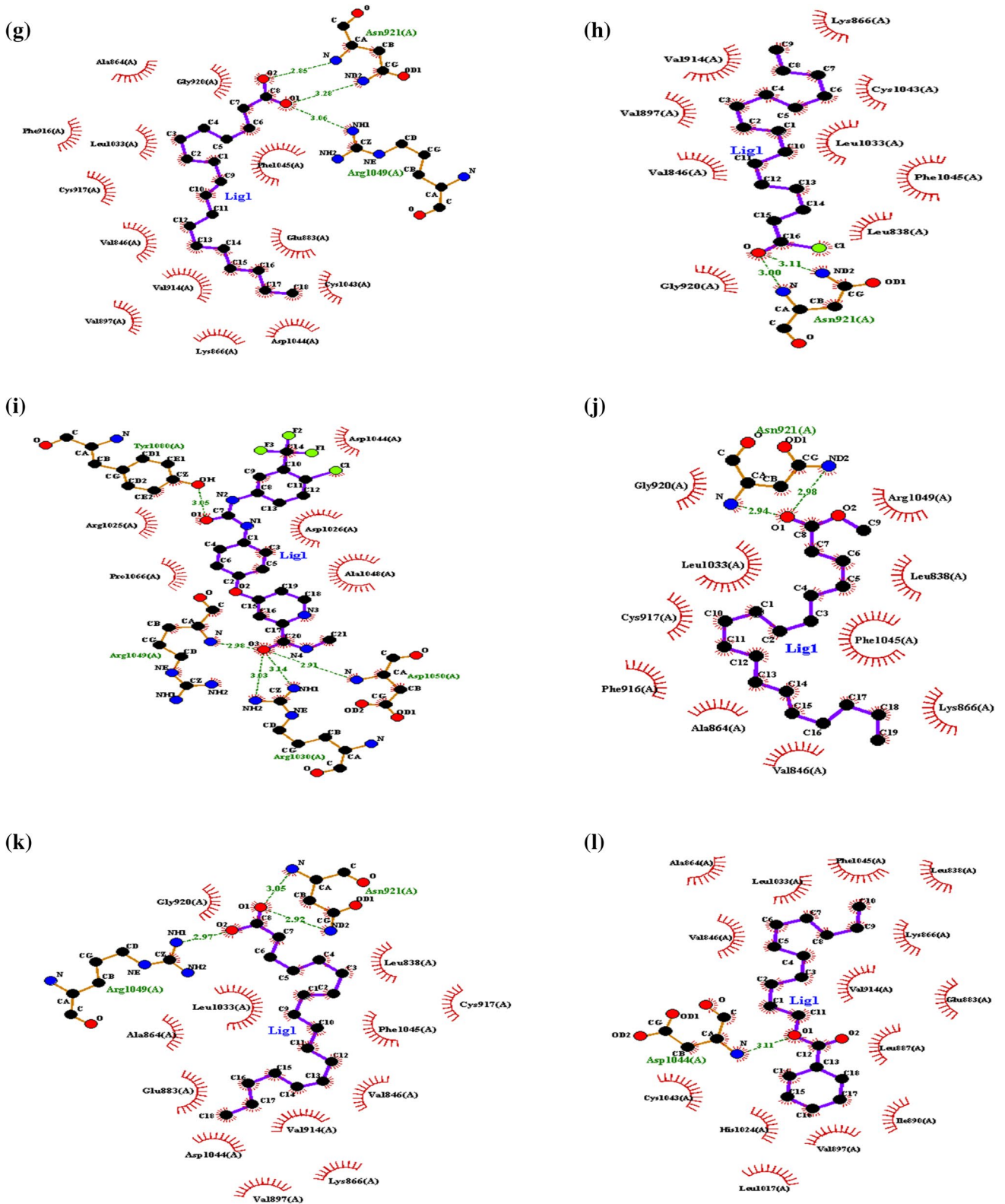


Fig. 4 (continued)

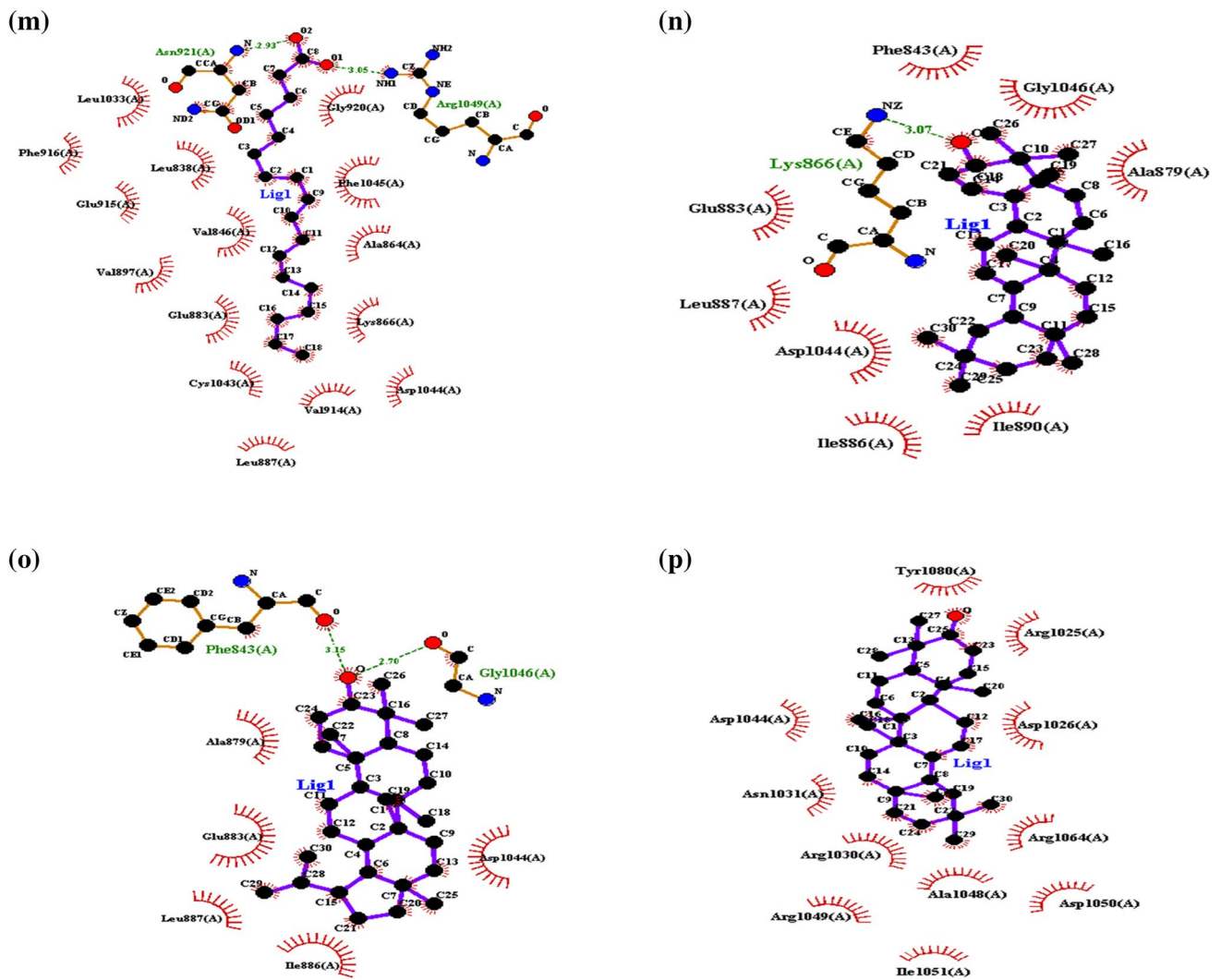


Fig. 4 (continued)

**Table 3** ADMET properties of the bioactive compounds from *Raphia taedigera* seed oil predicted using ADMETSAR server having the best binding signatures including our control drugs

S/N	Compound name	Blood brain barrier	Caco-2 permeability	HIA	Protein plasma binding	Sub-cellular localization	CYP2D6 inhibitor/substrate	CYP3A4 inhibitor/substrate	AMES mutagenicity	Human HT	Carcinogens	LD50 in rats (mol/kg)
1	Hexadecanoic acid, methyl ester	Positive	Positive	Positive	High	Mitochondria	No/no	No/no	Negative	Negative	Negative	
2	n-Hexadecanoic acid	Positive	Positive	Positive	High	Mitochondria	No/no	No/no	Negative	Negative	Negative	1.3275
3	Trans-13-octadecenoic acid, methyl ester	Positive	Positive	Positive	High	Plasma membrane	No/no	No/no	Negative	Negative	Positive	1.7357
4	Oleic acid	Positive	Positive	Positive	High	Plasma membrane	No/no	No/no	Negative	Negative	Negative	1.3991
5	Octadecanoic acid	Positive	Positive	Positive	High	Mitochondria	No/no	No/no	Negative	Negative	Negative	1.3275
6	Cis-13-Octadecenoic acid	Positive	Positive	Positive	High	Plasma membrane	No/no	No/no	Negative	Negative	Negative	1.4005
7	Cis-Vaccenic acid	Positive	Positive	Positive	High	Plasma membrane	No/no	No/no	Negative	Negative	Negative	1.3991
8	Palmitoyl chloride	Positive	Positive	Positive	High	Mitochondria	No/no	No/no	Negative	Negative	Positive	1.6088
9	Trans-13-Octadecenoic acid	Positive	Positive	Positive	High	Plasma membrane	No/no	No/no	Negative	Negative	Negative	1.4005
10	9,12-Octadecadienoic acid(Z,Z)	Positive	Positive	Positive	High	Plasma membrane	No/no	No/no	Negative	Negative	Negative	1.3991
11	4,4,6a,6b,8a,11,11,14b-Octamethyl-1,4,4a,5,6,6a,6b,7,8,8a,9,10,11,12,12a,14,14a,14b-octadecahydro-2H-picen-3-one	Positive	Positive	Positive	High	Mitochondria	No/no	No/no	Negative	Negative	Negative	1.8409
12	Cyclohexanecarboxylic acid, undecyl ester	Positive	Positive	Positive	High	Mitochondria	No/no	No/no	Negative	Negative	Negative	1.4527
13	Beta-Amyrin	Positive	Positive	Positive	High	Mitochondria	No/no	No/yes	Negative	Negative	Negative	2.0842
14	Lup-20(29)-en-3-one	Positive	Positive	Positive	High	Lysosome	No/no	No/yes	Negative	Negative	Negative	3.3838
15	Sorafenib	Positive	Negative	Positive	High	Mitochondria	No/no	No/yes	Negative	Positive	Negative	2.7885
16	Axitinib	Positive	Negative	Positive	High	Mitochondria	No/no	Yes/no	Negative	Positive	Negative	2.3649

AMES Salmonella typhimurium reverse mutation assay, *Blood Brain Barrier-P* blood brain barrier penetration, *Human HT* Human hepatocytes toxicity

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## Compliance with ethical standards

**Ethical Statement** I Awonyemi, Olatunde Isaac consciously assure that for the manuscript “In Silico Molecular Docking of Bioactive Molecules Isolated from *Raphia taedigera* Seed Oil as Potential Anti-cancer Agents Targeting Vascular Endothelial Growth Factor Receptor-2” the following is fulfilled: (1) This material is our original work, which has not been previously published elsewhere. (2) The paper is not currently being considered for publication elsewhere. (3) The paper reflects the our research and analysis in a truthful and complete manner. (4) The paper properly credits the meaningful contributions of co-authors and co-researchers. (5) The results are appropriately placed in the context of prior and existing research. (6) All authors have been personally and actively involved in substantial work leading to the paper, and will take public responsibility for its content.

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