

The Intervention of oil constituents from *Garcinia kola* against epidermal growth factor receptor in breast cancer using in-silico analysis

A. D. Folayan (✉ folayanadeniyi@gmail.com)

Federal University of Agriculture

J. K. Akintunde

Federal University of Agriculture

A. J. Akamo

Federal University of Agriculture

A. S. Oyelakin

Federal University of Agriculture

Research Article

Keywords: Breast cancer, Epidermal growth factor receptor, *Garcinia kola* oil, Docking, Gas chromatography-mass spectrometry (GC-MS), 1,2-Benzenediol, 3,5- bis (1,1-dimethyl ethyl)-

Posted Date: March 28th, 2023

DOI: <https://doi.org/10.21203/rs.3.rs-2736829/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

The most common form of cancer among women worldwide and the leading cause of cancer death among black women is breast cancer (BC). Important biological targets in the therapy of cancer, epidermal growth factor receptors (EGFR) have been found to be substantially expressed in cases of triple-negative breast cancer (TNBC). Thus, drugs that focus on this receptor may reduce the incidence of breast cancer. This study, therefore, aims at investigating the inhibitory potential of oil constituents from *Garcinia kola* against epidermal growth factor receptors in breast cancer using in-silico approaches. Human EGFR structure was obtained from Maestro module version 11.8. Docking of *Garcinia kola* oil constituents against human EGFR was done using Auto/Vina in Pymol 4.2 while physicochemical and pharmacokinetic parameters were assessed using Qikprop. Phytochemical analysis was carried out with GC-MS. This study revealed the presence of twenty phytochemicals in *Garcinia kola* oil. Docking of isolated compounds against EGFR showed that 1,2-Benzenediol, 3,5- bis (1,1-dimethyl ethyl)- and Phyto acetate had the best docking scores of -7.309 and -6.326 respectively. Many of the components of *Garcinia kola* oil may be eligible as oral medications because they met the criteria for drug-likeness while still being within allowable limits. A significant portion of the chemicals in *Garcinia kola* oil may act as novel EGFR inhibitors and may be a potent anti-breast cancer drug, according to in-silico data from molecular docking scores, binding free energy, projected pIC₅₀ values, and ADMET evaluation. To confirm the oil components of *Garcinia kola* as an anticancer agent, however, more research is needed.

Introduction

The most diagnosed form of cancer among the female population across the globe is breast cancer (BC) (WHO 2018). Although it has been noted that men can also be affected, the incidence is lower in men (0.5–1%) than in women (due to changes in the hormonal environment and low breast tissue) (Yalaza et al. 2016). BC has been rated the commonest cause of cancer death among black women while it is the second foremost cause of cancer mortality among women globally Miller et al. 2021; Giaquinto et al., 2022). A study has it that two women die of BC every 26 minutes (NBCC, 2022). In 2020, about 700, 000 deaths were documented to have arisen from BC globally (Anderson et al. 2021). Similarly, the American Cancer Society estimated that in 2022, more than 43, 000 women and a little above half a thousand men would die of BC (ACS 2022). Although, the mortality rate arising from BC has reduced in recent times, nevertheless, the incidence is on the increase and it will continue to rise in direct proportionality with population growth (Watkins 2019).

Several studies have been carried out to combat cancer via molecular targeted therapy (Lheureux et al. 2017; Song et al. 2019; Sun et al. 2021). One of the most distinguished molecular targets recognised in modern-day cancer research is the epidermal growth factor receptor members (EGFR)/ErbB family (Arienti et al. 2019). Currently, the suitability of a breast cancer therapy remedy is premised upon the molecular characteristics that are peculiar to various cancer subtypes. EGFR has been noted to be overexpressed in not less than 50% of all Triple Negative Breast Cancer (TNBC) cases (Masuda et al. 2012; Oshi et al. 2021). Consequent to this high rate of expression of EGFR in TNBC, agents that can inhibit EGFR have

become highly sought-after molecular targets in breast cancer treatment. A Plethora of studies have been carried out on EGFR inhibitors; however, the results still show a lot of gaps between the desired destination and the current status (Masuda et al. 2012). It is therefore highly imperative to continue these scientific inquiries on EGFR inhibitors to alleviate the risks of breast cancer.

There are copious in-silico approaches, however, the ones employed in this study include docking analysis, Adsorption, distribution, metabolism, excretion and toxicological (ADMET), and Molecular mechanics with generalized Born and surface area solvation (MM/GBSA) binding free energy. Today, an appropriate and cost-effective technique to comprehend the mechanism of action proteins with ligands to attain accuracy in drug design and discovery is molecular docking. This involves analysis of the configuration and orientation of molecules binding at the sites of molecular targets (Kitchen et al. 2004; Liu et al. 2018) It may sometimes involve techniques like homology modelling, X-ray crystallography and so on (Salmaso & Moro, 2018).

Following the result of the original algorithms which took place some 4 decades ago, docking has therefore emerged as the most commonly engaged method to forecast the orientation of binding of likely drugs on their targets (Kapetanovic 2018) thus, becoming an imperative implement in drug discovery (Meng et al. 2011). Therefore, engaging in-silico perspective to search for safe and effective natural agents that can act as potential inhibitors of proteins implicated in the pathophysiology of breast cancer is a dynamic zone of research.

Garcinia kola Heckel (Guttiferae) seed is believed to possess strong medicinal values and promote longevity (Farombi 2011; Dogara et al. 2022) In Africa, the extractive products of this plant have been used in managing numerous diseases like liver disorder, renal and testicular damage (Adedara et al. 2015), benign prostate hyperplasia (Kalu et al. 2016), and it possesses immunomodulatory properties (Cetkovic-Cvrlje et al. 2022). Kolaviron, a component of the seed, prevented insults to membrane integrity initiated at the initiation stage of colon cancer (Eboh et al. 2015) and is also a potent inhibitor of aromatase of breast cancer (Elekofehinti et al. 2016). In another study by (Folayan et al. 2020), the hexane fraction of the seeds ameliorated hepatorenal toxicity in mice. However, there is a paucity of data on the molecularly targeted inhibitory potential of *Garcinia kola* oil constituents against breast cancer. Thus, the goal of this study was to evaluate the potential of *Garcinia kola* oil constituents against EGFR, a protein implicated in breast cancer, using in silico perspective.

Methods

Collection of plants

Fresh *Garcinia kola* seeds were procured from a farmers' market in Ibadan, Nigeria. In one of our previous studies, the seeds had been certified at the Department of Botany, University of Ibadan, Nigeria while an existing voucher specimen was retrieved from the herbarium section (Folayan et al. 2020).

Plant preparation

The testa of the seeds was removed before slicing, cutting and air-drying for four weeks. The dried seeds were blended using an electric grinder. About 3 kg of the pulverized seed was fed into a Soxhlet extractor for the oil extraction using n-hexane. Consequently, the concentration of n-hexane was carried out using a rotary evaporator (40°C) and water bath to ensure the complete removal of solvent thus yielding a viscous deep-brown colour oil (18% yield). The resulting *Garcinia kola* oil was then kept in a small glass bottle for further investigation.

Gas Chromatography- mass spectrometry (GC-MS) analysis

Garcinia kola oil was examined via GC-MS using the Agilent technologies 7890 A GC system model instrument furnished with a VF – 5 Ms. bonded silica capillary column of length 30m and varying thickness of the film; 0.25mm diameter and 0.25 mm. An electron ionization mechanism with an ionization energy of 70 electron volts is integrated into the GC-MS detector. The mobile phase (Helium gas of 99.99% purity) flowed continually at 1 ml/min. The oven's temperature was set to range from 80°C for 120 seconds at 10°C/minute to 240°C for 360 seconds, while the temperatures for the injection and mass transfer lines were set at 200°C and 240°C, respectively. The proportion of individual isolated compounds in the oil was reported as % with a normalised peak area. Mass spectrum interpretation was carried out via the catalogue of the National Institute of Standards and Technology (NIST) library, containing spectral patterns well above 62,000. The structure of compounds was placed side-by-side with the spectra of the NIST library database for comparison (Fig. 2). The entire period expended on GC-MS was 35 minutes.

Molecular Docking studies

Molecular docking involves the binding of a molecule into the pocket of another within the 3D space. Attention has been focused recently on molecular docking perspectives for drug design and formulation. Various docking steps were engaged in this study before conclusions about the potency of constituents of *Garcinia kola* oil were reached.

Crystal Protein Preparation

Wizard of maestro v11.8 for protein preparation was used to get the EGFR crystal structure (PDB ID- 2J6M). The procedure defined by Elekofehinti et al. (2021) & Elekofehinti et al. (2020) was engaged to obtain the protein's structure. The protein was pre-processed in line with the method of the Schrodinger suite (2012). Further, refining of the protein took place via optimization of the Hydrogen bond link with PROPKA while eliminating H₂O molecules 3 H-bonds to non-waters (Olsson et al. 2011). The OPLS3 force field was used in carrying out minimization in order to evade the existence of steric clashes in the structure. When the non-hydrogen atoms' Root Mean Square Deviation (RMSD) reached 0.30 Å, the minimization process was terminated.

Phyto-compounds preparation

GC-MS served as the tool to identify the library of compounds extracted from *Garcinia kola* oil while these were drawn via MarvinSketch (version 19.26). Lig. prep was further used to prepare the compounds. The Lig. prep panel allows structural conversions; generation of variations in structures and removal of any undesirable structure(s). After stereoisomer computer analysis was enabled to yield not more than 32 per ligand. Maestro remained the output while the force field, OPLS3 operated within a pH range of 5.0 – 9.0 using epik (Schrodinger Suite, 2012).

Generation of receptor grid

A receptor grid creation panel was used to produce a receptor grid file that shows the receptor's active location for ligand docking. To unstiffen the receptor's non-polar regions, the radii of the atoms with fractional atomic charges have a fixed scaling factor of 1.0 and a partial cut-off of 0.25. At coordinates 9.8, 68.0, and 93.91, which correspond to the z, y, and x axes, respectively, the receptor grid box's resolution was located.

Glide extra precision docking

Using enhanced precision and a flexible ligand sampling set, isolated compounds are docked against the active pocket of the EGFR crystal. Lig. prep was used to prepare the compounds before docking.

Induced fit docking (IFD)

A computational biology tool called IFD provides a precise way of predicting the binding attraction of new inhibitors against the protein crystal (Iwaloye et al. 2020).

Calculation of binding free energy

Using prime 2018's MM-GBSA technology, the binding free energy for the ligand-receptor complex was computed. With the use of this technology, the difference in energies between the complex and free states of the protein and its ligand after energy consumption has been reduced is measured.

The equations below are used in calculating binding energy.

$$\Delta G_{\text{bind}} = \Delta E + \Delta G_{\text{solv}} + \Delta G_{\text{SA}} \quad (\text{i})$$

$$\text{Change in Energy } (\Delta E) = \text{MEPIC} - \text{MEP} - \text{MEI} \quad (\text{ii})$$

where MEPIC, MEP, and MEI, respectively, stand in for the minimized energies for the protein-inhibitor complex, the protein, and the inhibitor.

$$\Delta G_{\text{solv}} \text{ is equal to } \Delta G_{\text{solv}} (\text{complex}) - \Delta G_{\text{solv}} (\text{protein}) - \Delta G_{\text{solv}} (\text{ligand}) \quad (\text{iii})$$

$$\Delta G_{\text{SA}} \text{ is equal to } \Delta G_{\text{SA}} (\text{complex}) - \Delta G_{\text{SA}} (\text{protein}) - \Delta G_{\text{SA}} (\text{ligand}) \quad (\text{iv})$$

The surface area-related apolar contribution to the solvation energy in equation 4 above is denoted by the symbol GSA, and the surface energies of the complex, protein, and ligand are denoted, respectively, by GSA (complex), GSA (protein), and GSA (ligand).

Test to assess drug-likeness

Drug-likeness of oil constituents of *Garcinia kola* oil was determined using Lipinski's rule of five and Canva was used for predicting this parameter (Duan et al. 2010).

Machine learning principles using automated QSAR

Generation and preparation of the dataset

On the ChEMBL database online site (www.ebi.ac.uk/chem/), the experimental dataset containing inhibitors of the epidermal growth factor receptor was located. The online server was used to blast the FASTA sequence of the receptors in order to accomplish this. While using the data-warrior package (v.2) to convert the Ms. Excel document to structure data file (SDF) format, the compounds with no pIC₅₀ were cancelled. This allowed the bioactivities and corresponding pIC₅₀ of inhibitors of the epidermal growth factor receptor to be retrieved (Sander et al. 2015). It was done to enable lig. preparation by exporting the SDF format to the maestro workspace (Schrodinger Suite, 2012). The compounds prepared were subsequently transferred to Canvas cheminformatics (Duan et al. 2010). Having subjected the inhibitors to canvas for treatment, representatives were finally selected from each ensuing cluster. This study produced clusters while a representative was carefully chosen from individual clusters to build a QSAR model.

Auto QSAR Principle

Auto QSAR is a model responsible for building and applying QSAR models through automation (Dixon et al. 2016). To put it another way, it is a computer-based algorithm developed to create a model that can predict (Schrodinger Suite 2012). It factors the 1D, 2D and 3D structural data of a molecule alongside the IC₅₀ to be modelled, as a contribution. The descriptors and fingerprints are then computed using machine-based statistical techniques to create a predictive QSAR model. Several statistical indicators, such as ranking score, Root Mean Square Error (RMSE), Standard Deviation (SD), Q², and R² values, are used to evaluate the predictive model's accuracy (de Oliveira & Katekawa 2018).

Results

GC-MS was engaged for the characterization of the oil obtained from *Garcinia kola* seeds. The result revealed that the oil contains 20 phytochemicals as depicted in Table 1. This is in consonance with (Fapohunda et al. 2017; Dogara et al. 2022). In selecting suitable therapy for breast cancer, the level of mutation or expression of EGFR has become an interesting factor being considered before a treatment option is concluded due to its overexpression in TNBC which has been connected to a range of clinical

pathologies (Hashmi et al. 2019). However, the results from therapeutic drug search for EGFR inhibitors have yielded a not-too-encouraging outcome (Masuda et al. 2012), therefore, a rich survey of the literature was carried out in selecting a suitable plant with bioactive components which might possess medicinal properties for targeting EGFR via molecular docking analysis thus becoming an auspicious novel therapy in breast cancer treatment.

Garcinia kola oil emerged as a suitable candidate as a result of its antioxidant and anticancer activity, Olatunde et al. (2021) coupled with the oil's viscous nature; the quality of edible oils is directly proportional to its viscosity (Rukke & Schüller, 2017). This current study employed glide XP docking and IFD to precisely forecast binding affinity and compounds' docking score having bound to EGFR, thus, showing compounds that have robust interaction. Details of the docking results and the interacting residues of the selective ligand-protein complex are provided in Tables 2 and 3 respectively. The docking scores of the isolated compounds range from -2.870 to 7.309 kcal/mol.

It has been established that a protein's binding site is made up of important residues within its active pocket. A good evaluation of these residues thus provides more information on the molecular interaction between proteins and ligands (Chagoyen & Pazos, 2016). Of the several amino acid residues contained in the single-chain polypeptide, EGFR, ASP 800, LYS 745, MET 793, THR 854, LEU 718, LEU 844, CYS 797, ALA 743, VAL 726, THR 790 are important (Trabalzini et al. 2022). Table 3 gives an overview of the residues that interacted within the complex formed by ligand and protein. The details of the 2-D and 3-D binding poses of two of the isolated compounds with the epidermal growth factor receptor are also shown in Figures 4 through 7, revealing the residues in the protein's active region. Table 4 provides the assessment of binding free energy. For binding free energy calculation in this study, the main contributors are recognized as solvation energy ($\Delta G_{\text{bindSolvGB}}$), Hydrogen bond (ΔG_{HBond}), Coulomb interaction ($\Delta G_{\text{Coulomb}}$), and lipophilic energy ($\Delta G_{\text{solLipo}}$) that improve the affinity of binding of the isolated compounds against its target. Tables 5a and 5b, respectively, provide the determination of drug-likeness and pharmacokinetic characteristics of the isolated components of the oil. The best model generated was calculated using kernel-based partial least square regression (KPLS), which facilitates the use of descriptors and fingerprints as independent variables and fingerprint linear 34 is the model code generated. The parameters matching the best model produced by Auto QSAR were presented in Table 7. S.D, R^2 , RMSE and Q^2 values for the model were 0.8969, 0.8865, 0.2937, and 0.3404 respectively. For the best model produced, as displayed in Fig. 8, the scatter plot details the predicted pIC50 vs the experimental pIC50. 0.3404, R^2 of 0.8865, RMSE of 0.2937, and Q^2 of 0.8969. The scatter plot gives information about the predicted pIC50 against experimental pIC50 for the finest model created as shown in Fig. 8.

Discussion

With a docking score of -7.309 kcal/mol, 1,2-Benzenediol, 3,5-bis (1,1-dimethyl ethyl)- had the highest affinity, followed by Phyto acetate and squalene with values of -6.326 kcal/mol and -4.924 kcal/mol, respectively. Because IFD permits the protein to rotate while it is attached to a ligand, it provides a

superior method for predicting binding affinity. From our observation, the IFD scores of the isolated compounds followed a different trend from the docking score. The most substantial interaction was between 9,12,15-Octadecatrienoic acid, methyl ester, (Z, Z, Z), which had an IFD value of -634.82 kcal/mol, and methyl stearate and Hexadecanoic acid, methyl ester, which had IFD ratings of -634.46 kcal/mol and -632.21 kcal/mol, respectively. This implies that these three compounds bound more intimately to the active site of EGFR thus indicating strong molecular interaction. Our study's findings revealed that several of the isolated chemicals have H-bond interaction with different amino residues but we zeroed in on two which are 9,12,15-Octadecatrienoic acid, methyl ester, (Z, Z, Z)- and Methyl stearate. As shown in Figure 4, 9,12,15-Octadecatrienoic acid, methyl ester, (Z, Z, Z)- formed hydrogen interaction with THR 854 as revealed by the 2D binding pose. However, the 3D binding pose of 9,12,15-Octadecatrienoic acid, methyl ester, (Z, Z, Z)-with EGFR as shown in fig. 5 revealed a better interaction with more residues; VAL 742, MET 793, PRO 794, PHE 795, GLY 796. Consequently, figure 6 depicts the 2D binding pose of Methyl stearate, it revealed an interaction with ASP 1003 and LYS 728. Nevertheless, the 3D binding pose of Methyl stearate as shown in figure 7, illustrates interaction with MET 793, PRO 741, ILE 740, and VAL 742. These interactions corroborate the findings of (Ongko et al. 2022).

Table 2

Molecular weight and docking results

Compounds	Docking score	Induced fit docking (kcal/mol)	Molecular weight (kcal/mol)	Predicted pIC50
1,2-Benzenediol, 3,5-bis(1,1-dimethylethyl)-.	-7.309	-591.08	222.3	5.018
Phytol acetate	-6.326	-623.64	338.6	5.112
Squalene	-4.924	-592.43	410.7	5.154
Methyltris(trimethyl siloxy) silane	-4.840	-590.62	310.7	5.165
Tetrasiloxane, decamethyl-	-4.320	-589.63	310.7	5.165
9,12,15-Octadecatrienoic acid, methyl ester, (Z, Z, Z)-	-4.232	-634.82	292.5	5.051

2-Pentadecanone, 6,10,14-trimethyl-	-4.148	-587.86	268.5	5.126
9,12-Octadecadienoic acid (Z, Z)-, methyl ester	-3.883	-590.3	294.5	5.051
Bicyclo[3.1.1] heptane, 2,6,6-trimethyl-	-3.824	-584.39	138.3	5.223
Methyl stearate	-3.786	-634.46	298.5	5.029
3,7,11,15-Tetramethyl-2- hexadecen-1-ol	-3.746	-587.61	296.5	5.178
1,1,1,3,5,5,5-Hepta methyltrisiloxa	-3.532	-587.40	221.5	5.165
8,11-Octadecadienoic acid, methyl	-3.359	-588.42	294.5	5.029
Cyclotrisiloxane, hexamethyl-	-3.123	-589.83	222.5	5.165
Hexadecanoic acid, methyl ester	-3.084	-631.72	270.5	5.029
Methyl 9-cis,11-trans- octadecadienoate	-3.036	-588.04	279.4	5.043
7,10,13-Hexadecatrienoic Acid, methyl ester	-3.005	-621.29	264.4	5.051
Neophytadiene	-2.870	-588.57	278.5	5.205

Table 3

Interacting ligand-protein complex residues

Compounds	H-Bond
9, 12, 15 -Octadecatrienoic acid, methyl ester	THR 854
Methyl Stearate	LYS 728, ASP 1003

The free energy of binding is computed in order to verify docking scores. It uses a combination of solvation and calculations based on molecular mechanics. According to research, the MMGBSA approach is the most effective at ranking a ligand's affinity for its target when the two interact, Sun et al. (2014); Maffucci et al. (2018) due to the reproducible nature of binding energies obtained via MMGBSA (Genheden & Ryde 2015). Examining the least-energy positions predicted by the scoring method allowed us to verify that the docking was accurate. According to our findings, the binding free energy, or ΔG_{Bind} , was between -76.53 and -25.36 kcal/mol. Squalene, by far, formed the most stable complex with EGFR, however other compounds such as 2-Pentadecanone, 6,10,14-trimethyl, Phytoacetate, 8,11-Octadecadienoic acid, methyl, 3,7,11,15-Tetramethyl-2-hexadecen-1-ol, and Hexadecanoic acid, methyl ester, all showed good stability with the protein. Alpha amyrin, however, demonstrated the least stability.

Table 4

Binding free energy values

S/N	COMPOUND NAME	ΔG Bind ^a	ΔG Bind Coulomb ^b	ΔG Bind Solv GB ^c	ΔG -Bind Lipo ^d	ΔG Bind Hbond ^e
1	1,2-Benzenediol, 3,5-bis(1,1-dimethylethyl)-	-60.8	-17.06	15.66	-34.74	-0.62
2	Methyl tris (trimethyl siloxy) silane	-51.42	-0.91	9.71	-28.15	0
3	2-Pentadecanone, 6,10,14-trimethyl-	-76.23	-5.05	13.47	-50.91	-0.23
4	3,7,11,15-Tetramethyl-2-hexadecen-1-ol	-75.38	-10.69	19.45	-52.7	-1.42
5	Phyto acetate	-70	0.59	17.3	-53.06	-0.05
6	1,1,1,3,5,5,5-Heptamethyltrisiloxa	-39.18	-2.2	7.01	-24.27	-0.21
7	Bicyclo[3.1.1]heptane, 2,6,6-trimethyl-	-31.11	-0.97	4.89	-36.99	0
8	Alpha-Amyrin	-25.36	-8.14	24.3	-56.75	-1.35
9	Tetrasiloxane, decamethyl-	-36.25	-0.19	12.36	-21.44	0
10	Hexadecanoic acid, methyl ester	-74.99	-3.37	11.68	-49.11	-0.52
11	Neophytadiene	-68.75	-1.34	14.48	-57.69	0
12	9,12-Octadecadienoic acid (Z,Z)-, methyl ester	-66.73	-4.32	17.95	-46.3	-0.62
13	Cyclotrisiloxane, hexamethyl-	-34.26	-0.58	5.39	-17.17	-0.01
S/N	COMPOUND NAME	ΔG Bind ^a	ΔG Bind Coulomb ^b	ΔG Bind Solv GB ^c	ΔG Bind Lipo ^d	ΔG Bind Hbond ^e
14	Methyl stearate	-61.05	-2.9	19.86	-45.56	-0.26
15	7,10,13-Hexadecatrienoic acid, methyl ester	-60.63	-2.79	14.55	-48.93	-0.25
16	9,12,15-Octadecatrienoic acid, methyl ester, (Z,Z,Z)-	-66.68	-0.02	16.33	-46.69	-0.24
17	Methyl 9-cis,11-trans-octadecadienoate	-63.85	34.38	-23.36	-47.72	-3.25
18	8,11-Octadecadienoic acid, methyl	-72.02	-3.81	16.53	-52.15	-0.08

19	Squalene	-76.53	-0.04	24.55	-54.73	0
----	----------	--------	-------	-------	--------	---

^aMM-GBSA binding free energy (kcal/mol)

^binput from Coulomb energy

^cinput from solvation energy

^dinput from lipophilic binding

^einput from hydrogen bonding

Table 5a

ADMET Properties Evaluation (Compliance to R05)

S/N	NAME OF COMPOUND	RO5 ^a	MW ^b	QPlogPo/w ^c	HBA ^d	HBD ^e
1	1,2-Benzenediol, 3,5-bis(1,1-dimethylethyl)-	0	222.327	3.227	1.5	2
2	Methyl tris(trimethylsiloxy)silane	1	310.687	5.225	0.6	0
3	2-Pentadecanone, 6,10,14-trimethyl-	1	268.482	5.789	2	0
4	3,7,11,15-Tetramethyl-2-hexadecen-1-ol	1	296.535	6.304	1.7	1
5	Phytoacetate	1	338.573	7.29	2	0
6	1,1,1,3,5,5,5-Heptamethyltrisiloxa	0	221.50		2	0
7	Bicyclo[3.1.1]heptane, 2,6,6-trimethyl-	0	138.252	4.932	0	0
8	Alpha-Amyrin	1	426.724	7.038	1.7	1
9	Tetrasiloxane, decamethyl-	1	310.687	5.553	0.6	0
10	Hexadecanoic acid, methyl ester	1	270.454	5.811	2	0
11	Neophytadiene	1	278.52	9.382	0	0
12	9,12-Octadecadienoic acid (Z, Z)-, methyl ester	1	294.476	6.385	2	0
13	Cyclotrisiloxane, hexamethyl-	0	222.463	3.132	0.6	0
14	Methyl stearate	1	298.508	6.602	2	0
S/N	COMPOUND NAME	RO5 ^a	MW ^b	QPlogPo/w ^c	HBA ^d	HBD ^e
15	7,10,13-Hexadecatrienoic acid, methyl ester	1	264.407	5.638	2	0
16	9,12,15-Octadecatrienoic acid, methyl ester, (Z,Z,Z)-	1	292.461	6.372	2	0
17	Methyl 9-cis,11-trans-octadecadienoate	1	280.45	5.743	2	1
18	8,11-Octadecadienoic acid, methyl	1	294.476	6.436	2	0
19	Squalene	1	410.725	12.614	0	0
20	Beta-Amyrin	1	426.724	7.113	1.7	1

^arule of five

^bmolecular weight

^cpredicted octanol/water partition coefficient

^dhydrogen bond acceptor

^ehydrogen bond donor

Table 5b

ADMET (Pharmacokinetic properties)

S/N	COMPOUND NAME	QPlogBB ^a	QPlogKhsa ^b
1	1,2-Benzenediol, 3,5-bis(1,1-dimethylethyl)-	-0.303	0.313
2	Methyl tris(trimethylsiloxy)silane	1.149	1.732
3	2-Pentadecanone, 6,10,14-trimethyl-	-0.613	1.026
4	3,7,11,15-Tetramethyl-2-hexadecen-1-ol	-0.907	1.231
5	Phytol acetate	-1.085	1.679
6	1,1,1,3,5,5,5-Heptamethyltrisiloxa		
7	Bicyclo [3.1.1]heptane, 2,6,6-trimethyl-	-0.925	0.383
8	Alpha-Amyrin	0.175	2.049
9	Tetrasiloxane, decamethyl-	1.207	1.855
10	Hexadecanoic acid, methyl ester	-0.926	0.995
11	Neophytadiene	1.481	1.677
12	9,12-Octadecadienoic acid (Z, Z)-, methyl ester	-1.018	1.251
13	Cyclotrisiloxane, hexamethyl-	0.844	0.761
14	Methyl stearate	-1.152	1.278
15	7,10,13-Hexadecatrienoic acid, methyl ester.	-0.825	1.037
S/N	COMPOUND NAME	QPlogBB ^a	QPlogKhsa ^b
16	9,12,15-Octadecatrienoic acid, methyl ester, (Z,Z,Z)-	-0.869	1.255
17	Methyl 9-cis,11-trans-octadecadienoate	-1.468	0.728
18	8,11-Octadecadienoic acid, methyl	-0.925	1.249
19	Squalene	1.883	2.847
20	Beta-Amyrin	0.175	2.081

QPlogBB^a: Predicted blood/brain partition coefficient.

QPlogKhsa^b: Prediction of binding to human serum albumin.

The weight of the molecule, hydrogen bond acceptors, hydrogen bond donors, predicted octanol-water partition coefficient and a number of infractions of Lipinski's rule of five (RO5) are among the predicted ADMET attributes provided in (Table 5a). In addition to determining drug-likeness, RO5 helps determine the possibility that minute molecules compounds will become oral drugs for humans. According to Lipinski's rule, a molecule must meet at least 75% of the following requirements: molecular weight < 500 Da, octanol-water partition coefficient < 5, hydrogen bond donor ≤ 5 , and hydrogen bond acceptor ≤ 10 (Lipinski et al. 2001). The success of potential drug candidates who adhere to the rule of five is thought to be increased by their tendency to have a low rate of attrition in the last phase of preclinical testing thereby boosting *the success of the drug discovery* process (Akpe et al. 2021). Table 5b, on the other hand, displays the isolated compounds' pharmacokinetic characteristics, which were assessed by predicting their affinities for human serum albumin and blood/brain coefficient. The optimum range of these two parameters is -3.0 to 1.2 and -1.5 to +1.5 respectively. Our findings indicate that a significant portion of the isolated compounds fall under acceptable limits, and may therefore be suitable drug candidates that can pass the blood–brain barrier and saturate the entire brain.

The Auto QSAR panel's machine-based prediction model (pIC₅₀), which was used for screening, moved the process along. Combining several Canvas fingerprints with a collection of chemical compounds from the ChEMBL database yielded a total of 38 descriptors, producing a number of independent variables from which models could be built (Dixon et al., 2016). The dataset was divided into 76% training sets and 24% test sets at random. Table 6 displays the training and test sets' (observed and predicted) activity in the negative logarithm of inhibitor concentration (pIC₅₀). Nonetheless, the inhibitory (pIC₅₀) ability as reported in Table 3 ranges from 5.223 to 5.018, showing that all the component compounds have a reasonable level of EGFR inhibitory capacity. Our research revealed that the capacity of the oil components to inhibit EGFR was superior to that of other lead compounds against the 3C-like protease of the SARS-CoV-2 as described by Elekofehinti et al (2021). As a result, it may be concluded that *Garcinia kola* oil's components have strong inhibitory properties that are superior to those of many other substances.

Table 6

Auto QSAR details comparing predicted activities to observed activities

S/N	PubChem ID	Set	Observed pIC ₅₀	Predicted pIC ₅₀	Residue Error
1	Compound 1	train	6.7000	6.9529	0.2529
2	Compound 2	train	5.0000	5.0959	0.0959
3	Compound 3	train	5.1000	5.1351	0.0351
4	Compound 4	train	4.9900	5.1248	0.1348
5	Compound 5	train	7.3400	6.9928	-0.3472

6	Compound 6	train	5.4000	5.2729	-0.1271
7	Compound 7	train	4.4600	4.8168	0.3568
8	Compound 8	train	7.0900	6.9198	-0.1702
9	Compound 9	test	7.1600	7.1716	0.0116
10	Compound 10	train	4.4300	4.5415	0.1115
11	Compound 11	test	5.4000	4.7986	-0.6014
12	Compound 12	train	4.8200	5.2049	0.3849
13	Compound 13	train	4.3300	4.4458	0.1158
14	Compound 14	train	5.5500	5.0904	-0.4596
15	Compound 15	test	5.0200	4.7967	-0.2233
16	Compound 16	train	5.3100	4.9234	-0.3866
17	Compound 17	train	6.2400	6.7449	0.5049
18	Compound 18	train	4.9500	4.6733	-0.2767
19	Compound 19	test	4.9400	5.1078	0.1678
20	Compound 20	train	4.8000	4.4941	-0.3059
21	Compound 21	train	4.3400	4.3178	-0.0222
22	Compound 22	test	4.3400	4.7986	0.4586
23	Compound 23	test	4.6400	4.4865	-0.1535
24	Compound 24	train	4.4800	4.9864	0.5064
25	Compound 25	train	5.2900	5.4695	0.1795
26	Compound 26	test	6.8900	7.1634	0.2734
27	Compound 27	train	4.4600	4.8941	0.4341
28	Compound 28	train	6.0000	5.3175	-0.6825
29	Compound 29	train	5.6400	6.0756	0.4356

30	Compound 30	train	4.8500	4.9447	0.0947
31	Compound 31	test	5.9600	6.1267	0.1667
32	Compound 32	train	6.9600	7.2399	0.2799
33	Compound 33	train	7.4000	7.2574	-0.1426
34	Compound 34	train	6.1600	5.7246	-0.4354
35	Compound 35	test	5.4400	5.4571	0.0171
36	Compound 36	train	5.8900	5.9894	0.0994
37	Compound 37	train	6.5700	6.1964	-0.3736
38	Compound 38	train	6.7200	6.4271	-0.2929

Table 7

Criteria matching the most model from Auto-QSAR

Model Code	S.D	R ²	RMSE	Q ²
Kpls linear 34	0.3403	0.8865	0.2937	0.8969

It is imperative to validate models in order to confirm their authenticity. Approaches that use RMSE are part of the internal procedures used to validate a model (Wold & Ericksson, 1988; Yasri, A. & Hartsough). Table 7 presents some of the criteria for external validation; Cross-validated coefficient (Q²) value of 0.8969, and the correlation coefficient (R²) value of 0.8865. These values meet the conditions necessary to show the predictive ability of a model selected. It is crucial to note that docking accuracy increases with decreasing RMSD values. Indeed, RMSD values under 2.0 Angstrom should always be taken into account (Castro-Alvarez et al. 2017). As a result, this study's findings are encouraging given the significantly lower RMSD value. Taken together, *Garcinia kola* oil has shown excellent results by complying with permissible limits. This study also corroborates the findings of Olatunde et al. (2021) who reported the anticancer effect of the essential oil of *Garcinia kola*. They can therefore be further researched and developed as viable therapeutic options for the treatment of breast cancer, especially TNBC.

Conclusion

The relationship between Ligand and receptor is of great importance in drug design based on structure. Our study revealed a good relationship between the phytocompounds obtained from the oil of *Garcinia kola* via GC-MS analysis and the human EGFR. Furthermore, the bioactive constituents isolated from the oil of *Garcinia kola* showed good docking score, IFD, the free energy of binding, and predicted pIC50 values while satisfying the prerequisites for drug candidacy. This is incredibly reassuring since it implies that the oil extracted from *Garcinia kola* may inhibit the EGFR receptor, acting as a potent anti-breast cancer agent and maybe bringing about the long-awaited advancement in the treatment of TNBC. We, therefore, recommend that additional studies be conducted to validate the findings of this study.

Abbreviations

ADMET; Absorption, distribution, metabolism, excretion and Toxicological, BC; Breast cancer, IFD; GC-MS; Gas chromatography-mass spectrometry, IFD; Induced fit docking, PDB ID; Protein databank identification number, XP; docking Extra precision docking, MM-GBSA; Molecular mechanics/generalized born surface area, QSAR; Quantitative structure-activity relationship, RMSD; Root mean square deviation, RO5; Lipinski rule of five, QPlogBB: Predicted blood/brain partition coefficient, QPlogKhsa; Human serum albumin binding, QPlogPo/w: predicted octanol/water partition coefficient, RMSE; Root means square error

Declarations

Conflicts of interest

The authors declared no conflicts of interest

Funding

This study was not funded by any organisation

Acknowledgements

None

References

1. Adedara I.A., Awogbindin, I.O., Anamelechi, J.P. & Farombi, E.O. (2015). *Garcinia kola* seed ameliorates renal, hepatic, and testicular oxidative damage in streptozotocin-induced diabetic rats, *Pharmaceutical Biology*, 53:5, 695-704. DOI: 10.3109/13880209.2014.937504
2. Akpe, V., Murhekar, S., Kim, T. H., Brown, C. L., & Cock, I. E. (2021). Batch Effect Adjustment to Lower the Drug Attrition Rate of MCF-7 Breast Cancer Cells Exposed to Silica Nanomaterial-Derived

- Scaffolds. *Assay and drug development technologies*, 19(1), 46–61.
<https://doi.org/10.1089/adt.2020.1016>
3. American Cancer Society. *Cancer Facts & Figures 2022*. American Cancer Society; 2022. Accessed February 8, 2023. [cancer.org/ research/cancer-facts -statistics/ all-cancer-facts-figures/cancer-facts - figures-2022.html](https://cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2022.html)
 4. Anderson, B. O., Ilbawi, A. M., Fidarova, E., Weiderpass, E., Stevens, L., Abdel-Wahab, M., & Mikkelsen, B. (2021). The Global Breast Cancer Initiative: a strategic collaboration to strengthen health care for non-communicable diseases. *The Lancet. Oncology*, 22(5), 578–581.
[https://doi.org/10.1016/S1470-2045\(21\)00071-1](https://doi.org/10.1016/S1470-2045(21)00071-1)
 5. Arienti, C., Pignatta, S., & Tesei, A. (2019). Epidermal Growth Factor Receptor Family and its Role in Gastric Cancer. *Frontiers in Oncology*, 9. <https://doi.org/10.3389/fonc.2019.01308>.
 6. Castro-Alvarez, A., Costa, A. M., & Vilarrasa, J. (2017). The Performance of Several Docking Programs at Reproducing Protein-Macrolide-Like Crystal Structures. *Molecules (Basel, Switzerland)*, 22(1), 136.
<https://doi.org/10.3390/molecules22010136>
 7. Cetkovic-Cvrlje, M., Rogan, S., & Barbaro, E. (2022). Garcinia kola treatment exhibits immunomodulatory properties while not affecting type 1 diabetes development in an experimental mouse model. *International Journal of Immunopathology and Pharmacology*, 36.
<https://doi.org/10.1177/20587384211069831>
 8. Chagoyen, M., & Pazos, F. (2016). Characterization of clinical signs in the human interactome, *Bioinformatics*, 32(12): 1761–1765. <https://doi.org/10.1093/bioinformatics/btw054>
 9. de Oliveira, M. T., & Katekawa, E. (2018). On the virtues of automated quantitative structure-activity relationship: the new kid on the block. *Future medicinal chemistry*, 10(3), 335–342.
<https://doi.org/10.4155/fmc-2017-0170>
 10. Dixon, S. L., Duan, J., Smith, E., Von Bargen, C. D., Sherman, W., & Repasky, M. P. (2016). AutoQSAR: an automated machine learning tool for best-practice quantitative structure-activity relationship modeling. *Future medicinal chemistry*, 8(15), 1825–1839. <https://doi.org/10.4155/fmc-2016-0093>
 11. Dogara, A. M., Hamad, S. W., Hama, H. A., Bradosty, S. W., Kayfi, S., Al-Rawi, S. S., & Lema, A. A. (2022). Biological Evaluation of *Garcinia kola* Heckel. *Advances in pharmacological and pharmaceutical sciences*, 2022, 3837965. <https://doi.org/10.1155/2022/3837965>
 12. Duan, J., Dixon, S. L., Lowrie, J. F., & Sherman, W. (2010). Analysis and comparison of 2D fingerprints: insights into database screening performance using eight fingerprint methods. *Journal of molecular graphics & modelling*, 29(2), 157–170. <https://doi.org/10.1016/j.jmgm.2010.05.008>
 13. Eboh, A.S., Ere, D., C. Chuku, L., & A. Uwakwe, A. (2015). Kolaviron an Active Biflavonoid of Garcinia kola Extract Prevent 1,2-dimethylhydrazine Induced Oxidative Stress and Lipid Peroxidation in the Initiation Phase of Colon Carcinogenesis in Wistar Rats. *Journal of Cancer and Tumor International*, 2(2), 41–49. <https://doi.org/10.9734/JCTI/2015/16809>
 14. Ehiabhi Okhale, S., Ismail Buba, C., Oladosu, P., Egharevba, H. O., Ugbabe, G., A. Ibrahim, J., & Folashade Kunle, O. (2016). Chemical Constituents and Antimicrobial Activity of the Leaf Essential

- Oil of *Garcinia kola* Heckel (Clusiaceae) from Nigeria. *Chemical Science International Journal*, 13(4), 1–7. <https://doi.org/10.9734/ACSJ/2016/24019>
15. Elekofehinti, O. O., Iwaloye, O., Famusiwa, C. D., Akinseye, O., & Rocha, J. B. T. (2021). Identification of Main Protease of Coronavirus SARS-CoV-2 (M^{Pro}) Inhibitors from *Melissa officinalis*. *Current drug discovery technologies*, 18(5), e17092020186048. <https://doi.org/10.2174/1570163817999200918103705>
 16. Elekofehinti, O. O., Metibemu, D. S., Metibemu, A. O., Famuti, A., Adegbegi, J. A., Ejelonu, O. C., Shodehinde, S. A., Omotuyi, I. O., & Akinloye, O. A. (2016). Kolaviron Inhibition of Aromatase of Breast Cancer, a Step-ahead of Exemestane, Letrozole, and Anastrozole: A Molecular Docking Studies. *The International Journal of Science & Technoledge*, 4(6). Retrieved from <https://www.internationaljournalcorner.com/index.php/theijst/article/view/123888>
 17. Elekofehinti, O. O., Onunkun, A. T., & Olaleye, T. M. (2020). Cymbopogon citratus (DC.) Stapf mitigates ER-stress induced by streptozotocin in rats via down-regulation of GRP78 and up-regulation of Nrf2 signaling. *Journal of ethnopharmacology*, 262, 113130. <https://doi.org/10.1016/j.jep.2020.113130>
 18. Elekofehinti, O. O., Iwaloye, O., Molehin, O. R., & Famusiwa, C. D. (2021). Identification of lead compounds from large natural product library targeting 3C-like protease of SARS-CoV-2 using E-pharmacophore modelling, QSAR and molecular dynamics simulation. *In silico pharmacology*, 9(1), 49. <https://doi.org/10.1007/s40203-021-00109-7>
 19. Fapohunda, S., Awoyinka, A., Oluchi, O., Adaramola, F., Jegede, D., Aderiike, A., Aleshinloye, A., & Onigbinde, A. (2017). Evaluation of the nutraceutical potential of *Garcinia kola* seed oil. *Journal of Pharmacognosy and Phytochemistry*, 6(5), 1894–1901. <https://www.phytojournal.com/archives/2017/vol6issue5/PartAB/6-5-22-656.pdf>
 20. Farombi, E. O. (2011). Bitter Kola (*Garcinia kola*) Seeds and Hepatoprotection. *Nuts and Seeds in Health and Disease Prevention*, 221-228. <https://doi.org/10.1016/B978-0-12-375688-6.10026-X>
 21. Folayan, A., Akani, E., Adebayo, O.A., Akanni, O.A., Owumi, S.E., Abiola S.T., & Adaramoye, O.A. (2020): Ameliorative effects of hexane extract of *Garcinia kola* seeds Heckel (Clusiaceae) in cisplatin-induced hepatorenal toxicity in mice, *Drug and Chemical Toxicology*, 45(3), 1098-1108. <https://doi.org/10.1080/01480545.2020.1808671>
 22. Genheden, S. & Ryde, U. (2015) The MM/PBSA and MM/GBSA methods to estimate ligand-binding affinities. *Exp Opin Drug Discov*, 10, 49–461. <https://doi.org/10.1517/17460441.2015.1032936>
 23. Giaquinto, A. N., Miller, K. D., Tossas, K. Y., Winn, R. A., Jemal, A., & Siegel, R. L. (2022). Cancer statistics for African American/Black People 2022. *CA: a cancer journal for clinicians*, 72(3), 202–229. <https://doi.org/10.3322/caac.21718>
 24. Hashmi, A.A., Naz, S., Hashmi, S.K.Irfan, M., Hussai, Z.F., Khan E.Y., Asif, H & Faridi, N. (2019). Epidermal growth factor receptor (EGFR) overexpression in triple-negative breast cancer: association with clinicopathologic features and prognostic parameters. *Surg Exp Pathol* 2, 6. <https://doi.org/10.1186/s42047-018-0029-0>

25. Iwaloye, O., Elekofehinti, O.O., Oluwarotimi, E.A., Kikiowo, B.I., Fadipe, T.M. (2020). Insight into glycogen synthase kinase-3 β inhibitory activity of phyto-constituents from *Melissa officinalis* in silico studies. In *Silico Pharmacology*, 8(1):2. DOI: 10.1007/s40203-020-00054-x. PMID: 32968615; PMCID: PMC7487069.
26. Kalu, W., Okafor, P., Ijeh, I., & Eleazu, C. (2016). Effect of kolaviron, a bioflavonoid complex from *Garcinia kola* on some biochemical parameters in experimentally induced benign prostatic hyperplastic rats. *Biomedicine & Pharmacotherapy*, 83, 1436-1443.
<https://doi.org/10.1016/j.biopha.2016.08.064>
27. Kapetanovic I. M. (2008). Computer-aided drug discovery and development (CADD): in silico-chemico-biological approach. *Chemico-biological interactions*, 171(2), 165–176.
<https://doi.org/10.1016/j.cbi.2006.12.006>
28. Kitchen, D. B., Decornez, H., Furr, J. R., & Bajorath, J. (2004). Docking and scoring in virtual screening for drug discovery: methods and applications. *Nature reviews. Drug discovery*, 3(11), 935–949.
<https://doi.org/10.1038/nrd1549>
29. Lheureux, S., Denoyelle, C., Ohashi, P. S., De Bono, J. S., & Mottaghy, F. M. (2017). Molecularly targeted therapies in cancer: a guide for the nuclear medicine physician. *European journal of nuclear medicine and molecular imaging*, 44(Suppl 1), 41–54. <https://doi.org/10.1007/s00259-017-3695-3>
30. Lipinski, C.A., Lombardo, F., Dominy, B.W., Feeney, P.J. (2001) Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv Rev*, 46(13), 3–26. [https://doi.org/10.1016/S0169-409X\(00\)00129-0](https://doi.org/10.1016/S0169-409X(00)00129-0)
31. Liu, Z., Liu, Y., Zeng, G., Shao, B., Chen, M., Li, Z., Jiang, Y., Liu, Y., Zhang, Y., & Zhong, H. (2018). Application of molecular docking for the degradation of organic pollutants in the environmental remediation: A review. *Chemosphere*, 203, 139–150.
<https://doi.org/10.1016/j.chemosphere.2018.03.179>
32. Maffucci, I., Hu, X., Fumagalli, V., & Contini, A. (2018). An efficient implementation of the Nwat-MMGBSA method to rescore docking results in medium-throughput virtual screenings. *Frontiers Chem* 6:43. <https://doi.org/10.3389/fchem.2018.00043>
33. Masuda, H., Zhang, D., Bartholomeusz, C., Doihara, H., Hortobagyi, G. N., & Ueno, N. T. (2012). Role of epidermal growth factor receptor in breast cancer. *Breast cancer research and treatment*, 136(2), 331–345. <https://doi.org/10.1007/s10549-012-2289-9>
34. Meng, X. Y., Zhang, H. X., Mezei, M., & Cui, M. (2011). Molecular docking: a powerful approach for structure-based drug discovery. *Current computer-aided drug design*, 7(2), 146–157.
<https://doi.org/10.2174/157340911795677602>
35. Miller, K. D., Ortiz, A. P., Pinheiro, P. S., Bandi, P., Minihan, A., Fuchs, H. E., Martinez Tyson, D., Tortolero-Luna, G., Fedewa, S. A., Jemal, A. M., & Siegel, R. L. (2021). Cancer statistics for the US Hispanic/Latino population, 2021. *CA: a cancer journal for clinicians*, 71(6), 466–487.
<https://doi.org/10.3322/caac.21695>

36. National Breast Cancer Coalition (2022). Accessed February 8, 2023. Available at <https://www.stopbreastcancer.org/wp-content/uploads/2022/04/NBCC-Information-Packet-2022-v4.pdf>
37. Olatunde, O.Z., Tian, D., Yong, J., & Lu, C., (2021). Chemical composition of the essential oil extracted from the seeds of *Garcinia kola*, and its biological activities. *Biomedicine and Pharmacology Journal*. 14 (2). DOI: <https://dx.doi.org/10.13005/bpj/2163>
38. Olsson, M. H., Søndergaard, C. R., Rostkowski, M., & Jensen, J. H. (2011). PROPKA3: Consistent Treatment of Internal and Surface Residues in Empirical pKa Predictions. *Journal of chemical theory and computation*, 7(2), 525–537. <https://doi.org/10.1021/ct100578z>
39. Ongko, J., Setiawan, J. V., Feronytha, A. G., Juliana, A., Effraim, A., Wahjudi, M., & Antonius, Y. (2022). In-silico screening of inhibitor on protein epidermal growth factor receptor (EGFR). In *IOP Conference Series: Earth and Environmental Science* (Vol. 1041, No. 1, p. 012075). IOP Publishing.
40. Oshi, M., Gandhi, S., Tokumaru, Y., Yan, L., Yamada, A., Matsuyama, R., Ishikawa, T., Endo, I., & Takabe, K. (2021). Conflicting roles of *EGFR* expression by subtypes in breast cancer. *American journal of cancer research*, 11(10), 5094–5110. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8569361/>
41. Prime (2018) version 3.9, Schrodinger, LLC, New York, NY
42. Rukke, E.-O., & Schüller, R. B. (2017). The viscosity of a selection of edible oils and blends of oils at different temperatures. *Annual Transactions - The Nordic Rheology Society*, 25, 287–292. <https://nrs.blob.core.windows.net/pdfs/nrspdf-5ebdd55a-69c6-4800-b26e-09add3cb3a9a.pdf>
43. Salmaso, V., & Moro, S. (2018). Bridging Molecular Docking to Molecular Dynamics in Exploring Ligand-Protein Recognition Process: An Overview. *Frontiers in pharmacology*, 9, 923. <https://doi.org/10.3389/fphar.2018.00923>
44. Sander, T., Freyss, J., von Korff, M., & Rufener, C. (2015). Data Warrior: an open-source program for chemistry-aware data visualization and analysis. *Journal of chemical information and modelling*, 55(2), 460–473. <https://doi.org/10.1021/ci500588j>
45. Schrödinger Suite (2012) Protein Preparation Wizard; Epik version 2.3, Schrödinger, LLC, New York, NY, 2012; Impact version 5.8, Schrödinger, LLC, New York, NY, 2012; Prime version 3.1, Schrödinger, LLC, New York, NY
46. Song, B., Wang, L., Zhang, Y., Li, N., Dai, H., Xu, H., Cai, H., & Yan, J. (2019). Combined Detection of HER2, Ki67, and GSTP1 Genes on the Diagnosis and Prognosis of Breast Cancer. *Cancer biotherapy & radiopharmaceuticals*, 34(2), 85–90. <https://doi.org/10.1089/cbr.2018.2570>
47. Sun, G., Rong, D., Li, Z., Sun, G., Wu, F., Li, X., Cao, H., Cheng, Y., Tang, W., & Sun, Y. (2021). Role of Small Molecule Targeted Compounds in Cancer: Progress, Opportunities, and Challenges. *Frontiers in Cell and Developmental Biology*, 9. <https://doi.org/10.3389/fcell.2021.694363>
48. Sun, H., Li, Y., Shen, M., Tian, S., Xu, L., Pan, P., Guan, Y., & Hou, T. (2014) Assessing the performance of the MM/PBSA and MM/GBSA methods, improved docking performance using high solute

- dielectric constant MM/GBSA and MM/PBSA rescoring. *Phys Chem ChemPhys* 1(6):22035–22045. <https://doi.org/10.1039/c4cp03179b>
49. Trabalzini, L., Ercoli, J., Trezza, A., Schiavo, I., Macrì, G., Moglia, A., Spiga, O., & Finetti, F. (2022). Pharmacological and In Silico Analysis of Oat Avenanthramides as EGFR Inhibitors: Effects on EGF-Induced Lung Cancer Cell Growth and Migration. *International Journal of Molecular Science*, 23, 8534. <https://doi.org/10.3390/ijms23158534>
50. Watkins, E.J. (2019). Overview of breast cancer, *Journal of the American Academy of Physician Assistants*. DOI: 10.1097/01.jaa.0000580524.95733.3d. PMID: 31513033
51. Wold, S., & Ericksson, L. (1998). Partial least squares projections to latent structures (PLS) in chemistry. In: Ragu P, Schleyer P (eds) *Encyclopedia of computational chemistry*, Wiley, Chichester. 3, 2006–2021.
52. World Health Organisation (WHO). Breast cancer is now most common form of cancer: WHO taking action. Departmental news. 2021, Access date: 22nd March, 2023. <https://www.who.int/news/item/03-02-2021-breast-cancer-now-most-common-form-of-cancer-who-taking-action>
53. Yalaza, M., İnan, A., & Bozer, M. (2016). Male Breast Cancer. *The journal of breast health*, 12(1), 1–8. <https://doi.org/10.5152/tjbh.2015.2711>
54. Yasri, A. & Hartsough, D.J. (2001) Toward an optimal procedure for variable selection and QSAR modelling building. *Chem Inf Comput Sci* 41, 1218–1227. <https://doi.org/10.1021/ci010291a>

Table 1

Table 1 is available in Supplementary Files section.

Figures



Figure 1

Garcinia kola seeds (Okhale et al. 2016).

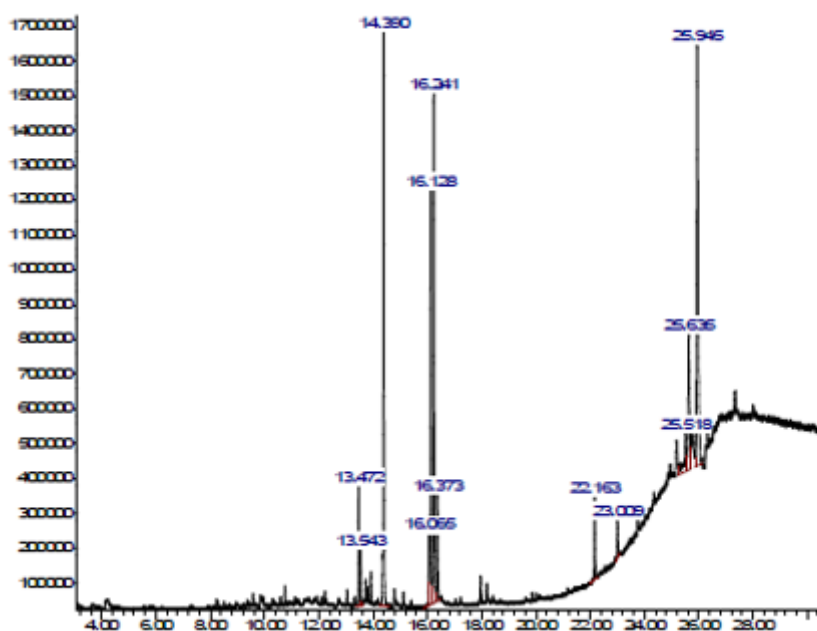


Figure 2

Chromatogram obtained from GC-MS

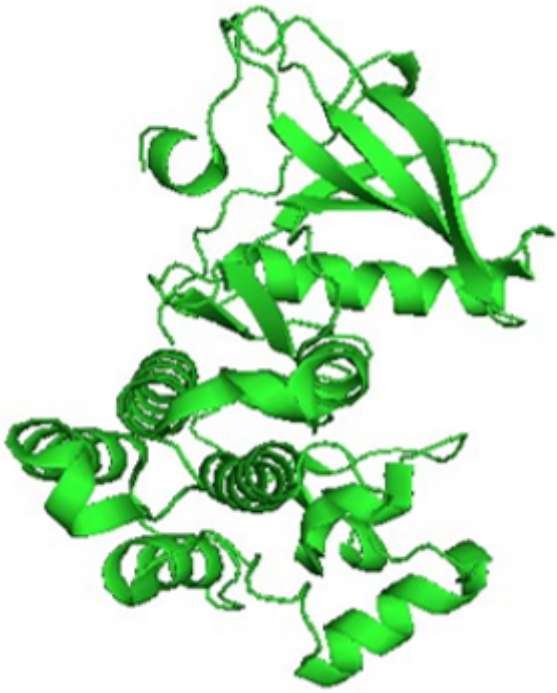


Figure 3

3-D structure of human epidermal growth factor receptor (EGFR)

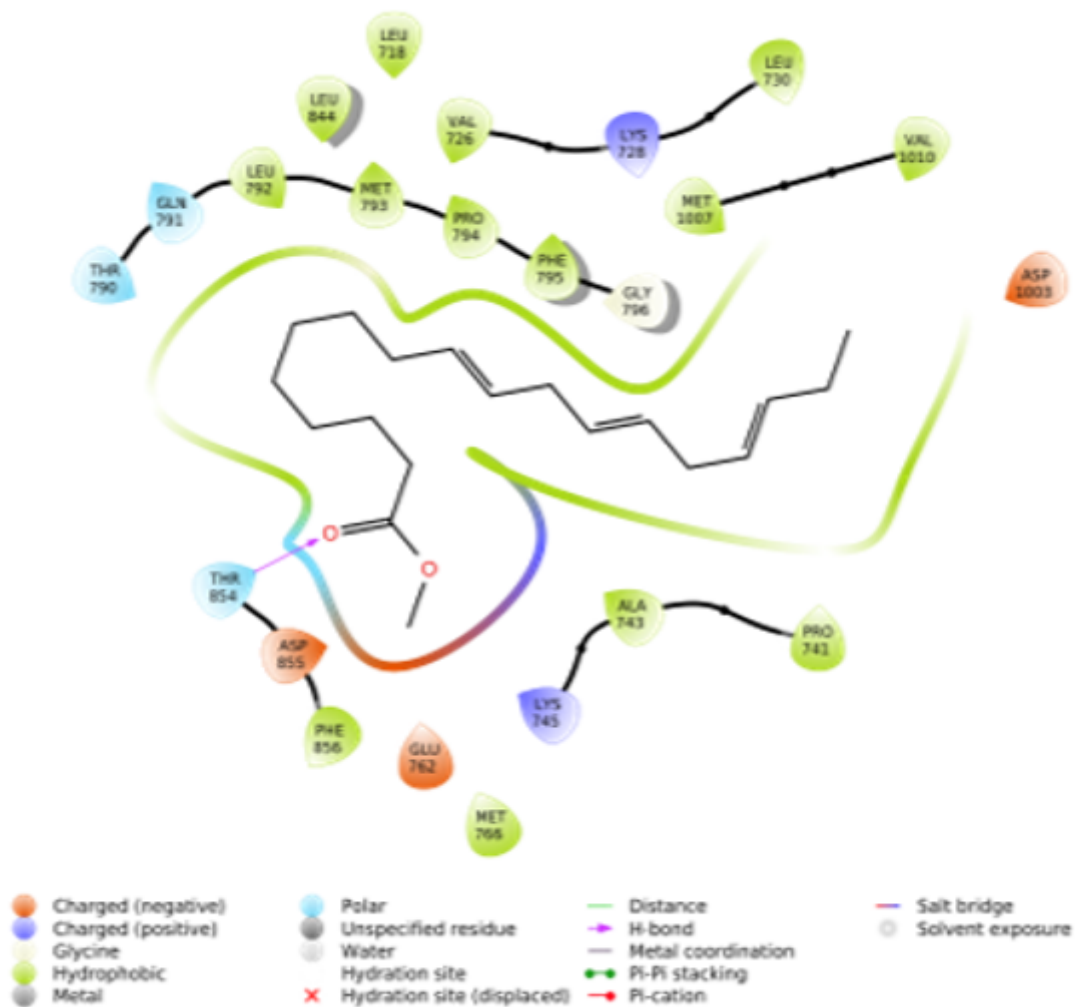


Figure 4

2-D structure of the binding pose of 9, 12, 15-Octadecatrienoic acid, methyl ester with epidermal growth factor receptor revealing the residues in the protein's active site.

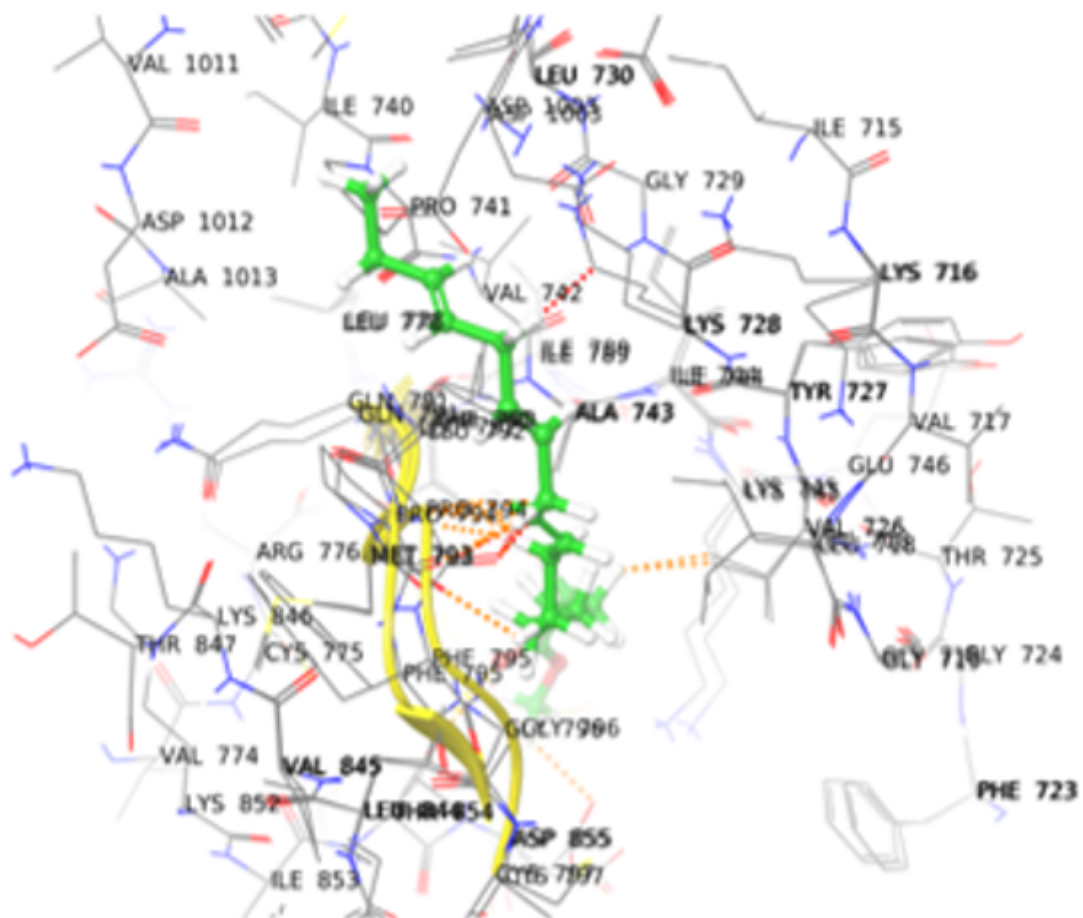


Figure 5

3-D structure of the binding pose of 9, 12, 15-Octadecatrienoic acid, methyl ester with epidermal growth factor receptor revealing the residues in the protein's active site.



Figure 6

2-D structure of the binding pose of methyl stearate with epidermal growth factor receptor revealing the residues in the protein's active site.

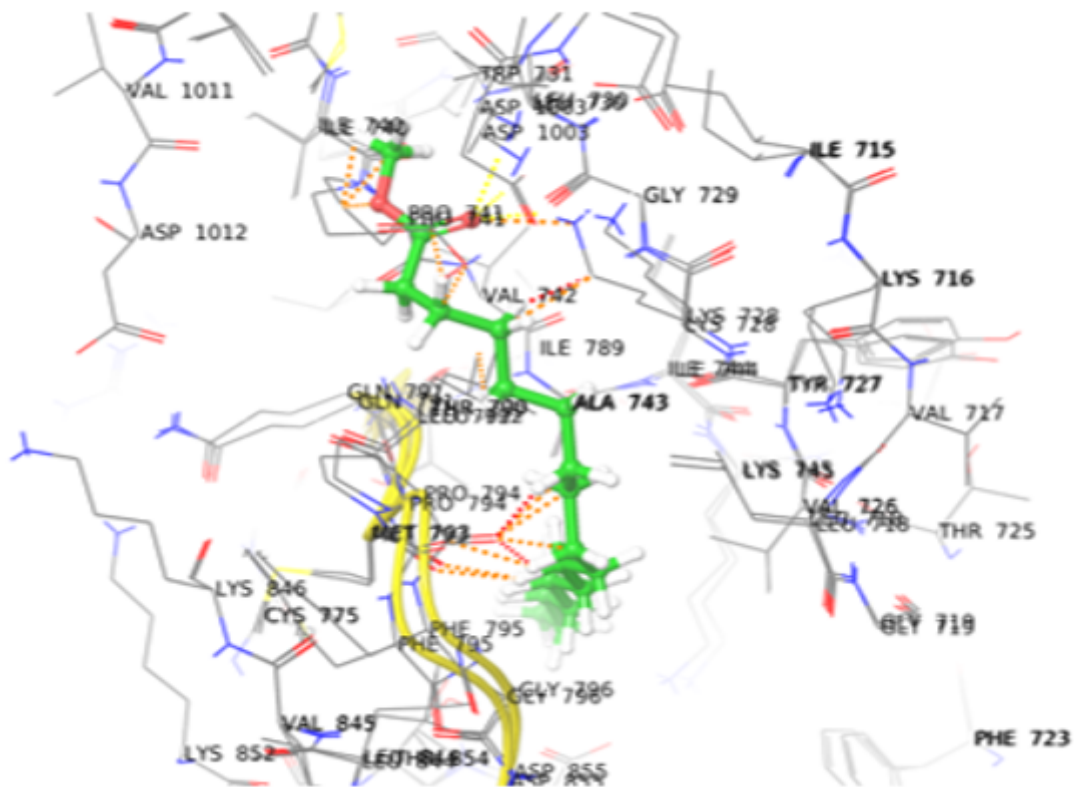


Figure 7

3-D structure of the binding pose of methyl stearate with epidermal growth factor receptor revealing the residues in the protein's active site.

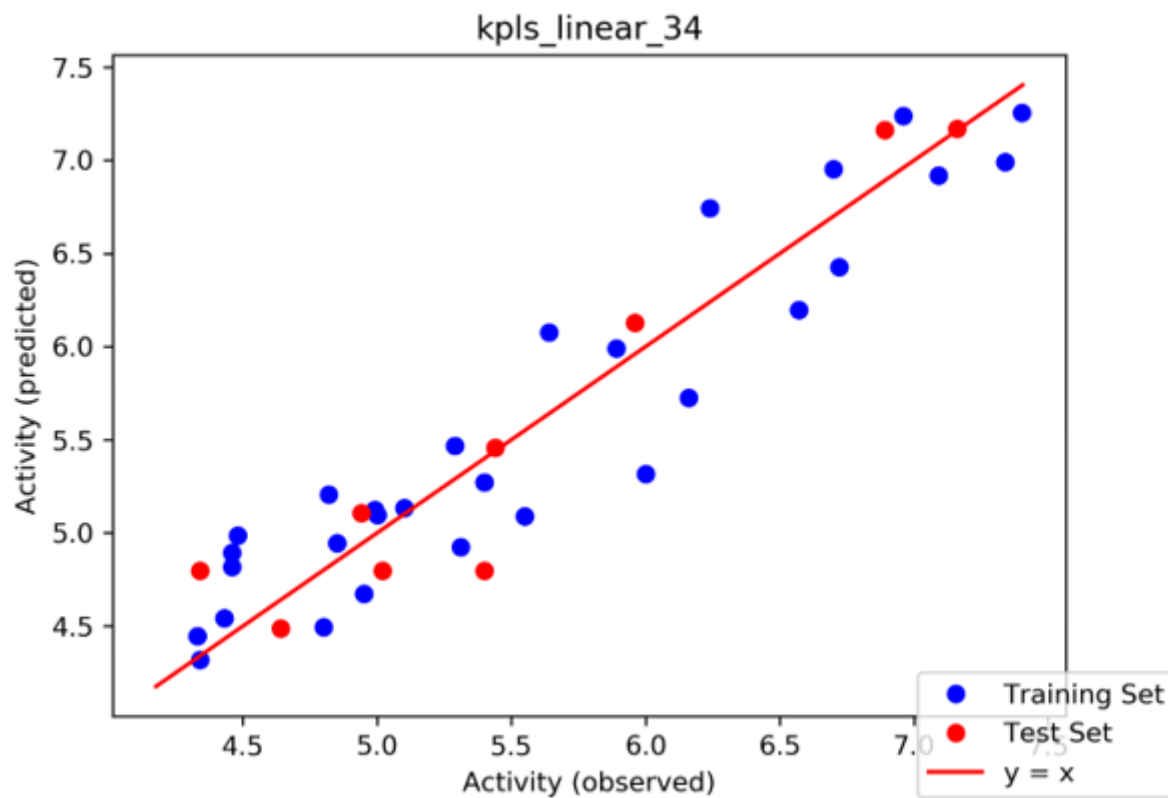


Figure 8

Analysis using scatter plots of the best QSAR model

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table1.docx](#)