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Pharmacological Analysis of Piper Longum for its Anti-cancer Potential Using Molecular Docking and In Silico Studies

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Abstract
Molecular docking has been the main focus of an increasing number of computational research in medicinal chemistry, which has made the technology seem promising for computer-aided drug design. Angiogenesis is significantly influenced by platelet-derived growth factors (PDGFs) and their tyrosine kinase receptors (PDGFRs), which have been linked to the pathophysiology of several tumor forms. PDGF can induce autocrine stimulation of cancerous cells, over stimulation of PDGFRs, or angiogenesis inside the tumor cells to promote tumor growth. These processes may offer potential targets for therapy. Additionally, PDGFR inhibition may improve medication delivery and decrease the interstitial fluid (IF) pressure within solid tumors. Using the drug likeness criteria of Lipinski's test (Rule of five), seven bioactive compounds from ethanolic extract of Piper longum were evaluated as anticancer agents against PDGFRs in this study. A molecular docking between active constituents and PDGFRs was carried out. To ascertain their pharmacokinetic actions, ligands with appropriate drug similarity and binding energy were examined further. These compounds are powerful anticancer agents, and additional information about them was provided by analyses such as ADME, and bioavailability radar analysis.

Keywords: Molecular docking, In silico studies, Anti-cancer, Piper longum, Drug discovery, ADMET, PDGFRs, Pharmacokinetics.

Introduction

Cancer is defined as a disease of the tissue growth regulation. For a normal cell to turn into a malignant one, mutations in genes that regulate cell proliferation and differentiation must occur. Two major categories comprise the impacted genes [1]. Tumor suppressor gene deactivation or under expression, improper overexpression of regular oncogenes, or the emergence of new oncogenes can all lead to malignant transformation. A normal cell must usually undergo alterations in numerous genes in order to become a cancerous cell.

There are numerous options for treating cancer. The main ones are hormone therapy, radiation therapy, chemotherapy, surgery, and targeted therapy. The patient's health and preferences, together with the type, location, and grade of the cancer, all influence which treatments are employed. The goal of the treatment might or might not be curative. Chemotherapy is the use of one or more cytotoxic anti-neoplastic medications (also known as chemotherapeutic agents) in a prescribed schedule to treat cancer [1]. Ionizing

radiation is used in radiation treatment in an effort to treat or improve. It functions by inducing damage to the DNA of malignant tissue, which triggers a mitotic catastrophe that kills the cancer cells. For the majority of isolated solid tumors, surgery is the main form of treatment; it may help with palliation and increase survival time. Despite the use of chemically created medications and treatments, the mortality rate due to cancer has not decreased significantly over the previous few decades. Nowadays, phytochemicals present in plants are proven to be an alternative source for cancer treatment.

Bioactive phytochemicals exhibit preferential behavior because they selectively target tumor cells leaving out healthy cells unaffected. The process of carcinogenesis is intricate and involves several signaling processes. Because phytochemicals target these events in various ways and have a pleiotropic action, they are the best option for an anticancer medication. In vivo and in vitro analysis demonstrate the anticancer properties of some phytochemicals. These bioactive compounds generally work by regulating molecular pathways linked to the proliferation and metastasis of cancer. The key processes encompass enhancing antioxidant status, immune system control, carcinogen inactivation, inhibition of metastasis, stimulation of apoptosis and cell cycle arrest [2]. These phytochemicals are known for targeting specific protein which inhibits or suppresses the protein. One among such protein target for anticancer potential phytochemicals are PDGFRs.

As members of the class of receptors expressed on the membrane of cancer cells, platelet-derived growth factors (PDGFs) and their tyrosine kinase (TK) receptors (PDGFRs) have been exhibited to play a pivotal role in the progression of cancers. Specifically, PDGFR was detected with aggressively behaving breast cancers. The two PDGFR subtypes alpha, and beta, are each encoded by a distinct gene. They are found on human chromosomes 4 and 5, and mouse chromosomes 5 and 18, respectively.CD140a is another name for platelet-derived growth factor receptor A found on human chromosome 4q12. The regulation of mesangial cell migration, chemotaxis, and proliferation is crucially dependent on PDGFR-α [3]. According to recent research, PDGFR-α may be a therapeutic target for thymic malignancies and may have a role in the onset and spread of hepatocellular carcinoma (HCC). Gist-Plus Syndrome and Idiopathic Hypereosinophilic Syndrome are two conditions linked to PDGFR-α.

CD140b is another name for platelet-derived growth factor receptor B. It is located on chromosome 5q32 in humans. The vascular smooth muscle cells that enclosing arteries and arterioles, as well as the pericytes that are intimately linked to capillary vessels, express the PDGFR-β receptor [4]. Genetic diseases linked to PDGFR-β like Premature Aging Syndrome, Penttinen Type. Current research on PDGFR-β focuses on either directly stimulating tumor cells in a hormonal fashion or boosting tumor stromal cells in a signaling pathway.

In the current study, PDGFRs are used as target to analyze the pharmacological likeness of bioactive compounds found in Piper longum for its anti-cancer potential using docking analysis and in silico studies to screen ADME potential of the extract. In previous studies Piper longum's anticancer potential was analysed through series of analysis such as MTT assay, MMP assay, Annexin V assay, lactate dehrdrogenous assay in A549 lung cancer cell line. The results from all the analysis concluded that Piper longum had significant anti-cancer potential [5]. This study examines the phytochemical aspect and pharmacological likeness of these active compounds.

Materials and Methods

Molecular docking

A. Ligand preparation

Seven bioactive compounds from Piper longum extract were identified by performing GCMS analysis as shown in Table.1 and their structures were downloaded in SDF format from https://pubchem.ncbi.nlm.nih.gov . The selected ligands were modified using UCSF Chimera and their non-standard residues are removed, hydrogen and charge are added using Doc prep option which makes it suitable for docking analysis.

Next, using the parameters from UCSF Chimera 1.17.3 the molecular docking were carried on.

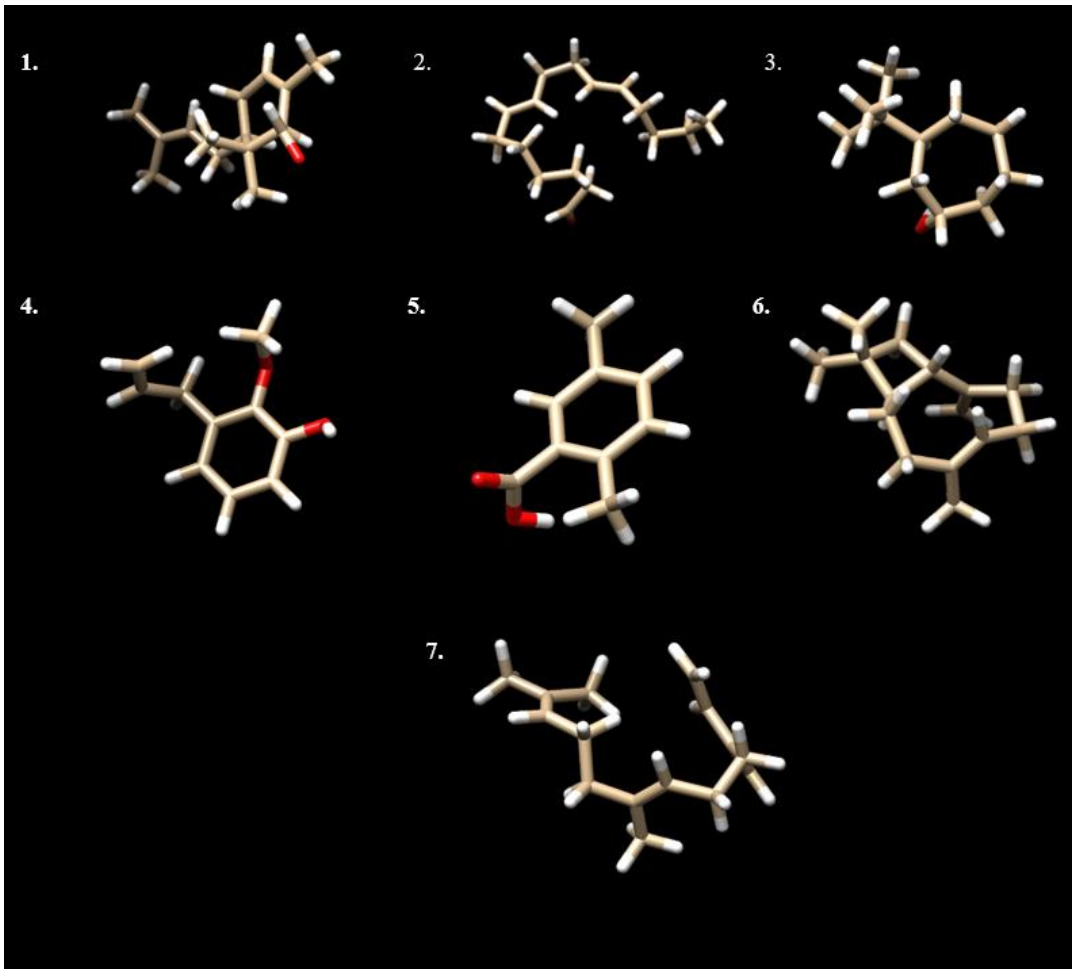

Figure 1. 3D structure of active constituents used in this study (1) 1-Formyl-2,2,6-Trimethyl-3-CIS-(3-Methyl But-2-Enyl)-5-Cyclohexene, (2) 7,11-hexadecadienal, (3) trans-3-tert-butylcycloheptanol, (4) Phenol,2-methoxy-3-(2-propenyl)-, (5) Benzoic acid,2,5-dimethyl-, (6) Caryophyllene, (7) Beta-farnesene.

Table 1. Results from GCMS Analysis

S.NO	COMPOUNDS	CHEMICAL FORMULA	MOLECULAR WEIGHT
1.	Benzoic acid,2,5-dimethyl-	C9H10O2	150

2.	**Beta-farnesene**	**C15H24**	**204**
3.	1-Formyl-2,2,6-Trimethyl-3-CIS-(3-Methyl But-2-Enyl)-5-Cyclohexene	C15H26O	220
4.	7,11-hexadecadienal	C16H28O	236
5.	trans-3-tert-butylcycloheptanol	C11H22O	220
6.	Phenol,2-methoxy-3-(2-propenyl)-	C10H12O2	164
7.	Caryophyllene	C15H24	204
8.	N- hexadecanoic acid	C16H3202	256
9.	Tetradecane, 1- IODO-	C14H29I	324
10.	2- methyl-Z, Z-3,13- octadecadienal	C19H360	280

B. Protein preparation

3D structures of Platelet-derived Growth Factor Receptor Alpha (PDGFR-α) and Platelet-derived Growth Factor Receptor Beta (PDGFR-β) were obtained from RCSB protein data bank (https://www.rcsb.org/) with PDB ID 8pqj for PDGFR-α and 3mjg for PDGFR-β. Using UCSF chimera water molecules were removed and hydrogen and charges were added using structure editing option in the tools and stored in PDBQT format.

C. Docking analysis

After the ligand and protein preparation were done, docking analysis was carried out using Auto dock vina. For scoring to take place, dimensions were set at 15×15×15 and grid box centered and resized using button option to facilitate favorable docking conformations [6]. The receptor options and ligand options were adjusted. The grid was stored as (.conf) file and ran auto grid. The binding energy/score, RMSD value, active torsions and H Bonds are all calculated automatically using parameters from UCSF Chimera.

Lipinski's Rule of five

A general guideline used to evaluate drug likeness and if a compound with a specific pharmacological or biological effect possesses significant physical and chemical properties that would probably render it a drug that is taken orally by humans is Lipinski's rule of five, also known as the rule of five (RO5) [7].

The Supercomputing facility for bioinformatics and computational biology (http://www.scfbio-iitd.res.in/software/drugdesign/lipinski.jsp) was utilized in this investigation to screen ligands for the RO5.

Analysis using Swiss ADME

Pharmacological characteristics such as drug likeness, bioavailability, lipophilicity, Gastrointestinal (GI) absorption and Blood- Brain barrier permeation were analysed using Swiss ADME(http://www.swissadme.ch/index.php) .

Results and Discussion

Table 2. Binding energy of active constituents against PDGFR-α AND PDGFR-β

S.NO	ACTIVE CONSTITUENTS	PDGFR- α	PDGFR-β
1.	Benzoic acid,2,5-dimethyl-	-6.6	-5.9
2.	Beta-farnesene	-5.8	-5.5
3.	1-Formyl-2,2,6-Trimethyl-3-CIS-(3-Methyl But-2-Enyl)-5-Cyclohexene	-5.4	-6.3

4.	7,11-hexadecadienal	-5.7	-5.2
5.	trans-3-tert-butylcycloheptaNOl	-5.5	-6.0
6.	Phenol,2-methoxy-3-(2-propenyl)-	-5.5	-5.8
7.	Caryophyllene	-5.7	-5.7
8.	N- hexadecanoic acid	-5.0	-5.2
9.	Tetradecane, 1- IODO-	-5.1	-4.7
10.	2- methyl-Z, Z-3,13- octadecadienal	-5.4	-5.6

Docking analysis

Among these 7 bioactive compounds in Table 2 which had significantly lower binding energy in both PDGFR-α and PDGFR-β were chosen for further analysis to examine their pharmacological characteristics.

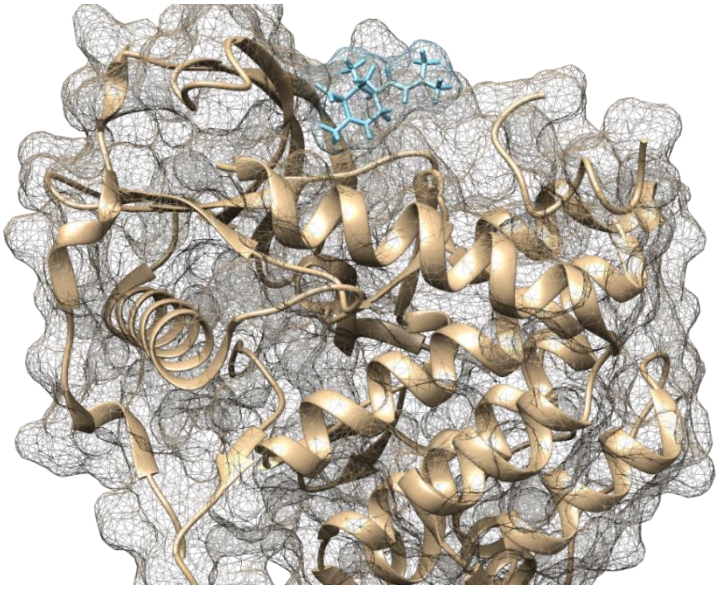

Figure 2. 1-Formyl-2,2,6-Trimethyl-3-CIS-(3-Methyl But-2-Enyl)-5-Cyclohexene in PDGFR-α (-5.4)

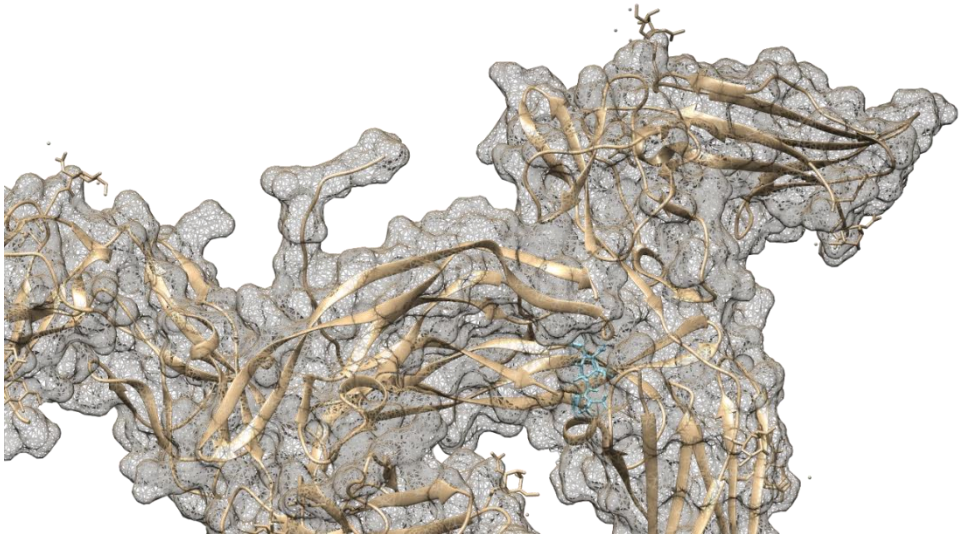

Figure 3. 1-Formyl-2,2,6-Trimethyl-3-CIS-(3-Methyl But-2-Enyl)-5-Cyclohexene in PDGFR-β (-6.3)

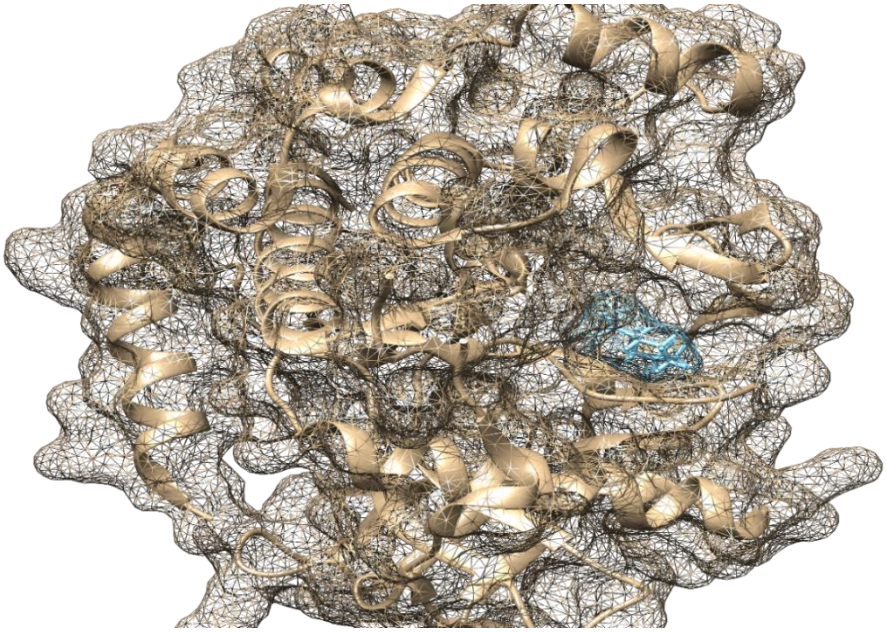

Figure 4. trans-3-tert-butylcycloheptanol in PDGFR-α (-5.5)

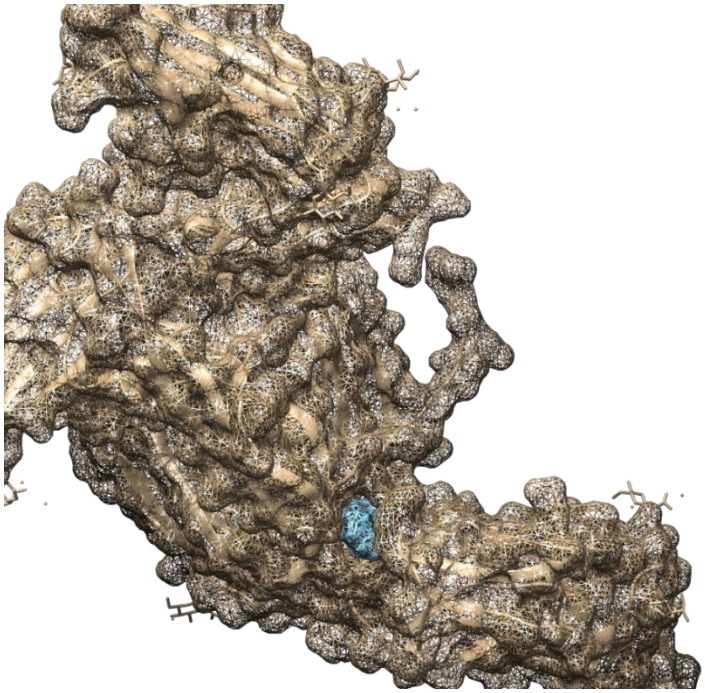

Figure 5. trans-3-tert-butylcycloheptanol in PDGFR-β (-6.0)

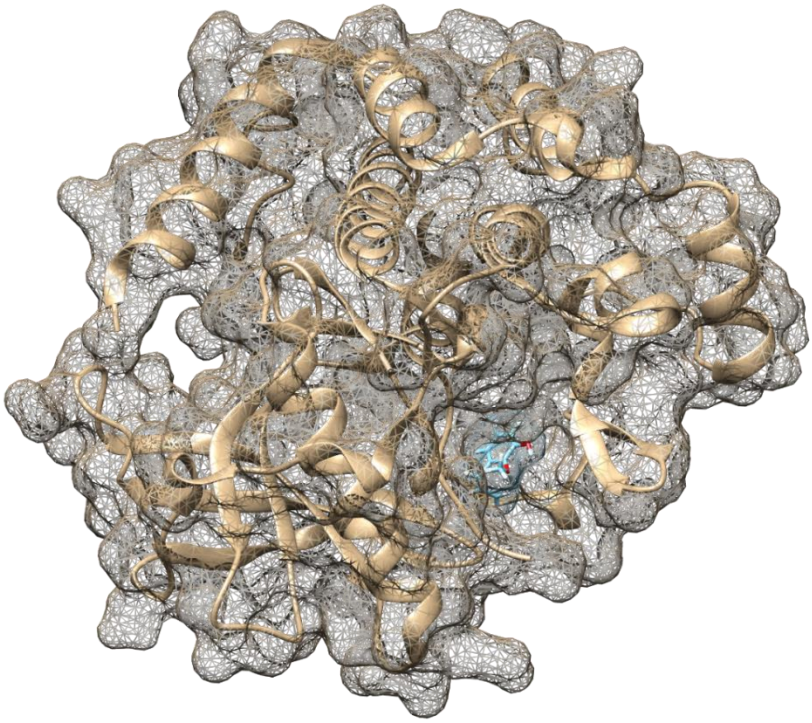

Figure 6. Phenol,2-methoxy-3-(2-propenyl)- in PDGFR-α (-5.5)

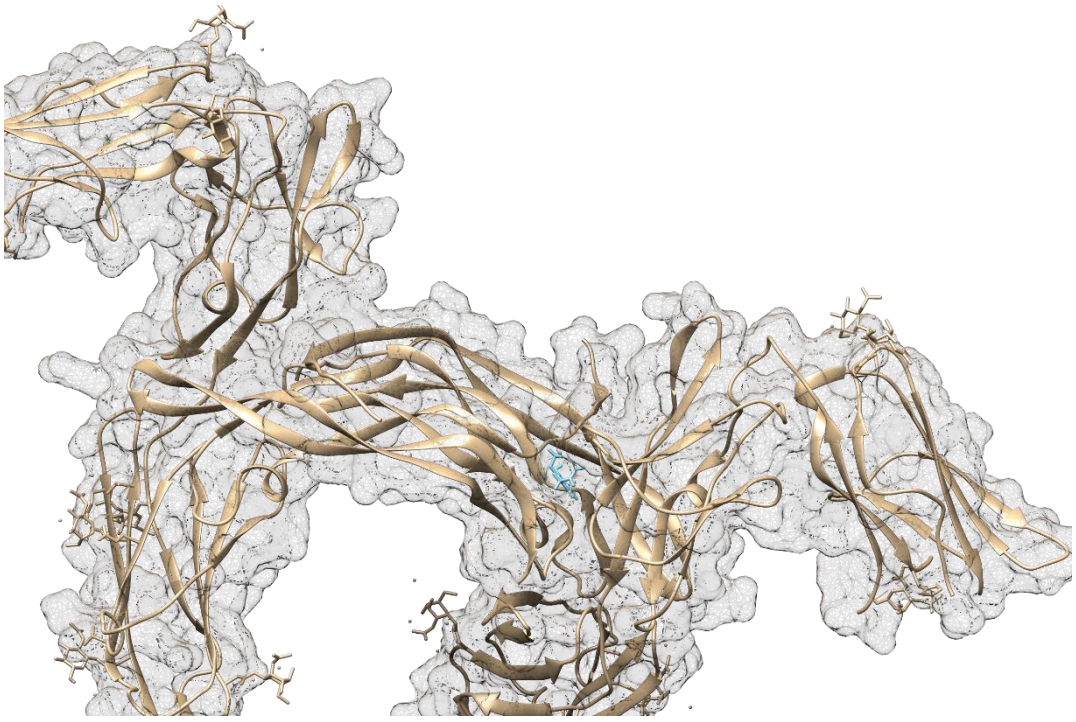

Figure 7. Phenol,2-methoxy-3-(2-propenyl)- in PDGFR-β (**-5.8**)

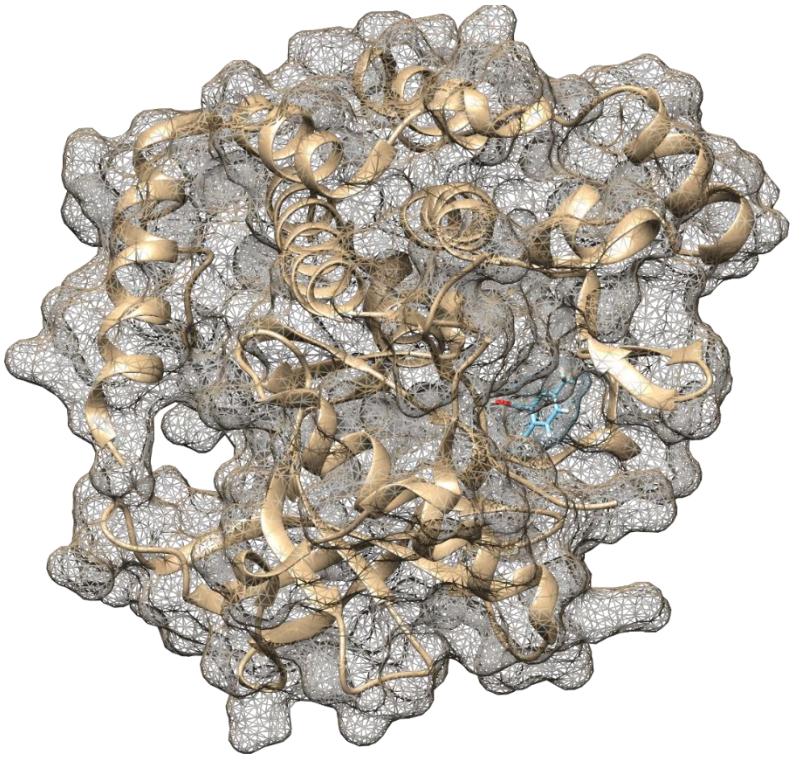

Figure 8. Benzoic acid,2,5-dimethyl- in PDGFR-α (**-6.6**)

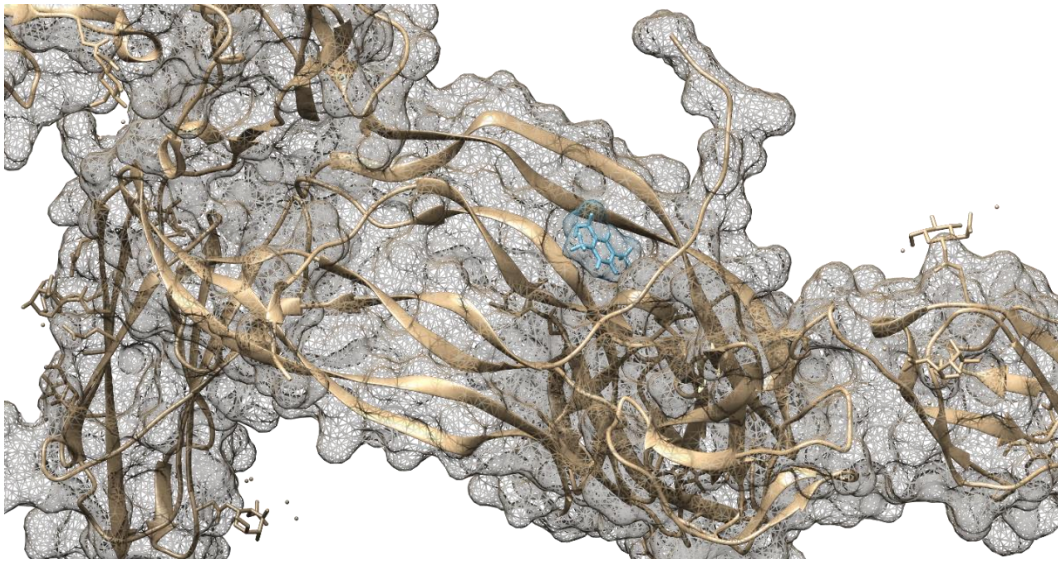

Figure 9. Benzoic acid,2,5-dimethyl- in PDGFR-β (-5.9)

Drug likeness analysis:

The Lipinski rule of five and Swiss ADME were used to screen the drug characteristics of the seven bioactive compounds. The ligands' bioavailability radar was also analyzed.

Lipinski's Rule of five

For a compound to be screened for its drug potential molar refractivity, hydrogen donor, hydrogen acceptor, molecular weight and lipophilicity are the five criteria that needs to assessed. The assessed results are shown in Table 3.

Table 3. Lipinski's Rule of Drug Likeness

ACTIVE CONSTITUENTS	MASS	HYDROGEN BOND DONOR	HYDROGEN BOND RECEPTOR	LOGP	MOLAR REFRACTIVITY
Benzoic acid,2,5-dimethyl-	150	1	2	2.001	42.87
Beta-farnesene	204	0	0	5.201	70.99
1-Formyl-2,2,6-Trimethyl-3-CIS-(3-Methyl But-2-Enyl)-5 Cyclohexene	220	0	1	4.150	69.24
7,11-hexadecadienal	236	0	1	5.218	76.18
trans-3-tert-butylcycloheptanol	170	1	1	2.973	52.03
Phenol,2-methoxy-3-(2-propenyl)-	164	1	2	2.129	48.55
Caryophyllene	204	0	0	4.725	66.74

In Lipinski' parameters it is necessary for the molecular mass to be less than 500 Dalton, for the lipophilicity to be high which is expressed as LogP<5, hydrogen bond acceptors <10, hydrogen bond donors<5 and molar refractivity value to be in-between 40-130. All these parameters are met by the 7 bioactive compounds except for beta- farnesene and 7,11-hexadecadienal whose lipophilicity were higher than 5.

Swiss ADME- Drug likeness analysis

Table 4. Drug Likeness Analysis of Active Constituents

ACTIVE CONSTITUENTS	BIOAVAILABILITY SCORE	LIPINSKI	GHOSE	VEBER	EGAN	MUEGGE
Benzoic acid,2,5-dimethyl-	0.85	YES	NO	YES	YES	NO
Beta- farnesene	0.55	YES	YES	YES	YES	NO
1-Formyl-2,2,6-Trimethyl-3-CIS-(3-MethylLBut-2-Enyl)-5-Cyclohexene	0.55	YES	YES	YES	YES	NO
7,11-hexadecadienal	0.55	YES	YES	NO	YES	NO
trans-3-tert-butylcycloheptanol	0.5	YES	YES	YES	YES	NO
Phenol,2-methoxy-3-(2-propenyl)-	0.55	YES	YES	YES	YES	NO

Caryophyllene	0.55	YES	YES	YES	YES	NO

Almost all 7 bioactive compounds are proven to have drug likeness through Lipinski test, Ghose test, Veber test and Egan test in Table 4. But all these compounds were analysed negative for drug likeness in Muegge test because of the molecular weight being less than 200 in some molecule and presence of heteroatoms in some molecules.

Pharmacokinetics analysis

Table 5. Pharmacokinetics Analysis of Active Constituents-1

ACTIVE CONSTITUENTS	GI ABSORPTION	BBB PERMEANT	P-gp SUBSTRATE	CYP1A2 INHIBITOR	CYP2C19 INHIBITOR
Benzoic acid,2,5-dimethyl-	HIGH	YES	NO	NO	NO
Beta-farnesene	LOW	NO	NO	YES	NO
1-Formyl-2,2,6-Trimethyl-3-CIS-(3-Methyl But-2-Enyl)-5 Cyclohexene	HIGH	YES	NO	NO	NO
7,11-hexadecadienal	HIGH	YES	NO	YES	NO
trans-3-tert-butylcycloheptanol	HIGH	YES	NO	NO	NO
Phenol,2-methoxy-3-(2-propenyl)-	HIGH	YES	NO	YES	NO
Caryophyllene	LOW	NO	NO	NO	YES

Table 6. Pharmacokinetics Analysis of Active Constituents-2

ACTIVE CONSTITUENTS	CYP2C9 INHIBITOR	CYP2D6 INHIBITOR	CYP3A4 INHIBITOR	SKIN PERMEATION	ESOL
Benzoic acid,2,5-dimethyl-	NO	NO	NO	-5.67 cm/s	-2.48
Beta-farnesene	YES	NO	NO	-3.27 cm/s	-4.44
1-Formyl-2,2,6-Trimethyl-3-CIS-(3-Methyl But-2-Enyl)-5 Cyclohexene	YES	NO	NO	-4.89 cm/s	-3.45
7,11-hexadecadienal	NO	NO	NO	-4.06 cm/s	-3.78
trans-3-tert-butylcycloheptanol	NO	NO	NO	-4.84 cm/s	-3.05

Phenol,2-methoxy-3-(2-propenyl)-	NO	NO	NO	-5.45 cm/s	-2.67
Caryophyllene	YES	NO	NO	-4.44 cm/s	-3.87

The pharmacological characteristics such as Absorption, Distribution, Metabolism and Excretion (ADME) were screened through Swiss ADME Table 5 & Table 6. The estimated solubility (ESOL) of the compounds revealed them all to be soluble. GI absorption was high for all bioactive compounds except for beta-farnesene and caryophyllene. Even in blood - brain barrier (BBB) permeant analysis except for beta-farnesene and caryophyllene all of the results were positive. In accordance with this the bioavailability score was in range for all compounds except benzoic acid,2,5-dimethyl- in Table 3. The skin permeation for all compounds falls in the same range of 3-6 cm/s.

The majority of bioactive substances are not inhibiting CYP3A4, CYP2D6, or CYP1A2, which are members of the cytochrome P450 enzyme family, which plays a decisive role in drug metabolism. When a substance interacts with cytochrome 450 isoenzymes, it may produce rapid metabolism if it is a substrate of any CYP and cause over production, or it may cause accumulation if it is an inhibitor. Both outcomes are unfavorable. CYP plays a major role in the formulation of anti-cancer medications [8]. The therapeutic efficacy of a medicine is determined by the increased endogenous expression of cytochrome P450 in malignancies and gene therapy mediated by cytochrome P450. To ascertain a compound's pharmacological anti-cancer potential, it is crucial to analyze it for CYP inhibition.

Bioavailability radar

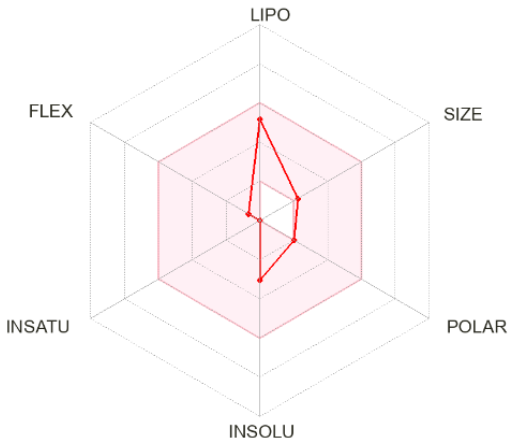

Figure 10.Phenol,2-methoxy-3-(2-propenyl)- Figure 11. trans-3-tert-butylcycloheptanol

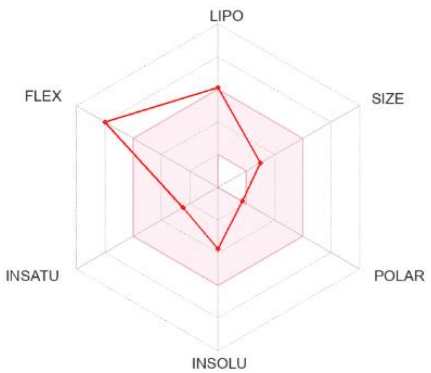

Figure 12.7,11-hexadecadienal

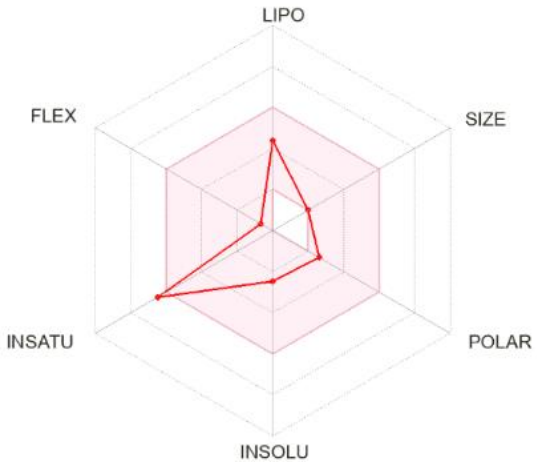

Figure 13.Benzoic acid,2,5-dimethyl-

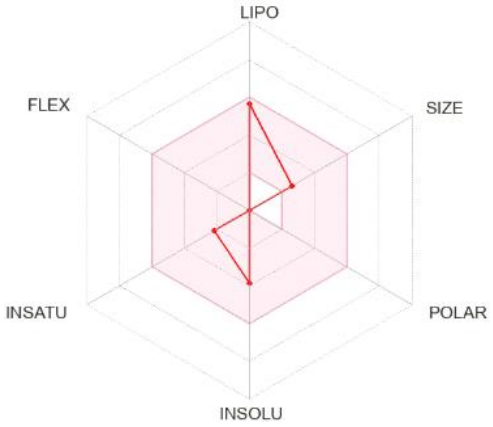

Figure14.Caryophyllene

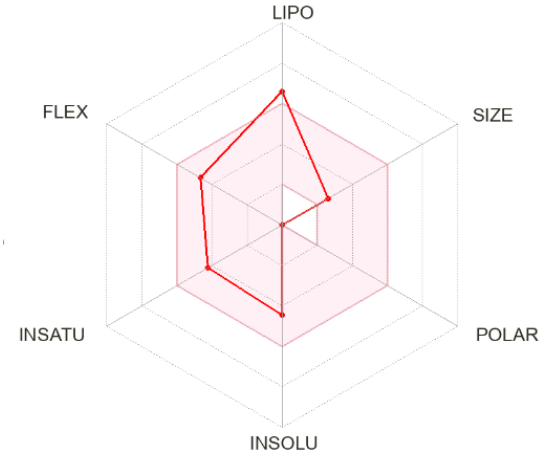

Figure 15. Beta-farnesene

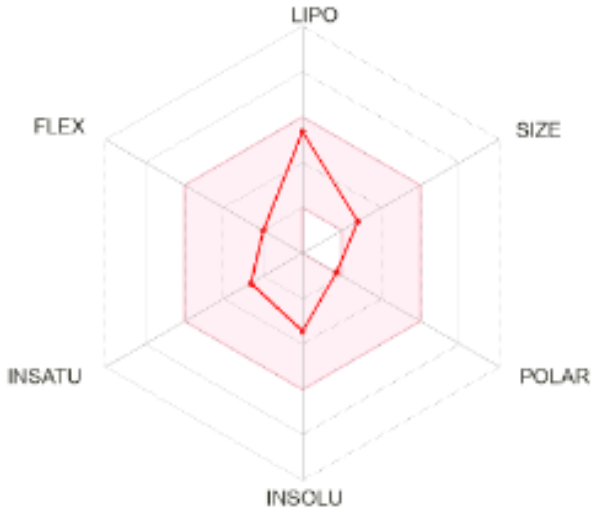

Figure 16. 1-Formyl-2,2,6-Trimethyl-3-CIS-(3-Methyl but-2-Enyl)-5-Cyclohexene

Figure 10-16. Radar Plots of Ligands

Bioavailability radar offers a quick evaluation of a compound's drug-likeness. When evaluating the criterion of a bioactive compound, the compound's radar plot must fall within the pink area to be deemed drug-like; as a result, the ligands are predicted either to be bioavailable or not based on the radar plot. This is illustrated in Figure10-16. Compounds' bioavailability is largely determined by two fundamental properties: polarity (polar) and flexibility (FLEX). Compounds with rotatable bonds > 10 are expected to have low oral bioavailability, whereas compounds with polarity dictated by topological polar surface (TPSA>20 Å2<130 Å2) are expected to have high oral bioavailability [9]. Trans-3-tert-butylcycloheptanol, Benzoic acid, 2,5-dimethyl-, Caryophyllene, 1-Formyl-2,2,6-Trimethyl-3-CIS-(3-Methyl but-2-Enyl)-5-Cyclohexene are the four active compounds among the tested that have been shown to be orally accessible by satisfying the radar plot.

Lipophilicity

Table 7. Lipophilicity of Active Constituents using Swiss ADME

S.NO	ACTIVE CONSTITUENTS	iLOGP	XLOGP3	WLOGP	MLOGP	SILICOS-IT
1.	Benzoic acid,2,5-dimethyl-	1.57	2.18	2.00	2.25	2.14
2.	Beta-farnesene	3.86	6.03	5.20	4.84	4.93
3.	1-Formyl-2,2,6-Trimethyl-3-CIS-(3-Methyl But-2-Enyl)-5 Cyclohexene	2.99	3.88	4.15	3.46	3.92
4.	7,11-hexadecadienal	3.93	5.19	5.22	4.10	5.60
5.	trans-3-tert-butylcycloheptanol	2.59	3.52	2.97	2.74	2.48
6.	Phenol,2-methoxy-3-(2-propenyl)-	2.27	2.61	2.13	2.01	2.48
7.	Caryophyllene	3.29	4.38	4.73	4.63	4.19

Lipophilicity of a compound or drug is evaluated in dosage formation to assess the capacity of drug/compound to permeate the lipid bilayer barrier of almost all cellular membranes including enterocytes [10]. It is necessary for the drug to possess high lipophilicity to facilitate absorption. Bioactive

compounds tested here all have high lipophilicity which meets the criteria to make the bioactive compounds capable of oral and GI absorption Table 7.

Conclusion

Through all these assessments it is proven that the 7 bioactive compounds with low binding energy have significant drug likeness according to Lipinski's test and Swiss ADME. The pharmacokinetic screening of these bioactive compounds confirmed that almost all of them have significantly great GI absorption, BBB (blood-brain barrier) permeation, skin permeation and solubility. Almost all of the compounds were non-inhibitors of cytochrome P450 enzymes. These enzymes play a vital role in drug metabolism whose inhibition or over expression could cause alteration in the drug's mechanism. The bioavailability radar offers a quick look on the bioavailability of the drug and its drug potential where four among seven tested compounds were positive. Lipophilicity analysis brings about the conclusive results of the compounds potential to be absorbed. According to the lipophilicity analysis through Swiss ADME most of them had high absorption capacity. This study concludes that the bioactive compounds present in Piper longum holds significant anti-cancer potential making them a suitable alternative solution for cancer treatment.

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