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Computational Analysis of Phytocompounds of *Curcuma caesia* (black turmeric) against CFLAR Protein Expressed in Lung cancer

Chandra Sekhar Tripathy[1*], M.Sc., Regional Medical Research Centre, Bhubaneswar, Odisha, India

Abstract:- Lung cancer is a cancer that starts in the lungs and spreads throughout the body. The lungs are two spongy organs in the chest that take in oxygen and release carbon dioxide as we inhale and exhale. Lung cancer is the most common cancer that kills people around the world. Lung cancer is most common in smokers, although it can also strike persons who have never smoked. The amount of time and number of cigarettes you smoke raises your risk of lung cancer. However, physiologically the protein CFLAR (CASP8 and FADD-like apoptosis regulator) is found to be widely associated with lung cancer and is also over expressed. *Curcuma caesia* is an herbal plant with lots of known medicinal properties. *Curcuma caesia* has 50 known phyto-compounds (PCs). In the present investigation all the 50 PCs have been put to *in silico* processes including docking analysis to find out the PCs that best stop over-expression of the CFLAR protein in Lung cancer. Tau-Cadinol and Delta-Cadinene are found to be champion molecules of this plant against Lung cancer.

Keywords:- *CFLAR, Lung cancer , docking , in silico ,Curcuma caesia.*

I. INTRODUCTION

Cancer is one of the most lethal complications on the planet. According to the World Health Organization's (WHO) most recent data, roughly 9.6 million fatalities occurred worldwide in 2018 (1). Lung cancer accounts for more than a quarter of all fatalities worldwide. Nearly 60% of lung cancer patients are diagnosed with metastasis at an advanced stage, when cells proliferate rapidly and survival chances are slim. By 2025, it is expected that there will be 20 million new instances of cancer. Lung cancer is characterised by the uncontrolled proliferation of abnormal cells in one or both lungs. These aberrant cells do not perform the activities of healthy lung tissue and do not develop into them. The aberrant cells eventually create tumours that obstruct the lung's ability to function. Tobacco usage is responsible for 80% to 90% of all lung cancers. Exposure to secondhand cigarette smoke is also a substantial risk factor for lung cancer, with lower ages of exposure being linked to a higher risk of lung cancer (2). Many carcinogens operate synergistically when mixed with tobacco smoke, and risk factors are often dose and duration dependent (3). On the basis of the appearance of lung cancer cells under the microscope, doctors divide lung cancer into two major categories. Small cell lung cancer is virtually exclusively found in heavy smokers. Non-small cell lung cancer (NSCLC): Non-small cell lung cancer (NSCLC) is a catch-all name for a variety of lung tumours that behave similarly. Squamous cell carcinoma, adenocarcinoma, and large cell carcinoma are examples of non-small cell lung malignancies. In the early stages of lung cancer, there are usually no signs or symptoms. Lung cancer signs and symptoms usually appear after the disease has progressed. Lung cancer signs and symptoms include: Chronic coughing, Coughing up blood, Shortness of breath, Chest discomfort, Wheezing, Hoarseness, Unexplained weight loss , Bone pain and Headache etc. X-ray images, CT scans, Sputum cytology, Lung tissue samples(biopsy) are used to diagnose lung cancer. Quit smoking, avoid secondhand smoke, test your house for radon, avoid carcinogens at work, and eat a healthy diet rich in fruits and vegetables Exercise on a regular basis are some of the preventive percussion can be taken into account to keep away from this lung cancer (4) . When the particular treatment is discussed and to improve patient survival, new therapeutic targets and lead molecules against lung cancer proliferation and metastasis are urgently needed. Apoptosis has long been thought to play a crucial function in tissue homeostasis by eradicating undesirable cells selectively. Loss of apoptosis or apoptosis-signaling pathways in deformed cells due to genetic changes or mutations is considered to be a crucial role in carcinogenesis. Cancer cell apoptosis has been found as a valuable technique for cancer treatment. Here, in this study an apoptotic regulator protein namely **CFLAR (CASP8 and FADD-like apoptosis regulator)** found to be linked to lung carcinoma from research studies and taken for consideration in drug discovery (5). CFLAR is important gene in the apoptotic pathway and it plays a vital role in proper functioning of apoptosis in cell. Certain cases of mutation in CFLAR due to carcinogenesis or mutagenesis, proliferation takes place. At that condition ligand molecules binding with the CFLAR can block their activity to minimize their gain of proliferating nature. This activity may help the other influenced gene of the apoptotic pathway to normalize or replenish their active apoptotic pathway.

Here for predicting out the drug candidate for the Lung cancer therapeutic a plant namely *Curcuma caesia* is taken into account. It is commonly known as Black turmeric or Kali Haldi . It is indigenous plant found in tropical and sub-tropical regions of Asia in countries like India, Bhutan, Thailand ,Indonesia ,Malaysia etc (6). It belongs to *Curcuma* genus and member of the ginger (family Zingiberaceae). It has anti-inflammatory, hepatoprotective, blood purifier, antioxidant, anti-asthmatic, anti-tumor, stomachic, and carminative activities, according to the study. A deep violet

blotch runs the length of the leaf's lamina. Rhizome is fragrant, carminative, and stimulating, and a rhizome paste is used to treat diarrhoea and as a poultice for rheumatoid arthritis, sprains, and bruises. Kali haldi, as it is commonly known, is a relatively unknown and unexplored medication. Kali haldi's rhizome and leaves are used in several parts of the world. It is utilised as a brain and heart tonic. *Curcuma caesia Roxb*. dried rhizomes and leaves are used to treat piles, leprosy, asthma, cancer, wounds, impotency, fertility, tooth ache, vomiting, and allergies. Leucoderma, piles, bronchitis, asthma, tumours, tuberculous glands of the neck, spleen enlargement, and epilepsy are all common uses for rhizomes. *Curcuma caecia Roxb* dry rhizome and leaves are used in the treatment of Piles, leprosy, asthma, cancer, wounds, fever, impotency, fertility, tooth ache, vomiting, and allergies in North-East and Central India. Fresh rhizome decoction is used as an antidiarrhoeiaric and for stomach pain alleviation. During snake bites and scorpion bites, fresh curcuma caesia rhizome paste is used. The dried powder was blended with Andrographis paniculata Wall ex Nees seed powder and administered to insect and snake bites (7). **Figure 1** showing the picture of *Curcuma caesia* whole plant and its rhizome.

Looking into such medicinal properties of this plant, the current *in silico* work is done to predict out the best phytochemicals which can be better therapeutic drug candidates against this Lung cancer disease by targeting the CFLAR protein .

II. MATERIAL METHOD

- *Gene target selection of Lung cancer*

In Lung cancer cell lines the CFLAR (CASP8 and FADD-like apoptosis regulator) protein (gene name) is frequently found. The best human derived protein in NMR (Nuclear magnetic resonance) structure is obtained from PDB database (8) with PDB Id 6M6O and having UniProt database (9) entry id O15519, mass 55,344 Da. This is the protein that is chosen for this *in silico* study. The CFLAR protein's 3D structure was viewed using Discovery studio visualizer version 2019. The structure's chain A was chosen for the research.

- *Prediction of binding sites of the CFLAR protein of Lung cancer*

A protein's binding sites determine the active sites of molecules where tiny molecules will connect. As a result, the CastP website (10) was used to predict the CFLAR protein's binding locations, which were then utilized in the study.

- *Reported phytocompounds from Curcuma caesia (Kali haldi or Black turmeric)*

Curcuma caesia contains a number of phytochemicals that have therapeutic effects. The PubChem database (11) was employed to retrieve the details information about the phytocompounds.

- *Lipinski rule of five – Ro5*

Any oral active medicine must meet the following criteria: Molecular mass (=500 D), logP (=5), hydrogen bond donor (=5), hydrogen bond acceptors (=10), and Molecular refractivity (in silico study) (40-130). The most essential selection criterion is the rule of five (RO5) (12). If any of the conditions are not followed, the candidate compound is excluded as a potential source. The TargetNet web server was used to forecast the RO5 for all of the phytochemicals used in the study (13) (http://targetnet.scbdd.com/calcnet/calc rule text/#). Protox-II server (14) and Toxicity checker server under mcule environment (15) program were used to check the harmful nature of the substances that pass through the RO5.

- *Molecular docking of selected compounds from Curcuma caesia against the Lung cancer protein CFLAR (CASP8 and FADD-like apoptosis regulator)*

Curcuma caesia compounds that are RO5-following and non-toxic were further processed for a molecular docking study against the CFLAR (CASP8 and FADD-like apoptosis regulator) protein. The inquiry used the widely used software Autodock 4.2 tool (16) to test the efficacy of the ligands chosen for investigation in order to conduct molecular docking investigations. The best-docked complexes were described and processed for further computational investigation based on binding energy values, ligand efficiency, inhibition constant, and intermolecular hydrogen (H)-bonds. Thymoquinone (17), a commonly used drug in lung cancer, was used in a comparison experiment with the CFLAR protein in this study.

III. RESULTS

- *Selected gene*

CFLAR (CASP8 and FADD-like apoptosis regulator) protein expression has been consistently elevated in lung cancer research studies. The UniProt database was used to gather detailed information about this protein. The 3D structure of the CFLAR protein may be found in the PDB database under the PDB ID 6M6O. The chain A of the structure under inquiry is shown here.

- *Binding sites of CFLAR protein*

Using the CastP server, the active sites of the CFLAR (CASP8 and FADD-like apoptosis regulator) protein obtained. The predicted binding of CFLAR protein are ASP18, GLU21, MET24, PHE27, ARG65, VAL66, ARG67, MET101, ALA102, GLY105, GLU106, ASP107, LEU108, ASP109, LYS110, VAL113, SER114, LYS131, GLU132, LYS133, SER134, PHE135, LEU136 and VAL139. These are the obtained binding sites of CFLAR protein.

- *Phytocompounds of Curcuma caesia*

Curcuma caesia is a well-known herbal remedy. The medicinal effects of this plant are still being studied. In the current study, the phytocompounds from *Curcuma caesia* were obtained from a number of research papers. The 50 phytocompounds (PCs) listed in Table 1 were sourced from the literature (18,19) and cross-checked against the PubChem database.

- *Lipinsk's rule of 5 and Toxicity*

Lipinski's Rule of Five is important in medication development. This rule is frequently used to examine if

compounds (are expected to) exhibit the required pharmacokinetic properties, thereby qualifying them as potential candidates for orally active systemic medicines (candidate moieties) that are in accordance with anthropo-homeo physiology. The ADME (Absorption, Distribution, Metabolism, and Excretion) properties are included in Rule-5 because of its parametric distribution and quantitative evaluation. Lipinsk's 5 has grown critical as a result. As a result, the 50 *Curcuma caesia* PCs were tested against Lipinsk's rule of five using the TarGetNet server. The findings are listed in Table 2.

- *Finding*

Out of 50 PCs, two breach the Lipinsk's rule of five. As a result, these two computers were retired. The toxicity of the remaining 48 compounds was determined. Two web servers, ProTox-II server and Toxicity Checker Tool, were used to check the toxicity of the PCs. The Toxicity test/s were only passed by 18 PCs. The findings are listed in Table 3. These 18 compounds were selected for the docking study and analysis against the CFLAR protein of lung cancer along with the reported drug Thymoquinone having PubChem ID 10281; molecular formula $C_{10}H_{12}O_2$, Molecular Weight 164.20) and Canonical smile id - CC1=CC(=O)C(=CC1=O)C(C)C. The 3D-structures of the PCs and the reported drug were downloaded from the PubChem database in .SDF format and converted into .pdb format using the Discovery studio tool.

- *Molecular docking*

The Autodock 4.2 has been used for the docking of the molecules. The grid box value taken for the study is for X-dimension = 94, Y-dimension = 108 and Z-dimension =66 with 0.375 Angstrom spacing. In the docking study, it was found that, the PCs namely **tau-Cadinol** shows the highest binding affinity of -6.41 kcal/mol, with an ligand efficiency of -0.4, inhibition constant 20.13 µm and forms conventional hydrogen bond with GLY105 and LEU108 with average distance of 1.98969Å vis-à-vis the CFLAR protein of Lung cancer. **Delta-Cadinene** shows the second highest binding affinity of -6.16 kcal/mol, with an ligand efficiency of -0.41, inhibition constant 30.04 µm and other 16 (of the 18) follow. Table 4 summarizes the docking results. **Figure 2 and 3** represents 2D and 3D interaction of CFLAR protein of Lung cancer with tau-Cadinol. **Figure 4 and 5** represents 2D and 3D interaction of CFLAR protein of the Lung cancer with Delta-Cadinene. On the other hand, the reported drug **Thymoquinone** showed a very less binding affinity of -5.48 kcal/mol against the CFLAR protein of the Lung cancer. Table 5 represents the other docking parameters result of the reported drug.

IV. DISCUSSION

In attempt to uncover natural chemicals as lead molecules against various diseases, a vast number of in silico studies have lately been conducted. *Curcuma caesia* is a medicinal plant that contains numerous bioactive components, which is why this plant (whole\part) is used to treat various maladies. Lung cancer is a threat for the entire human society. The protein CFLAR plays the lead role in Lung cancer neoplasogenesis. It is expressed extensively in Lung cancer. So, in the current *in silico* investigation, the protein CFLAR is being targeted. Data pertaining to 50 PCs of the *Curcuma caesia* were collected from various research papers. Each molecule was put to in silico investigation. In this study TargetNet webserver used to check the Lipinsk's rule of 5, in which 48 PCs out of 50 PCs of *Curcuma caesia* passed the rule of 5. After that, the 48 PCs were put to toxicity testing by the web servers like ProTox II server and Toxicity checker tool and only 18 PCs were found to be non-toxic (fit for human use). These 18 have been computationally assayed. Autodock 4.2 tool used to dock these 18 PCs against the CFLAR protein. Furthermore, the reported drug namely Thymoquinone which is commonly used as an effective frontline drug by clinicians (worldwide) has taken studied. In the docking analysis it was found that (out of the 18 compounds of the *Curcuma caesia* selected for the docking analysis) the PC **tau-Cadinol** shows the highest binding affinity of -6.41 kcal/mol against the CFLAR protein of the Lung cancer followed by **Delta-Cadinene** with second highest binding affinity of -6.16 kcal/mol. And whereas the reported drug **Thymoquinone** showed binding affinity of -5.48 kcal/mol, which is less by an order of 50%.

V. CONCLUSION

The current work may be able to show the compounds **tau-Cadinol and Delta-Cadinene's** optimal inhibitory affinity against the crucial protein CFLAR involved in lung cancer by combining the results of several in-silico analyses. These evaluated compounds passed drug ability and molecular docking tests with flying colours. These compounds may provide novel approaches and methodologies for the creation of therapeutic drug options for lung cancer, according to the study. It is suggested that candidate chemicals be extracted and a lead molecule be synthesised from *Curcuma caesia* as a result of the findings. Before moving on with clinical trials, these lead compounds can be processed for in-vitro and in-vivo studies to establish their efficacy and measure their anti-cancer potency.

Conflict of interest: The author declares no conflict of interest. This study is non-commercial; not funded; non donor driven.

Ethical issues: None.

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Table legends

Table 1: Description of Phytochemical compounds present in *Curcuma caesia*
Table 2: Lipinski rule of five analyses of the phytoconstituents present in *Curcuma caesia* using TarGetNet Server
Table 3- Toxicity Checking The Phycompounds Using Protox-II Tool and Toxicitychecker tool
Table 4: Docking of screened Compounds from *Curcuma caesia* against Lung cancer
Table 5: Docking of reported drug against Lung cancer

Figure legends

FIFURE 1. A and B shows *Curcuma caesia* plant picture . C shows the rhizomes picture of *Curcuma caesia*
FIGURE 2. 2D-interaction of tau-Cadinol with CFLAR protein expressed in Lung cancer
FIGURE 3. 3D-interaction of tau-Cadinol with CFLAR protein expressed in Lung cancer
FIGURE 4. 2D-interaction of delta-Cadinene with CFLAR protein expressed in Lung cancer
FIGURE 5. 3D-interaction of delta-Cadinene with CFLAR protein expressed in Lung cancer

TABLES

Table 1: Description of Phytochemical compounds present in *Curcuma caesia*

SL. No.	Chemical name	Molecular formula	PMID	SMILE ID
1.	Tropolone	$C_7H_6O_2$	10789	C1=CC=C(C(=O)C=C1)O
2.	Ledol	$C_{15}H_{26}O$	92812	CC1CCC2C1C3C(C3(C)C)CCC2(C)O
3.	beta-Elemenone	$C_{15}H_{22}O$	10955018	CC(=C1CC(C(CC1=O)(C)C=C)C(=C)C)C
4.	alpha-Bulnesene	$C_{15}H_{24}$	94275	CC1CCC2=C(CCC(CC12)C(=C)C)C
5.	Spathulenol	$C_{15}H_{24}O$	92231	CC1(C2C1C3C(CCC3(C)O)C(=C)CC2)C
6.	Eucalyptol	$C_{10}H_{18}O$	2758	CC1(C2CCC(O1)(CC2)C)C
7.	Epicurzerenone	$C_{15}H_{18}O_2$	5317062	CC1=COC2=C1C(=O)C(C(C2)(C)C=C)C(=C)C
8.	Camphor	$C_{10}H_{16}O$	2537	CC1(C2CCC1(C(=O)C2)C)C
9.	ar-Turmerone	$C_{15}H_{20}O$	160512	CC1=CC=C(C=C1)C(C)CC(=O)C=C(C)C
10.	(Z)-beta-Ocimene	$C_{10}H_{16}$	5320250	CC(=CCC=C(C)C=C)C
11.	Ar-Curcumene	$C_{15}H_{22}$	92139	CC1=CC=C(C=C1)C(C)CCC=C(C)C
12.	beta-Elemene	$C_{15}H_{24}$	6918391	CC(=C)C1CCC(C(C1)C(=C)C)(C)C=C
13.	Borneol	$C_{10}H_{18}O$	64685	CC1(C2CCC1(C(C2)O)C)C
14.	gamma-Curcumene	$C_{15}H_{24}$	12304273	CC1=CC=C(CC1)C(C)CCC=C(C)C
15.	beta-Caryophyllene	$C_{15}H_{24}$	5281515	CC1=CCCC(=C)C2CC(C2CC1)(C)C
16.	endo-Fenchol	$C_{10}H_{18}O$	439711	CC1(C2CCC(C2)(C1O)C)C
17.	3-Carene	$C_{10}H_{16}$	26049	CC1=CCC2C(C1)C2(C)C
18.	Camphene	$C_{10}H_{16}$	6616	CC1(C2CCC(C2)C1=C)C
19.	p-Menth-3-ene	$C_{10}H_{18}$	10369	CC1CCC(=CC1)C(C)C
20.	alpha-Pinene	$C_{10}H_{16}$	6654	CC1=CCC2CC1C2(C)C
21.	2-Nonanone	$C_9H_{18}O$	13187	CCCCCCCC(=O)C
22.	Beta-Linalool	$C_{10}H_{18}O$	6549	CC(=CCCC(C)(C=C)O)C
23.	2-Nonanol	$C_9H_{20}O$	12367	CCCCCCCC(C)O
24.	Terpinen-4-ol	$C_{10}H_{18}O$	11230	CC1=CCC(CC1)(C(C)C)O
25.	L-alpha-Terpineol	$C_{10}H_{18}O$	443162	CC1=CCC(CC1)C(C)(C)O
26.	trans-Carveol	$C_{10}H_{16}O$	94221	CC1=CCC(CC1O)C(=C)C
27.	L-Bornyl acetate	$C_{12}H_{20}O_2$	93009	CC(=O)OC1CC2CCC1(C2(C)C)C
28.	delta-Elemene	$C_{15}H_{24}$	12309449	CC(C)C1=CC(C(CC1)(C)C=C)C(=C)C
29.	beta-Germacrene	$C_{15}H_{24}$	90475698	CC1=CC=C(CCC(=C)CCC1)C(C)C
30.	Thujopsene	$C_{15}H_{24}$	442402	CC1=CCC2(CCCC(C23C1C3)(C)C)C
31.	beta-Gurjunene	$C_{15}H_{24}$	6450812	CC1CCC2C(C2(C)C)C3C1CCC3=C
32.	Humulene	$C_{15}H_{24}$	5281520	CC1=CCC(C=CCC(=CCC1)C)(C)C
33.	4,11-Selinadiene	$C_{15}H_{24}$	6429320	CC1=C2CC(CCC2(CCC1)C)C(=C)C
34.	beta-Cubebene	$C_{15}H_{24}$	93081	CC1CCC(C2C13C2C(=C)CC3)C(C)C
35.	beta-Selinene	$C_{15}H_{24}$	442393	CC(=C)C1CCC2(CCCC(=C)C2C1)C
36.	Isolongifolene	$C_{15}H_{24}$	11127402	CC1(CCC=C2C13CCC(C3)C2(C)C)C
37.	Curzerene	$C_{15}H_{20}O$	572766	CC1=COC2=C1CC(C(C2)(C)C=C)C(=C)C
38.	alpha-Gurjunene	$C_{15}H_{24}$	15560276	CC1CCC2C(C2(C)C)C3=C(CCC13)C
39.	delta-Cadinene	$C_{15}H_{24}$	441005	CC1=CC2C(CCC(=C2CC1)C)C(C)C
40.	Selina-3,7(11)-diene	$C_{15}H_{24}$	522296	CC1=CCCC2(C1CC(=C(C)C)CC2)C
41.	alpha-Guaiene	$C_{15}H_{24}$	5317844	CC1CCC(CC2=C1CCC2C)C(=C)C
42.	gamma-Gurjunene	$C_{15}H_{24}$	90805	CC1CCC(C=C2C1CCC2C)C(=C)C

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43.	Caryophyllene oxide	$C_{15}H_{24}O$	1742210	CC1(CC2C1CCC3(C(O3)CCC2=C)C)C
44.	Agarospirol	$C_{15}H_{26}O$	21675005	CC1CCC=C(C12CCC(C2)C(C)(C)O)C
45.	Procerin	$C_{15}H_{18}O_2$	594578	CC(=CCC1=CC=C(C(=O)C=C1C(=C)C)O)C
46.	Cycloisolongifolene, 8,9-dehydro-9-formyl-	$C_{16}H_{22}O$	615367	CC1(CC(=CC23C14C2CC(C4)C3(C)C)C=O)C
47.	tau-Cadinol	$C_{15}H_{26}O$	160799	CC1=CC2C(CCC(C2CC1)(C)O)C(C)C
48.	delta-Cadinol	$C_{15}H_{26}O$	3084311	CC1=CC2C(CCC(C2CC1)(C)O)C(C)C
49.	Germacrone	$C_{15}H_{22}O$	6436348	CC1=CCC(=C(C)C)C(=O)CC(=CCC1)C
50.	1,2-Longidione	$C_{15}H_{22}O_2$	534856	CC1(CCCC2(C3C1C(CC3)C(=O)C2=O)C)C

Table 2: Lipinski rule of five analyses of the phytoconstituents present in *Curcuma caesia* using TarGetNet Server

SL. NO	PHYTOCHEMICALS NAME	TPSA (Topological polar surface area) (<140)	MR (Molar Refractivity) (40-130)	MOLECULAR WEIGHT (<=500 D)	HBD-Hydrogen bond donor (<=5)	HBA1-Hydrogen bond acceptors (<=10)	LogP (<=5)	Lipinski rule of five
1.	Tropolone	37.3	34.735	122.12134	1.0	2.0	0.7524	100%
2.	Ledol	20.23	68.8168	222.36634	1.0	1.0	3.4657	100%
3.	beta-Elemenone	17.07	70.623	218.33458	0.0	1.0	4.0703	100%
4.	alpha-Bulnesene	0.0	69.043	204.35106	0.0	0.0	4.7252	100%
5.	Spathulenol	20.23	68.3428	220.35046	1.0	1.0	3.3858	100%
6.	Eucalyptol	9.23	47.117	154.24932	0.0	1.0	2.7441	100%
7.	Epicurzerenone	30.21	69.1615	230.30222	0.0	1.0	3.7114	100%
8.	Camphor	17.07	45.636	152.23344	0.0	1.0	2.4017	100%
9.	ar-Turmerone	17.07	69.749	216.3187	0.0	1.0	4.0239	100%
10.	(Z)-beta-Ocimene	0.0	48.762	136.23404	0.0	0.0	3.475	100%
11.	Ar-Curcumene	0.0	69.549	202.33518	0.0	0.0	4.8449	100%
12.	beta-Elemene	0.0	70.423	204.35106	0.0	0.0	4.7472	100%
13.	Borneol	20.23	46.5978	154.24932	1.0	1.0	2.1935	100%
14.	gamma-Curcumene	0.0	70.683	204.35106	0.0	0.0	5.0354	100%
15.	beta-Caryophyllene	0.0	68.783	204.35106	0.0	0.0	4.7252	100%
16.	endo-Fenchol	20.23	46.5978	154.24932	1.0	1.0	2.1935	100%
17.	3-Carene	0.0	45.222	136.23404	0.0	0.0	2.9987	100%
18.	Camphene	0.0	45.222	136.23404	0.0	0.0	2.9987	100%
19.	p-Menth-3-ene	0.0	47.596	138.24992	0.0	0.0	3.3888	100%
20.	alpha-Pinene	0.0	45.222	136.23404	0.0	0.0	2.9987	100%

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21.	2-Nonanone	17.07	45.577	142.23862	0.0	1.0	2.9359	100%
22.	Beta-Linalool	20.23	50.4358	154.24932	1.0	1.0	2.6698	100%
23.	2-Nonanol	20.23	46.5388	144.2545	1.0	1.0	2.7277	100%
24.	Terpinen-4-ol	20.23	48.7958	154.24932	1.0	1.0	2.5037	100%
25.	L-alpha-Terpineol	20.23	48.7958	154.24932	1.0	1.0	2.5037	100%
26.	trans-Carveol	20.23	48.2838	152.23344	1.0	1.0	2.2797	100%
27.	L-Bornyl acetate	26.3	56.335	196.286	0.0	2.0	2.7643	100%
28.	delta-Elemene	0.0	70.423	204.35106	0.0	0.0	4.7472	100%
29.	beta-Germacrene	0.0	70.683	204.35106	0.0	0.0	5.0354	75%
30.	Thujopsene	0.0	66.623	204.35106	0.0	0.0	4.5591	100%
31.	beta-Gurjunene	0.0	67.143	204.35106	0.0	0.0	4.2709	100%
32.	Humulene	0.0	70.423	204.35106	0.0	0.0	5.0354	75%
33.	4,11-Selinadiene	0.0	68.783	204.35106	0.0	0.0	4.8693	100%
34.	beta-Cubebene	0.0	67.143	204.35106	0.0	0.0	4.2709	100%
35.	beta-Selinene	0.0	68.783	204.35106	0.0	0.0	4.7252	100%
36.	Isolongifolene	0.0	66.623	204.35106	0.0	0.0	4.5591	100%
37.	Curzerene	13.14	68.74	216.3187	0.0	0.0	4.0712	100%
38.	alpha-Gurjunene	0.0	67.143	204.35106	0.0	0.0	4.415	100%
39.	delta-Cadinene	0.0	69.043	204.35106	0.0	0.0	4.7252	100%
40.	Selina-3,7(11)-diene	0.0	68.783	204.35106	0.0	0.0	4.8693	100%
41.	alpha-Guaiene	0.0	69.043	204.35106	0.0	0.0	4.7252	100%
42.	gamma-Gurjunene	0.0	69.043	204.35106	0.0	0.0	4.5811	100%
43.	Caryophyllene oxide	12.53	68.266	220.35046	0.0	1.0	3.9364	100%
44.	Agarospirol	20.23	70.4568	222.36634	1.0	1.0	3.92	100%
45.	Procerin	37.3	73.353	230.30222	1.0	2.0	3.2942	100%
46.	Cycloisolongifolene, 8,9-dehydro-9-formyl-	17.07	69.256	230.34528	0.0	1.0	3.594	100%
47.	tau-Cadinol	20.23	70.7168	222.36634	1.0	1.0	3.7759	100%
48.	delta-Cadinol	20.23	70.7168	222.36634	1.0	1.0	3.7759	100%
49.	Germacrone	17.07	70.883	218.33458	0.0	1.0	4.3585	100%
50.	1,2-Longidione	34.14	67.757	234.33398	0.0	2.0	2.997	100%

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Table 3- Toxicity Checking The Phycompounds Using Protox-II Tool and Toxicitychecker tool

S.N.	Phytocompound	Tools	Toxic/Non-Toxic
1.	Tropolone	ProTox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
2.	Ledol	ProTox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
3.	beta-Elemenone	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
4.	alpha-Bulnesene	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
5.	Spathulenol	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
6.	Eucalyptol	ProTox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
7.	Epicurzerenone	ProTox-II	Toxic
		Toxicitychecker	Toxic
8.	Camphor	ProTox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
9.	ar-Turmerone	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
10.	(Z)-beta-Ocimene	ProTox-II	Toxic
		Toxicitychecker	Toxic
11.	Ar-Curcumene	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
12.	beta-Elemene	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
13.	Borneol	ProTox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
14.	gamma-Curcumene	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
15.	beta-Caryophyllene	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
16.	endo-Fenchol	ProTox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
17.	3-Carene	ProTox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
18.	Camphene	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
19.	p-Menth-3-ene	ProTox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
20.	alpha-Pinene	ProTox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
21.	2-Nonanone	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
22.	Beta-Linalool	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
23.	2-Nonanol	ProTox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
24.	Terpinen-4-ol	ProTox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
25.	L-alpha-Terpineol	ProTox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
26.	trans-Carveol	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
27.	L-Bornyl acetate	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
28.	delta-Elemene	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic

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29.	Thujopsene	ProTox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
30.	beta-Gurjunene	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
31.	4,11-Selinadiene	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
32.	beta-Cubebene	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
33.	beta-Selinene	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
34.	Isolongifolene	ProTox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
35.	Curzerene	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
36.	alpha-Gurjunene	ProTox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
37.	delta-Cadinene	ProTox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
38.	Selina-3,7(11)-diene	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
39.	alpha-Guaiene	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
40.	gamma-Gurjunene	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
41.	Caryophyllene oxide	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
42.	Agarospirol	ProTox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
43.	Procerin	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
44.	Cycloisolongifolene, 8,9-dehydro-9-formyl-	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
45.	tau-Cadinol	ProTox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
46.	delta-Cadinol	ProTox-II	Non-Toxic
		Toxicitychecker	Non-Toxic
47.	Germacrone	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic
48.	1,2-Longidione	ProTox-II	Non-Toxic
		Toxicitychecker	Toxic

Table 4: Docking of screened Compounds from *Curcuma caesia* against Lung cancer

Sl. No.	Phytocompound	Binding Energy(kcal/Mol)	Ligand Efficiency	Inhibition Constant (µm)	No. of H Bonds	H-Bond Forming Residues	Average Distance of H-Bonds (Å)
1.	Tropolone	-5.1	-0.57	181.7	2	LYS174,ASP96	2.071945
2.	Ledol	-5.69	-0.36	67.03	3	LYS174,ASP96	2.485293333
3.	Eucalyptol	-4.72	-0.43	349.54	1	PHE135	2.155
4.	Camphor	-5.19	-0.47	156.67	1	LYS174	1.88859
5.	endo-Fenchol	-5.18	-0.47	159.02	2	LYS174,ASP96	2.097185
6.	3-Carene	-3.96	-0.4	1.24	N/A	N/A	N/A
7.	p-Menth-3-ene	-4.75	-0.48	332.01	N/A	N/A	N/A
8.	alpha-Pinene	-4.64	-0.46	399.23	N/A	N/A	N/A
9.	2-Nonanol	-3.89	-0.39	1.41	N/A	N/A	N/A
10.	Terpinen-4-ol	-4.75	-0.43	327.7	1	LEU178	1.83915
11.	L-alpha-Terpineol	-4.67	-0.42	377.0	2	PHE135,LEU136	2.18425
12.	Thujopsene	-5.45	-0.36	101.66	N/A	N/A	N/A
13.	Isolongifolene	-5.66	-0.38	71.42	N/A	N/A	N/A

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14.	alpha-Gurjunene	-5.54	-0.37	86.6	N/A	N/A	N/A
15.	**delta-Cadinene**	-6.16	-0.41	30.04	N/A	N/A	N/A
16.	Agarospirol	-6.0	-0.38	39.98	2	LYS174,ASN90	2.058925
17.	**tau-Cadinol**	-6.41	-0.4	20.13	2	GLY105,LEU108	1.98969
18.	delta-Cadinol	-6.04	-0.38	37.4	1	LEU108	2.20978

Table 5: Docking of reported drug against Lung cancer

Sl. No.	Reported Drug	Binding Energy(kcal/Mol)	Ligand Efficiency	Inhibition Constant (µm)	No. of H Bonds	H-Bond Forming Residues	Average Distance of H-Bonds (Å)
1.	Thymoquinone	-5.48	-0.46	96.31	2	ASP96,LYS174	2.21881

FIGURES

(A) (B)

(C)

Fig 1. A and B shows *Curcuma caesia* plant picture. C shows the rhizomes picture of *Curcuma caesia*

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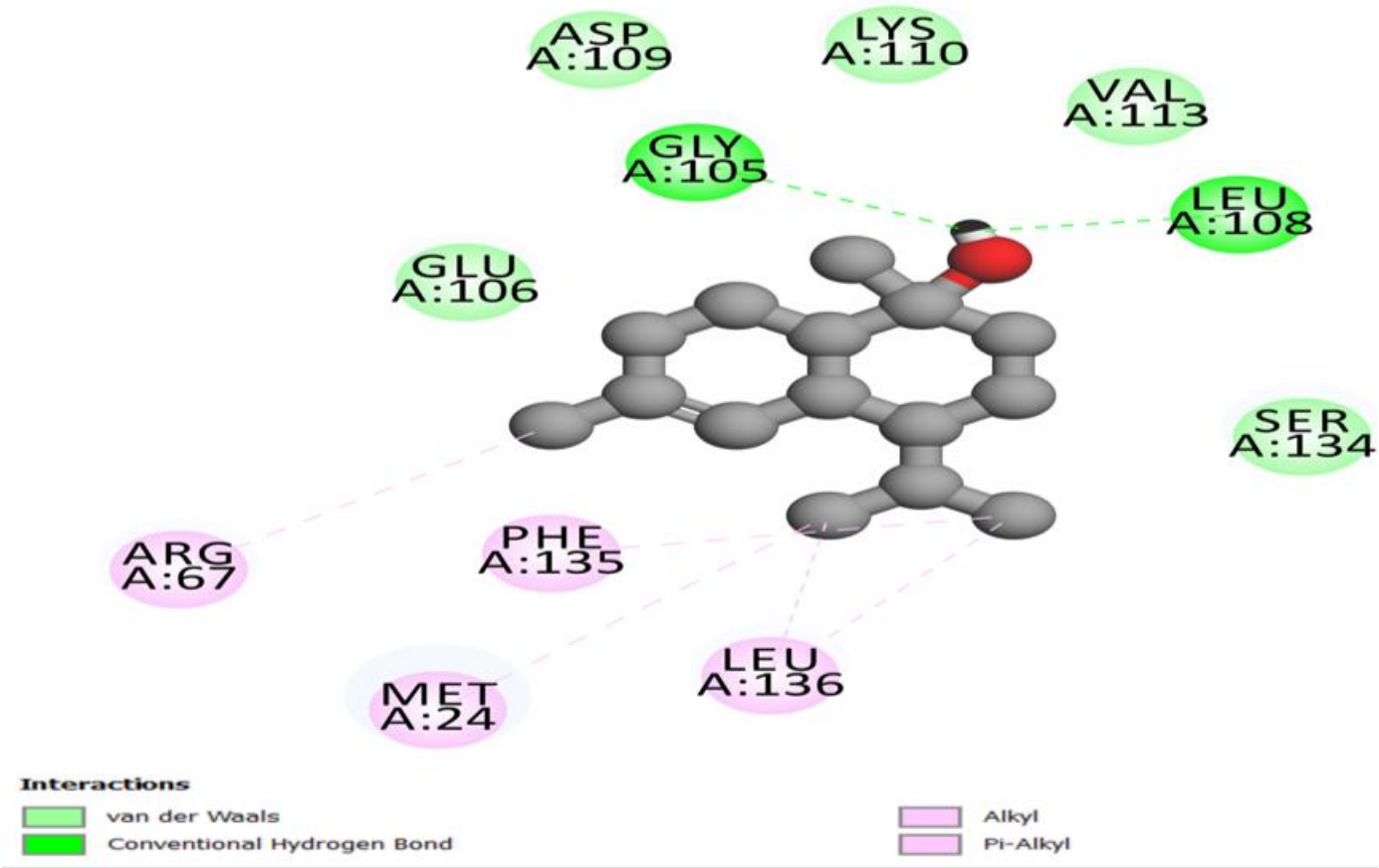

FIG 2. 2D-interaction of tau-Cadinol with CFLAR protein expressed in Lung cancer

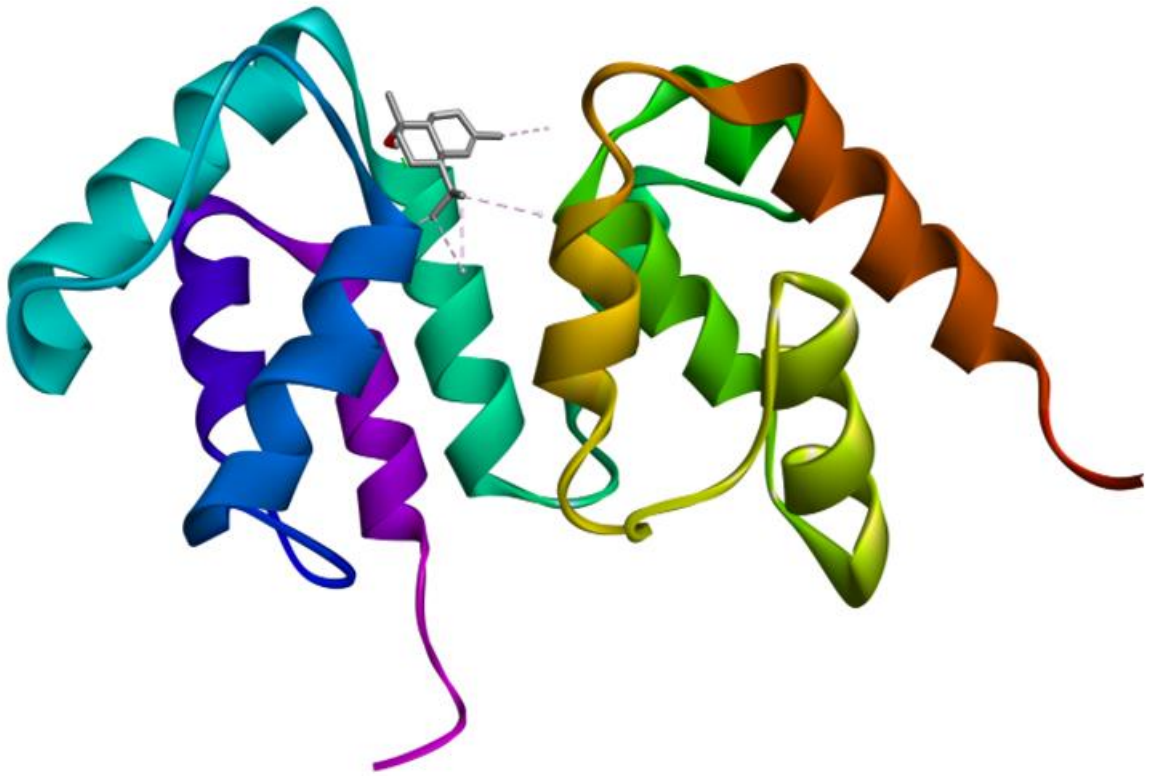

FIG 3. 3D-interaction of tau-Cadinol with CFLAR protein expressed in Lung cancer

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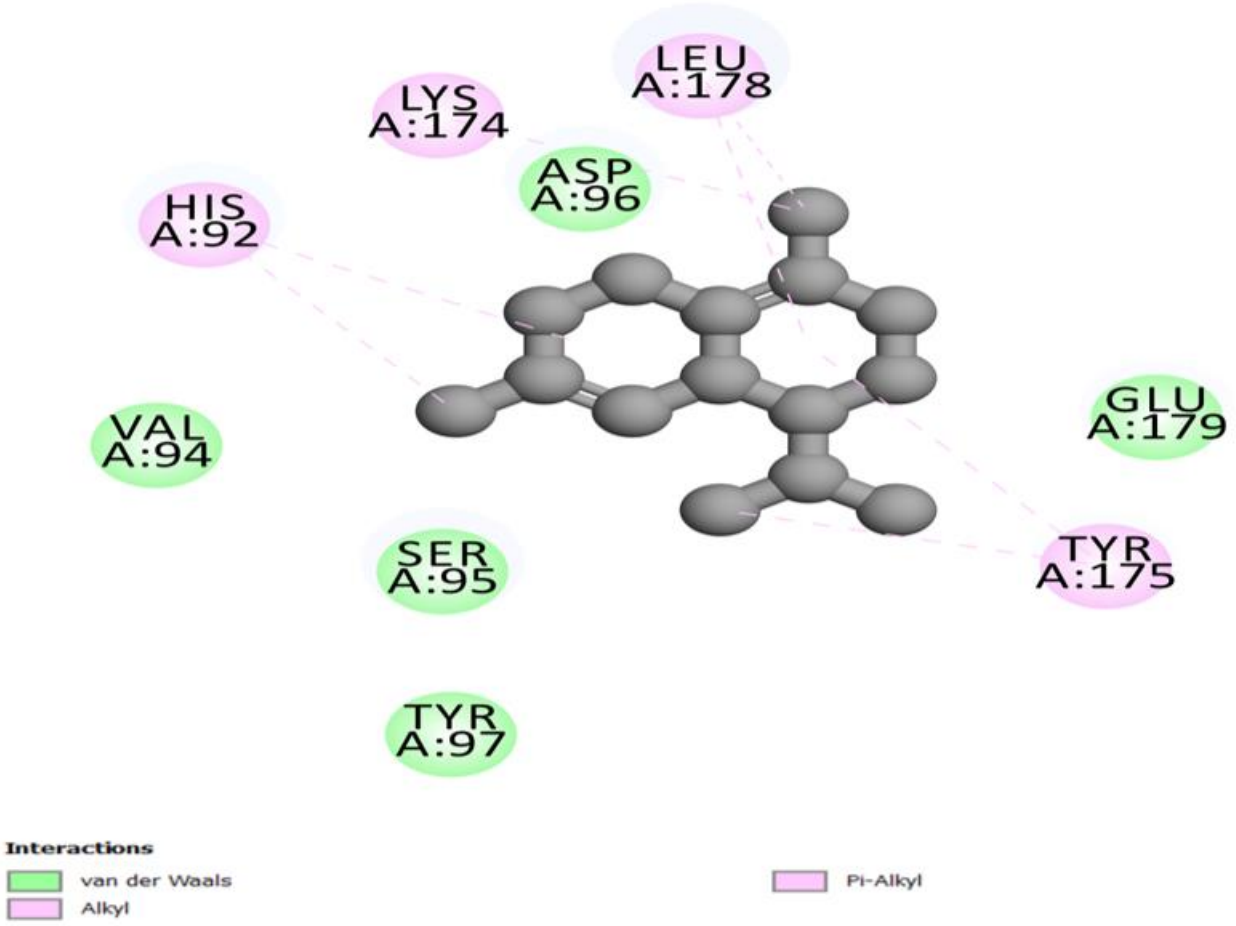

FIG 4. 2D-interaction of delta-Cadinene with CFLAR protein expressed in Lung cancer

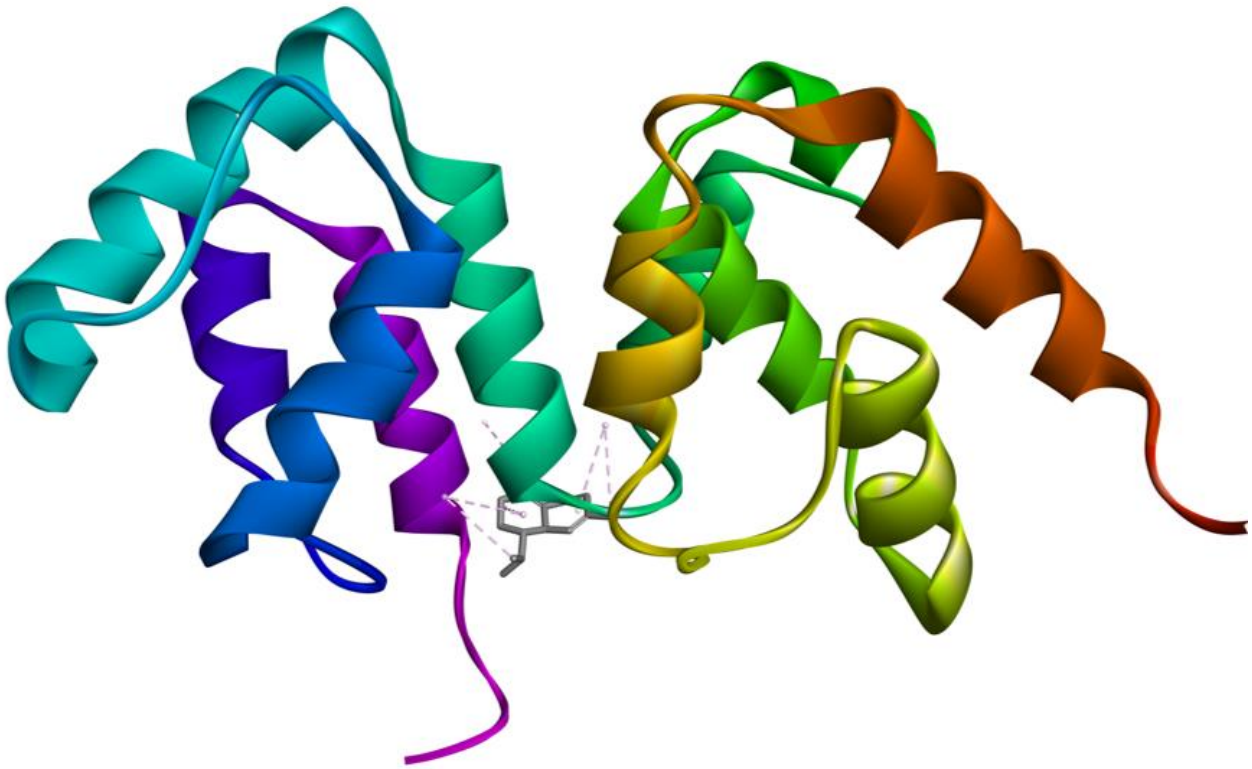

FIG 5. 3D-interaction of delta-Cadinene with CFLAR protein expressed in Lung cancer