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Original Research Article

Exploring the Cucurbitacin E (CuE) as an Anti-Lung Cancer Lead Compound through Molecular Docking, ADMET, Pass Prediction and Drug Likeness Analysis

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ABSTRACT

Cucurbitacin E (CuE) is a potent bioactive compound derived from the family of cucurbitaceae. CuE has recently been demonstrated to have outstanding potential to inhibit the growth of different kinds of cancer cells. CuE has been proven to have a strong anticancer effect on lung cancer in different in vitro and in vivo studies up to this date. In the present study, molecular docking of CuE was performed against three major proteins respectively myosin 9b [5C5S (Chain: A, B, C, D)], epidermal growth factor receptor (EGFRK) [1M17 (Chain: A)] and yes-associated protein (YAP) [3KYS (Chain: A, C)] associated with lung cancer. Different types of computers based softwires like GaussView 6.0, Gabedit, Swiss-PDB, Pymol, PyRx (Version 0.8), Discover Studio (2021) etc. are used for computational study. On the other hand, for developing the pharmacokinetic profile of the drug several online servers like Drug bank online, Pub Chem, RCSB:PDB, Webmo server, Online smile convertor, ADMET prediction, PASS prediction, Drug likeness analysis etc. are used. The molecular docking results showed that CuE possessed the best ligand protein interaction with 5C5S (Chain: A) protein where the binding score was -9.1 kJ/mol. Moreover, the non-bonding interactions ensure the significant binding affinity of CuE with 5C5S (Chain: A) protein to show antineoplastic effect against lung cancer. However, the present study reveals that CuE is the potent anti-lung cancer lead compound confirmed by the ligand protein interactions, ADMET calculation, PASS prediction and drug likeness analysis. Therefore, this study may be helpful towards the research community to think CuE as the best antineoplastic agent for treating lung cancer.

Keywords: Cucurbitacin E, Anti-lung cancer, Molecular docking, ADMET study, PASS prediction, Drug likeness

Introduction

Cancer is a rapid growth of atypical cells that proliferate in excess of their normal limits, which can subsequently affect surrounding tissues and spread to other organs.[1] According to several scientific reports, there are believed to be 200 or so different forms of cancer in humans.[2] In 2020, there were reportedly 18.1 million cases of cancer in which 9.3 million cases were in men and 8.8 million in women across the globe. Lung cancer is the second-most prevalent cancer in the world, where it's the highest prevalent observed in men and the second most prevalent in women. The number of newly diagnosed lung cancer incidents in 2020 was above 2.21 million and the death report was 1.8 million.[3] Lung cancer is divided into non-small cell lung carcinoma (NSCLC) which may affect 85% people[4] and small cell lung carcinoma (SCLC) which may affect 15% people.[5] There are several treatment processes for treating lung cancer like chemotherapy, radiation therapy, surgery, Immunotherapy, bone marrow transplantation, hormone therapy etc. However, this may lessen the mortality rate and improve the quality of life but still now full recovery remains in a challenge. Therefore, scientists have been exploring for the last few years to discover some natural remedies for cancer treatment which will have comparatively low side effects than the chemical therapeutic agents.

In the present time, scientists have screened and evaluated several compounds derived from different medicinal plant herbs for better treatment and prevention of lung cancer.[6-8] Cucurbitacins are tetracyclic triterpenoids, a set of multiple bioactive compounds which have been isolated and purified from the plants of cucurbitaceae family. Cucurbitacins are highly oxidated steroids which have cucurbitane nucleus and various types of oxidative functional groups at different position of their chemical structure. They are categorized into 12 different groups from cucurbitacin A to T with over 200 derivatives. Among all other Cucurbitacins, Cucurbitacin E (CuE) is the major bioactive component (Figure 1) which is well known for its bitterness and cytotoxic effects. [9, 10] Moreover, some safety studies associated with CuE revealed that although CuE possessed cytotoxic effect, but it possessed no toxic effect when it had been used for treating the lung cancer of xenografted mice.[11] However, several studies confirmed that CuE possessed different pharmacological effects like antioxidant activity, anti-inflammatory activity, neuro protective activity, anti-cancer activity, antifeedant activity, effects in visceral obesity, effects in rheumatoid arthritis, anti-angiogenic effects, immunomodulatory effects among which anti-cancerous effects of CuE is the most prominent. Due to the cytotoxic effects, CuE had been used as a primary led compound for various anticancer drugs development against various

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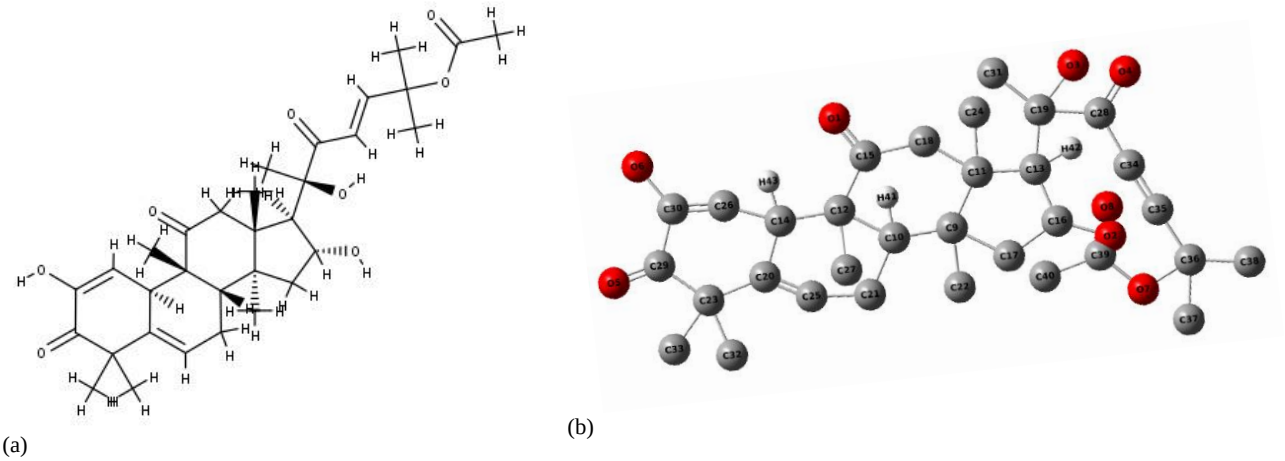
cancers like breast cancer, lung cancer, colon cancer, prostate cancer, bladder cancer etc.[12] Therefore; the present study analyzed the anti-lung cancer effects of CuE against lung cancer using different *in silico* studies. The PASS prediction (prediction of activity spectra for substances) it had been estimated that among all other pharmacological effects, the anti-lung cancer effect of CuE was the most. In addition the ADMET study and drug likeliness analysis were performed to evaluate the pharmacokinetic effects as well as the physical properties of CuE. This study identified the three major proteins respectively 5C5S, 1M17 and 3KYS associated with lung cancer. The 5C5S protein was identified in 95D cell the sublines of human lung giant carcinoma cell[13] which had four subunit protein chains respectively 5C5S (Chain: A), 5C5S (Chain: B), 5C5S (Chain: C), 5C5S (Chain: D). On the other hand, 1M17 protein found in epidermal growth factor receptor (EGFR), which was associated with apoptosis and non-small cell lung cancer (NSCLC).[14] Another selected protein named 3KYS had been recognized as yes-associated protein which is considered as a premier moderator of the Hippo signaling pathway and at the same time acts as a promoter for tumorigenesis and metastasis in human (NCLC).[15] This study explored the novel CuE bioactive compound to perform molecular docking on all of these protein chains. The present study may draw the attention of the research community to think CuE as an anti-lung cancer agent.



(a) (b)

Figure 1: (a) 2D and (b) 3D structure of CuE

Materials and Methods

Establishing Dataset for Computational Study

Initially some literatures had been studied to find out some proteins responsible for causing lung cancer.[13-15] From the literature study we selected three major proteins respectively myosin 9b [5C5S (Chain: A, B, C, D)], epidermal growth factor receptor (EGFRK) [1M17 (Chain: A)] and yes-associated protein (YAP) [3KYS (Chain: A, C)] which were responsible for lung cancer. Against these three proteins molecular docking studies of CuE had been performed just to explore the optimal binding affinity by which we evaluated the anti-lung cancer effect of CuE.

Software and online tools used for this study

A variety of necessary softwares and online resources were used to determine the possible anti-lung cancer effect of CuE. For conducting our computational work, we have used both softwares like GaussView software (version 6.0), Gabedit software (version 250), Swiss-PDB viewer software (version 4.1.0), PyMOL software (version 1.7.4.5), PyRx software (version 0.8), Discover Studio software (version 2021), Marvin Sketch software (version 5.7) etc. and different websites respectively PubChem (https://pubchem.ncbi.nlm.nih.gov), RCSB:PDB (https://www.rcsb.org), Online smile convertor (https://cactus.nci.nih.gov/translate), ADMET prediction (http://biosig.unimelb.edu.au/pkcsm/prediction), PASS prediction (http://www.way2drug.com/passonline), Drug likeness (http://www.swissadme.ch) etc. The 3D structure of the drug (CuE) had been retrieved from PubChem whereas; the 2D structure of the drug was designed by using Marvin Sketch software. Then the drug both cleaned and symmetrized by using Gauss View software. For energy minimization of the ligand (CuE), we used Gabedit softwire. On the other hand, for energy minimization of the protein molecules, we used Swiss-PDB (Version: 4.1.0). Later on, for protein visualization, Discover Studio was used whereas, for docking visualization Pymol was used. Finally, for the docking analysis between legand and protein molecules, PyRx software was used. However, different websites like Pub Chem were used for downloading legand's 3D structure, RCSB:PDB was used for downloading protein's structure in PDB format and online smile convertor was used for creating smile number required for the ADMET prediction, PASS prediction and also for Drug likeness analysis.

Ligand Preparation

In this study, CuE was used as a ligand and for its preparation using PubChem website and from there the drug was saved in MDL MOL format[16]. The energy minimization saved file was run through the Gabedit software. The ligand molecules used for our docking study against the targeted proteins have been represented in Table 1.

Protein Preparation

For the preparation of protein, some targeted proteins (PDB ID: 5C5S, 1M17, 3KYS) were selected from literature study[13-15]. Then the 3d Crystal structure of the myosin 9b RhoGAP domain, epidermal growth factor receptor kinase domain and human YAP and TEAD complex proteins were retrieved from RCSB Protein Data Bank (PDB)[17] where their resolutions were respectively 2.20 Å, 2.60 Å, 2.80 Å. After that, all the protein structures were visualized through Discovery Studio (2021) for removing water molecules, hetero atoms and co-crystallized ligands and finally after added hydrogen atoms the protein molecule is saved as PDB format. Then for energy minimization, the prepared proteins were run through Swiss-PDB viewer (version: 4.1.0) by which the bad protein interactions had been minimized. Different proteins with their PDB ID, chain and crystal structure are presented in the Table 2.

Molecular Docking and Visualization

Generally, the purpose of molecular docking simulation in computer aided drug design (CADD), is to forecast the binding affinity between a ligand molecule and a particular protein molecule.[18,19] In this study, PyRx software (Version 0.8) software was used for the molecular docking analysis to understand the binding mechanism between both the drug and protein molecules, where the drug was indicated as a ligand molecule and the proteins as macromolecules.[20] The grid box sizes for each docking were recorded with X, Y and Z directions while

performing docking (Table 3). The lowest binding affinity for each docking was documented after docking. Following molecular docking, the drug protein complex was prepared by using Pymol software and saved as a pdb format to see the further non-bonding interactions. The non-bonding interactions were performed for analyzing, visualizing and finally explaining the docking results and different kinds of reactions between the ligand and amino acid residues of the targeted protein. The schematic representation of the entire molecular docking has shown in (Figure. 2).

Table 1: Molecular formula, weight and 2D structure for Ligand (CuE)

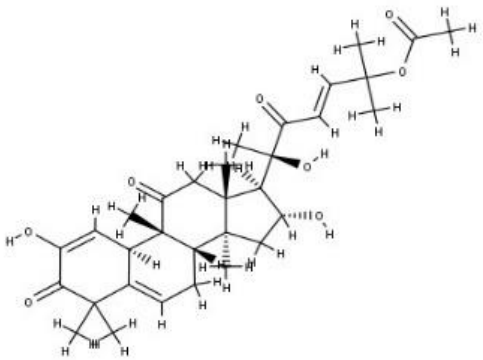
Ligand	Molecular Formula	Molecular Weight	2-D Structure
Cucurbitacin E (CuE)	$C_{32}H_{44}O_8$	556.687 Da	

Table 2: Crystal structure of different targeted Proteins liable for lung Cancer

Name of the Proteins	**PDB ID**	**Chain**	**Crystal Structure of Protein Targets**
Myosin 9b RhoGAP domain	5C5S	A, B, C. D	
Epidermal growth factor receptor kinase domain	1M17	A	

Human YAP and TEAD complex	3KYS	A, C	

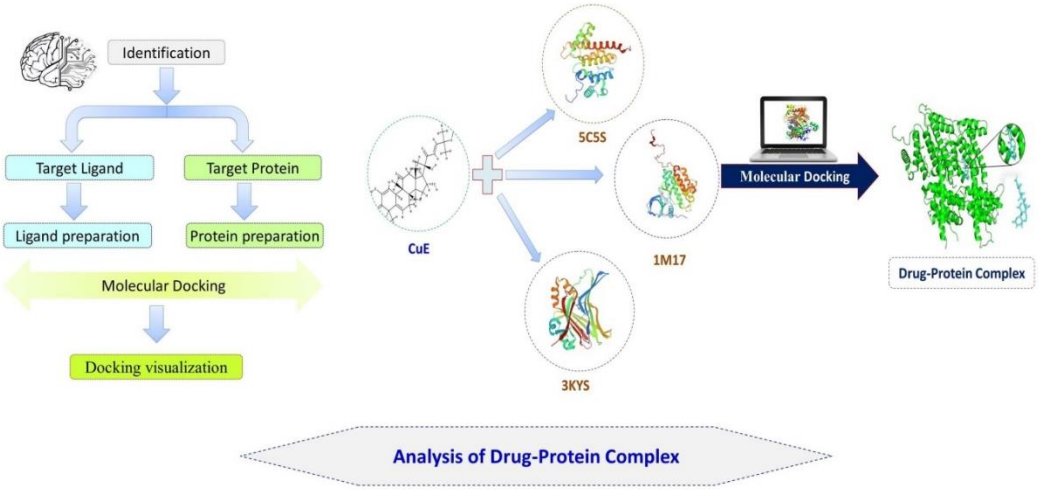


Figure 2: Schematic representation of molecular docking of CuE.

Table 3: Grid box size results for different docking performance

Docking	Grid Box Size		
	X	Y	Z
CuE and 5C5S (A)	18.7422	48.5517	33.3801
CuE and 5C5S (B)	18.7422	48.5517	33.3801
CuE and 5C5S (C)	18.7422	48.5517	33.3801
CuE and 5C5S (D)	18.7422	48.5517	33.3801
CuE and 1M17 (A)	23.4917	9.7534	59.3414
CuE and 3KYS (A)	-11.876	8.6315	-2.5826
CuE and 3KYS (C)	-11.876	8.6315	-2.5826

ADMET, PASS and Drug Likeness Prediction

Several computational methods were used in computer aided drug-design (CADD) for the prediction of pharmaceutical potential and pharmacokinetic analysis of a drug compound. For pharmacokinetic analysis of a drug compound first of all a smile number was created from an online website named online smile convertor (https://cactus.nci.nih.gov/translate/). Usually, a drug's pharmacological parameters consist of its absorption, distribution, metabolism, excretion, and toxicity studies, all of which were predicted by using the pkCSM website (http://biosig.unimelb.edu.au/pkcsm/prediction).[21] Pass predictions are generally based on SAR analysis which are able to predict interactions of a drug molecule with different targeted proteins.[22] Moreover, several pharmacological actions of CuE including antineoplastic effects (e.g lung cancer, cervical cancer, sarcoma, etc.), hepatic disorder, and sickle cell anemia etc. were predicted from its pass prediction using an online website called PASS online (http://www.way2drug.com/passonline/). Additionally, drug likeness predictions were explored from the available online website named Swiss ADME (http://www.swissadme.ch/).[23,24] These sites actually assist a researcher to manage time and to reduce the number of empirical experimentations and to promote the success of research outcomes[25].

Results and Discussion

Pre-molecular docking analysis

Pre-molecular docking analysis is a process of making ready both the ligand and protein molecules for molecular docking analysis. The first step of pre-molecular docking study is the energy minimization of both ligand and protein molecules so that it become quite easy to perform the docking analysis. In case of ligand (CuE) after energy minimization, the lowest energy was recorded at 124.746448 (Kcal/mol) by Gabedit software. The lowest energy minimized structure is presented below (Figure 3). The file was saved as a mol file after energy minimization. On the other hand, for different selected proteins (5C5S, 1M17, 3KYS), the minimum recorded energy by Swiss-Pdb were respectively -42505.965 Kj Mol-1, -13711.414 Kj Mol-1 and -28104.957 Kj Mol-1. Then all the energy minimized proteins were saved as PDB files after energy minimization. The molecular docking simulation was conducted by PyRx software considering CuE as the micro molecule (Ligand) and protein as a macromolecule. Docking had been performed against all individual protein target chains.

Molecular docking (MD) and binding interactions analysis

For reducing the spread of lung cancer, CuE was docked with multiple targeted proteins which are responsible for causing lung cancer as enlisted in Table 4. The binding site of the targeted protein molecules were recognized and docked with CuE with several binding energies (KJ/mol) in an acceptable range. This docking procedure was also done to determine the binding affinity of CuE at the target binding site. The best docking results were analyzed based on different binding energy.

The negative value of binding affinity indicates the strongest bonding within the ligand molecule and receptor protein. However, the highest binding energy we found for the docked protein [5C5S(Chain:A)] was -9.1KJ/mol whereas, the lowest binding energy we found for the lowest docked protein [3KYS (A)] was -6.7KJ/mol and these are all less than -10KJ/mol which predicts that this binding energy is effective and suitable for further investigation. Docking simulation through PyRx software was used to determine the binding characteristics of CuE with a number of selected proteins. The binding affinity of CuE drug with protein molecules and ligand protein interactions were summarized in Table 4. From all the binding energy results we have estimated the lowest value of binding energy with myosin 9b Rho GAP domain (A) protein. The docking interaction of CuE exhibits the highest binding affinity towards the target lung cancer protein myosin 9b Rho GAP domain (A) [PDB ID: 5C5S (Chain:A)] compared to other proteins which were presented in Table 2. Depending on the binding energy ranging from the lowest to highest, the myosin 9b Rho GAP domain (A) protein was selected for further investigation of drug protein complex interaction analysis and different types of non-bonding interactions analysis like hydrogen interaction, hydrophobic interaction, charge interaction, ionizability interaction etc. After selecting the best protein for ligand interaction, we had made the complex interaction of CuE with 5C5S (Chain:A) protein where the top three residual binding sites were predicted (Figure 4 and Figure 5). Different non-bonding interactions like hydrogen bond interaction, hydrophobic bond interaction, non-bonding charge interaction and non-bonding ionizability interaction etc. are involved in the binding of CuE with 5C5S (Chain:A) protein.

In this study, only the non-bonding hydrogen interactions were highlighted as the others were less important for the study (Figure 6). A total of three hydrogen bonds were formed (two conventional hydrogen bond and one carbon hydrogen bond) with several residual contact of CuE respectively Glu143 (3.27847Å), Ser315 (2.18245 Å), Arg243 (3.74987 Å). In the hydrogen bond surface, the residues including Glu143 helps in developing robust acceptor areas, while residues like Ser315 and Arg243 help in creating strong donor regions on the drug-protein interaction surface. These hydrogen-bonds not only stabilized CuE-5C5S (Chain:A) structure, but also helped to record the distance between its donors and acceptors for several target residues (Table 5). This observation indicated that CuE was capable of binding at the desired binding site of the protein 5C5S (Chain:A) by which it can significantly contribute in reducing the lung cancer proliferation.

ADMET, PASS and Drug likeness analysis

ADMET Analysis

The ADMET studies generally evaluate a drug's pharmacokinetic characteristics by calculating its absorption, distribution, metabolism, excretion, and toxicity. This study predicted the fate as well as the effects of a drug inside the body. For example, if a drug is administered orally, then how much its absorption will be in the gastrointestinal tract is being predicted by ADMET study. Because if there is poor absorption of a drug, then ultimately its distribution and metabolism will be affected which may cause neurotoxicity or nephrotoxicity. Finally, this study will assist oneself to understand how a drug deposits within a particular organ. Thus, ADMET study plays a significant role in drug discovery as well as in computer aided drug design[26]. As a result, the rates of failing a particular drug compound in clinical trials become reduced and ultimately its efficacy is improved[27]. However, a smile number was originally generated for ADMET analysis using an online smile converter website (CC(=O)OC(C)(C)\C=C\C(=O)C(C)(O)C1C(O)CC2(C)C3CC=C4C(C=C(O)C(=O)C4(C)C)C3(C)C(=O)CC12C). Then from the pkCSM website by using a smile number the ADMET prediction results were being documented. All the computed results for ADMET study of CuE drug were tabulated in Table 6.

From the analysis of pure water solubility, we found the value is -4.367log mol/L which indicates that the CuE drug is not very water soluble. The intestinal permeability was being investigated from the Caco-2 permeability test[28]. It had been estimated according to binning criteria that if the Caco-2 permeability range is $0.500 < P_{app} < 2.50$ ($x10^{-6}$ cm/s), then it will be moderately permeable[26]. In case of CuE we found that the permeability of Caco-2 is 0.54 log Papp in 10^{-6} cm/s, which showed that CuE is moderately permeable. On the other hand, the predicted value we found for the intestinal absorption of CuE is 83.084 which indicates that the high absorption of CuE takes place in the small intestine. In case of skin permeability estimation, it had been estimated from one research study that if the log kp of a compound becomes greater than -2.5, then it is acceptable. In case of CuE, the value was recorded as -3.427 log kp which indicates that its skin permeability is very low.

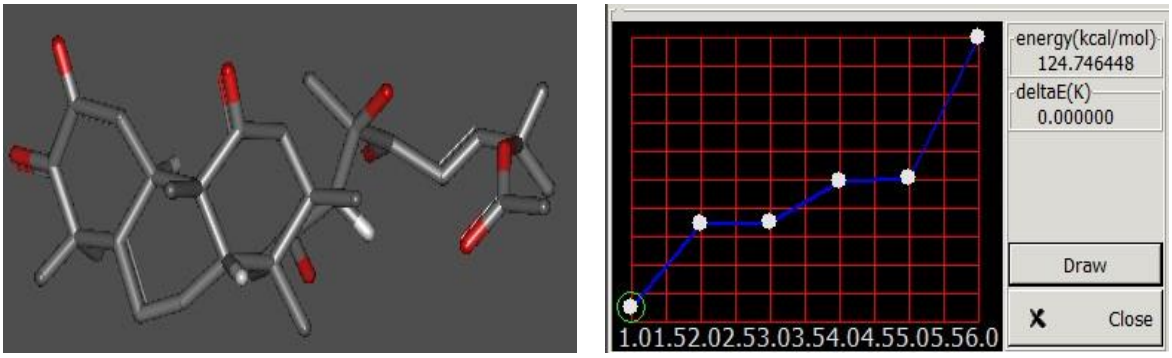


Figure 3: Energy minimization of CuE

Table 4: The list of ligand-protein interactions according to the binding energy of CuE

Ligand	Protein	Docked conformation of ligand Protein Interactions	Binding Energy (KJ/mol)
CuE	5C5S (A)		-9.1

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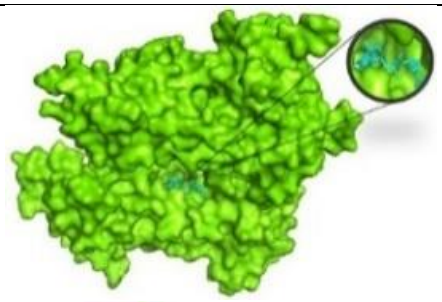
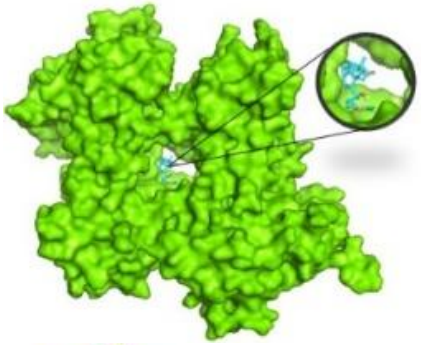
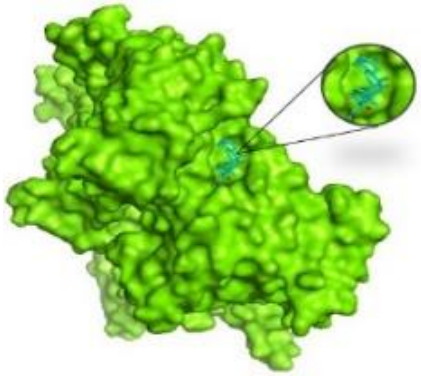
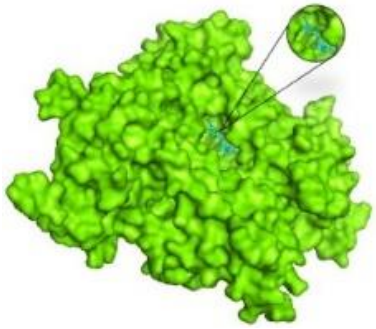
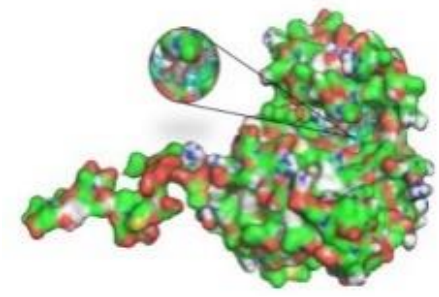
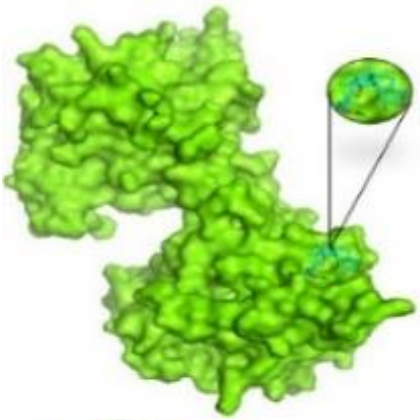
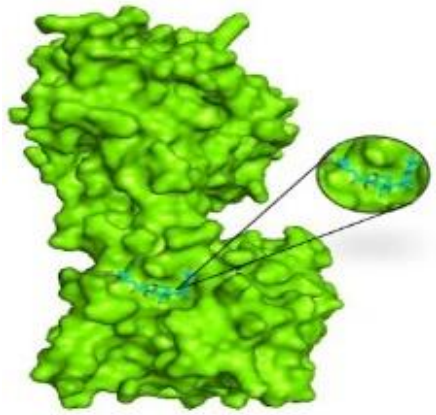
		
5C5S (B)		-7.3
5C5S (C)		-8.3
5C5S (D)		-8.9
1M17 (A)		-7.8

3KYS (A)		-6.7
3KYS (C)		-8.6

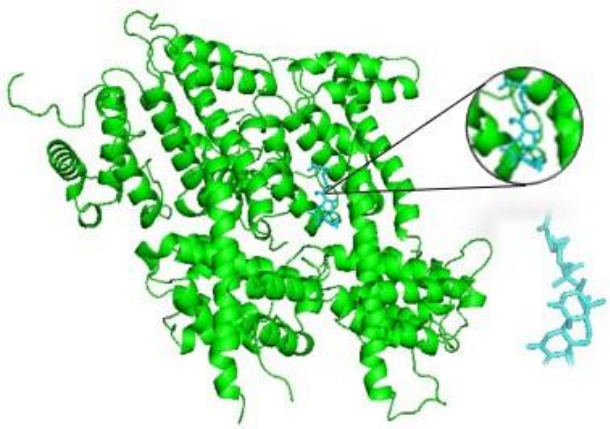


Figure 4: Ligand (CuE) and protein [5C5S (Chain:A)] complex interaction.

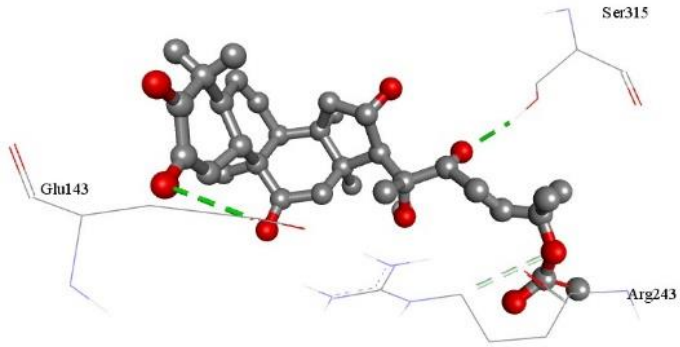


Figure 5: Non-Bonding interactions Analysis

A consistent volume of drug distribution in the blood plasma, known as VDss, is required for the total dosages of a drug substance. The distribution of a drug in tissue depends on this volume of drug distribution (VDss). The distribution of a drug becomes high in tissue rather than plasma when the VDss becomes high. On the other hand, when the log VDss<-0.15 and high when VDss>-0.45, then automatically the VDss becomes low[29]. Here, in our findings the VDss value for CuE was 0.053log L/kg which indicates that CuE has a very low volume of distribution. The fraction unbound reveals the portion, that will be released into blood plasma as predicted in Table 6. The blood brain barrier (BBB) is an essential aspect to evaluating if a drug can cross into the blood brain barrier. According to research findings, it has been estimated that if the logBB>-0.3, it indicates that a drug has a great chance to cross the BBB whereas, a drug with a logBB>-1 indicates the poor distribution of drug into the brain. In our findings, the logBB value for CuE was -1.242 which indicates that CuE has a very poor distribution into the blood brain. Another parameter is CNS Permeability where the logPS value for CuE was -2.877 and this indicates that the drug will be unable to enter into the CNS[30].

The presence or absence of different metabolic substrates and their presence were also being predicted in Table 6 which indicates that only the CYP3A4 substrate and CYP3A4 inhibitor attains in the metabolism of CuE and others are not. Moreover, the total clearance for CuE drug was 0.108 log ml/min/kg which will be helpful in dose rate setting. On the other hand, OCT2 substrate plays an important role in renal drug clearance. However, the prediction indicated that the OCT2 substrate is absent in the case of CuE.

The mutagenic effect of a compound was determined by the AMES test. If the test shows positive results, then it confirms that the compound is mutagenic. The AMES test for CuE predicted that it is non-mutagenic. On the other hand, the maximum tolerated dose for CuE was -0.795log mg/kg/day which indicated that even at the lower dose CuE is effective. HERG, the primary hypothesis for the development of long QT syndrome, serves as an illustration of the blockage of potassium channels. The prediction indicated that CuE is unlikely to be a HERG I or II inhibitor. The LD50 means the amount of drug substances at which

50% of the experimental animal's die was used in the measurement of acute toxicity for CuE. In case of CuE the predicted LD_{50} value was 3.861 mol/kg. Studies on chronic toxicity are intended to determine the lowest dose of a medicine that might have harmful effects and the highest dose at which there won't be any bad consequences. Here, the predicted value for chronic toxicity of CuE was 1.619 log (mg/kg bw/day). However, the predicted values for toxicity study also showed that the CuE is associated with hepatotoxicity whereas skin sensation is absent.

PASS Prediction Analysis

PASS Prediction refers to the prediction of activity spectra for substances. More than 300 pharmacological and biochemical effects of a particular drug can be predicted on the basis of the structural formula of a drug substance from the PASS Prediction. However, this prediction is done on the basis of the analysis of SAR (Structural Activity Relationship). This PASS Prediction can be efficiently used to find new target mechanisms for a particular drug substance. For, knowing the antineoplastic activity of CuE PASS Prediction analysis had been performed which were being demonstrated in Table 7. The terms Pa and Pi, respectively, indicate the chance of activation and chance of inactivation. From the predicted results we can see that the Pa value is high for the antineoplastic effect of CuE against lung Cancer. This indicates that CuE will be highly effective for lung cancer treatment.

Drug Likeness Prediction Analysis

The idea of drug-likeness prediction analysis is crucial for the virtual screening of a pharmacological molecule. It helps in qualitatively identifying a compound's potential as an oral medication and its corresponding bioavailability. A bioactive component's suitability for ADMET testing was determined by drug likeness prediction analysis.

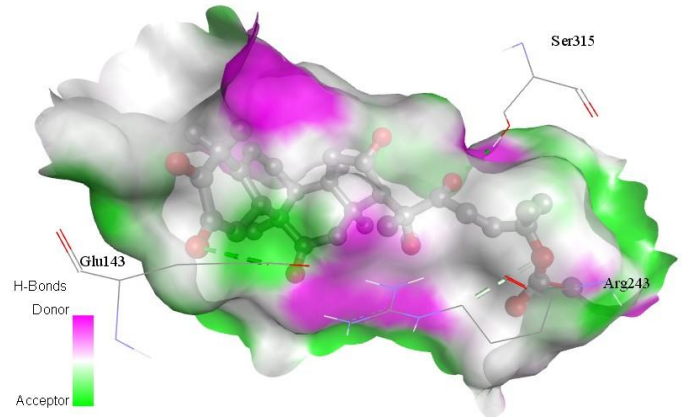


Figure 6: Hydrogen bond surface of 5C5S (Chain: A) with CuE.

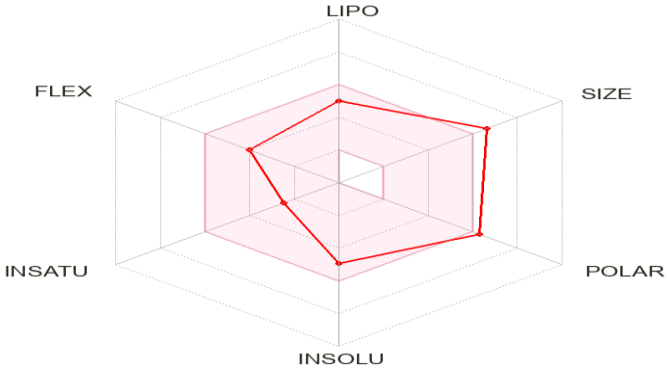


Figure 7: The bioavailability radar plot image for CuE

Table 5: Binding affinity and non-bonding interactions of CuE with 5C5S (A)

Ligand Name	Binding Affinity	Residues in Contact	Interaction types	Distances (Å)
CuE	-9.1	Glu143	Conventional Hydrogen Bond	3.27847
		Ser315	Conventional Hydrogen Bond	2.18245
		Arg243	Carbon Hydrogen Bond	3.74987

Table 6: Pharmacokinetic Properties of CuE

Pharmacokinetic Properties	CuE Drug	
	Parameters	**Predicted Value**
Absorption	Water Absorption (log mol/L)	-4.367
	Caco-2 (log Papp in 10^{-6} cm/s)	0.54
	Intestinal Absorption (% Absorbed)	83.084
	Skin Permeability (log Kp)	-3.427
	P-glycoprotein substrate	Yes
	P-glycoprotein I inhibitor	Yes
	P-glycoprotein II inhibitor	Yes
Distribution	VDss (human, log L/kg)	0.053
	Fraction unbound (human, FU)	0.059
	BBB permeability (log BB)	-1.242
	CNS permeability (log PS)	-2.877
	CYP2D6 substrate	No

Metabolism	CYP3A4 substrate	Yes
	CYP1A2 inhibitior	No
	CYP2C19 inhibitior	No
	CYP2C9 inhibitior	No
	CYP2D6 inhibitior	No
	CYP3A4 inhibitior	Yes
Excretion	Total Clearance (log ml/min/kg)	0.108
	Renal OCT2 substrate	No
	AMES Toixicity	No
	Max. Tolerated Dose in (human, log mg/kg/day)	-0.795
Toxicity	HERG I Inhibitor	No
	HERG II Inhibitor	No
	Oral Rat Acute Toxicity (LD50, mol/kg)	3.861
	Oral Rat Chronic Toxicity (LOAEL, log mg/kg bw/day)	1.619
	Hepatotoxicity	Yes
	Skin sensation	No

Table 7: Pass prediction of CuE

SL No	Activity of CuE	Pa	Pi
1.	Antineoplastic (Lung Cancer)	0.923	0.003
2.	Antineoplastic (cervical cancer)	0.857	0.002
3.	Antineoplastic (sarcoma)	0.829	0.003
4.	Antineoplastic (breast cancer)	0.446	0.025
5.	Prostate cancer treatment	0.321	0.036
6.	Antineoplastic (lymphoma)	0.166	0.084
7.	Antineoplastic antibiotic	0.103	0.046

However, the drug likeness of CuE with different parameters was listed in Table 8. The drug likeness analysis was basically done on the basis of Lipinski five rules which are again associated with both of the drug's solubility and permeability. The more a drug compound deviates from the Lipinski rule, the more its absorption and permeation will be poor[31]. According to the data analysis of drug likeness for CuE, the drug matched all of the Lipinski rule's parameters with the exception of MW. The drug-likeness analysis prediction shown in Table 8 may also be obtained from the bioavailability radar plot picture for CuE (Figure 7). Basically, two important parameters like flexibility (as measured by the number of rotatable bonds) and polarity (determined by topological polar surface area) were emphasized in the prediction of the bioavailability of orally administered drugs. It had been estimated that if a drug molecule has more than 10 rotatable bonds, it is thought to have low oral bioavailability[32].

On the other hand, a higher oral bioavailability is indicated by a lower topological polar surface area[33]. From the above figure we can see that the flexibility value of CuE is very close to its standard value. The polar value, however, precisely matched the conventional value. Although CuE's molecular size is somewhat larger than its standard value, its lipophilicity and insolubility values are still quite near to those values. This suggests that CuE will have an excellent oral bioavailability.

Conclusion

In this work, CuE had been studied to explore its anti-lung cancer effect through computational study. From the molecular docking study, it had been estimated that CuE showed the best anti-lung cancer effect when it binds with the myosin 9b [5C5S (Chain: A)] protein. The pharmacokinetic study like the ADMET study, PASS prediction and drug likeness analysis also showed that CuE is non-carcinogenic and safe for oral administration. Considering all the present investigations, we can conclude that CuE is highly effective for lung cancer treatment and at the same time it's our hope that this investigation will draw the attention of the scientific community to think CuE as an effective anti-lung cancer agent.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

Table 8: Different parameters of CuE

SL No.		Parameters	Values	Lipinski rules
		MW (g/mol)	**556.69 g/mol**	**<500**
1.	Physicochemical Properties	ROTB (n)	6	<10
		HBA (n)	8	<10
		HBD (n)	3	<5
		Log *S* (ESOL)	-4.94 (MS)	-
2.	Lipophilicity	TPSA ($Å^{2}$)	138.20	<140

		CLog $P_{o/w}$	3.46	<5
3.	Drug-likeness	Score for Bioavailability	0.55	-
		The Lipinski filter	Yes (1)	-
4.	Pharmacokinetics	GIA	Low	-
		BBB permeant	No	-
		P-gp substrate	Yes	-
		CYP3A4 inhibitor	Yes	-
		LogKp (Skin Permeation)	-7.39 cm/s	<5

MW- Molecular weight, ROTB-Rotatable bonds, HBA- H-bond acceptors, HBD- H-bond donors, MS-Moderately soluble, TPSA- Topological polar surface area, CLog $P_{o/w}$ - Partition coefficient logarithm of compound between n-octanol and water , GIA- Gastrointestinal absorption, BBB-Blood brain barrier, P-gp-P-glycoprotein.

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