In silico screening: identification of a novel CDK-1 inhibitor from *Chrysophyllum cainito* leaves

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Abstract: - Increasing evidence suggests that OSCC overexpresses CDK-1 to promote its advancement, which intervene in the paclitaxel effects. As a result of drug resistance and immune evasion, treating the advanced stage of OSCC has proven challenging. Therefore, a CDK-1 inhibitor with high inhibitory activity, excellent pharmacokinetic activities, and minimal adverse effects is urgently needed. Our study has uncovered novel CDK-1 inhibitors, which would be beneficial and expected to reinstate the paclitaxel-resistant while treating combined with our novel inhibitors in the future.

Key Words: — ***CDK-1, Drug resistance, OSCC, Immune evasion, Novel CDK-1 inhibitors.***

I. INTRODUCTION

Oral squamous cell carcinoma (OSCC) is the most well-known cancer that affects men as well as women, ranked as the sixth cancer by Global cancer statistics (Almangush *et al.,* 2021). The survival and affected rate of OSCC are around 50%, even if a variety of treatments are available, including surgery, chemotherapy alone or in combination with radiation therapy. It all ensued because of the chance of aforesaid treatment resistance (Smyth *et.al.,* 2017; Ben-Hamo *et.al.,* 2019).

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However, the prevalence is increasing year after year in a country like India (Babu *et al.,* 2021). Due to the increase of unhealthy habits such as tobacco, intake of alcohol and pan masala facilitates an early stage of OSCC. Moreover, inadequate diet, poor oral hygiene, and viral infections, i.e., HPV 16, withal reinforce its progression swiftly (Anwar *et al.,* 2020). Mounting research has suggested that the following strategies, such as tobacco restriction, immunization, and regular cancer screening tests, may prevent the risk of cancer cases and deaths. However, 15-year retrospective research in India found that lifestyle changes and habits in entire nations are responsible for this predicament. It has alarmed the nation and is still steadily augmenting because people are unaware without knowing its side effects (Babu *et al.,* 2021). Studies have demonstrated that treating OSCC-III and IV is difficult and awful because of recurrence, lymph node metastases, medicament resistance, and immune evasion. Wherefore, five years of OSCC survival rate is yet to remain low.

The subsequent findings unfurl the reason behind this incidence. In medicament resistance, e.g., paclitaxel (interfere with the functions of tubulins in cancer) is an FDA approved medicament identified from the bark of medicinal plants (named Taxus brevifolia) that has been used extensively by patients across the world. Although, many reports have proved that prolonged or excessive intake can incite resistance by producing excessive CDK-1. Thereby, it intervenes in the functions of paclitaxel, according to the study (Prabhu *et al.,* 2021; Bae *et al.,* 2015). Withal, Chen and a co-worker revealed the significance of this incident by exploring CDK-1 in OSCC patients (Chen *et al.,* 2015). Thereof, it was observed disproportionately in OSCC recurrent cases, which are strongly associated with recurrence in incised patients and lymph node metastasis, indicating it could be responsible for an advanced stage of cancer progression (Chen *et al.,* 2015). As a result, in this investigation, we have intended to identify novel CDK-1 inhibitors from Chrysophyllum cainito leaves because it is a little-studied medicinal plant that seems to encompass significant potential anti-cancer medicament through our previous study (Prabhu *et al.,* 2021).

II. MATERIALS AND METHODS

2.1 Plant collection and authentication

The fresh plants of *C. cainito* were obtained in Coimbatore District, Tamil Nadu, India, at latitude 11.01º N, longitude: 76.95º E. Subsequently, the collected specimen was authenticated through a botanical survey of India, Tamilnadu agricultural university, Coimbatore (Prabhu *et al.,* 2021).

2.2 Soxhlet extraction and GCMS analysis

C. cainito was cleaned with milli-Q water, then milled and sieved for soxhlet methanol extraction. In order to do that, we used a 1:10 methanol ratio for extraction on the specimen for 12 hours at 65°C to obtain the residue. Ensuingly, the collected and dried sample was further analyzed in GCMS equipment. For the detailed procedure and GCMS identified phytocompounds lists refer to our recently published journal (Prabhu *et al.,* 2021). This study is a protraction of research into the CDK-1 molecule (PDB ID: 4YC3 is available on the PDB website for cost) (Prabhu *et al.,* 2021).

2.3 Molecular docking

A molecular docking investigation was carried out by utilizing the maestro module with the user-friendly Schrodinger docking suite, whereby we have predicted an interaction between *C. cainito* compounds (refer to our published journal, Prabhu *et al.,* 2021) and the binding sites of a CDK-1 protein (4YC3). The glide score (Glide, 2012) has used to predict the bonding between the receptor CDK-1 (PDB ID: 4YC3) and phytonutrients of *C. cainito*. In general, in silico screening assessments can be done in two different ways: XP (Extra Precision) or SP (Standard Precision), but we had used XP methods owing to its extra precision features.

2.4 Preparation of protein

The x-ray crystal structure of a CDK-1 protein is available on the Protein Data Bank (PDB) website (https://www.rcsb.org/) with the PDB ID: 4YC3. In the Schrodinger Suite, the protein preparation wizard tool was used to prepare the CDK-1 protein perfectly (Schrodinger Suite, 2018). In order to do so, the input protein molecule (CDK-1) prepared for docking investigations utilizing wizard tool, which included removing redundant chains, water and altering the orientation of hetero groups at the raw PDB structure. To create fully accessible and dockable ligand libraries and we have used the LigPrep tool: which encompasses options for default parameters such as selective ionisation states, tautomers, tautomeric combinations, ring conformations, stereo chemistries, low energy framework and the addition of hydrogen bond, correct chiralities, and versatile filters (Lig Prep, 2012).

2.5 Analysis of ADME/T property

The Schrodinger software QikProp tool has used to evaluate the ADME/T characteristics of two compounds, as indicated in table 1. Several medicament likeliness molecules fail in human trials by far owing to their poor ADME characteristics. In order to evade such circumstances, we used the QikProp tool, which predicts important physicochemical characteristics such as human oral absorption and other pharmacokinetic aspects of molecules.

III. RESULTS AND DISCUSSION

This present study extends our previous work with the same CDK-1 molecule, but earlier, we had investigated the 5HQ0 structure with the *C. cainito* ligands, refer to Prabhu *et al.,* 2021 for those details.

Figure.1. shows the GCMS interpreted details of cyclopenteno [4.3-b] tetrahydrofuran, 3-[(4-methyl-5-oxo-3-phenylthio) tetrahydrofuran-2-yloxymethylene]- (CTT) and cyclopropylmethanol.

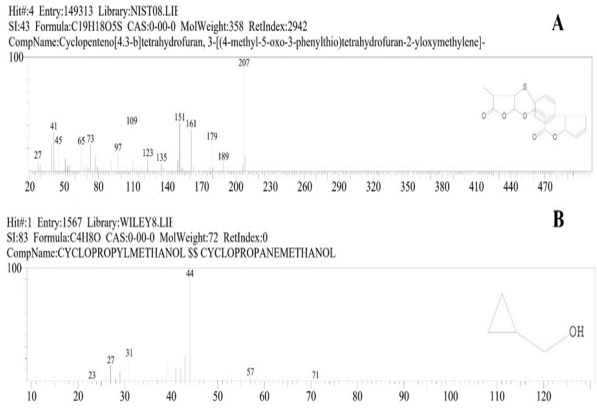

Fig.1. Displays CTT and CPM part of interpreted GCMS chromatogram details such as formula, molecular weight and name, etc.

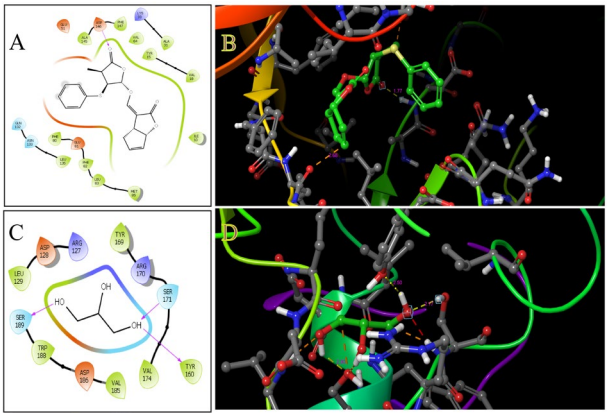

Fig.2. displays the CDK-1 and ligands interactions. A & C image demonstrate the 2-D view of CTT and CPM interaction on CDK-1 (arrows indicates the site of ligand binding). B & D shows Rippon representation of the same ligand and CDK-1 in a detailed view of 3D.

Figure 2 illustrates the interaction between CDK-1 molecule (Over 4YC3) and *C. cainito* ligands. Notably, two ligand molecules have interacted excellently over the CDK-1 domain from *C. cainito* ligands also shown in table 1. In detail, CTT molecule has interacted strongly with CDK-1 than cyclopropylmethanol (CPM) albeit it holds good interaction with the same molecule. Because of its multiple amino acid binding features. That two-molecule interaction information such as glide score/docked score and hydrogen bond are given in Table 1. Correspondingly, studies have suggested that an upsurge in the values of negativity, i.e., GScore is better because it creates a stronger binding between protein and ligand. The site of amino acid interaction and bond length on CDK-1 protein is provided in Table.2. Correspondingly, studies have suggested that an upsurge in the values of negativity, i.e., GScore is better because it creates a stronger binding between protein and ligand. The site of amino acid interaction and bond length on CDK-1 protein is provided in Table.2.

Table.1. Energy data of two interacted ligands on CDK-1 are listed

S. No	Interacted ligands	GScore	DScore	HBond
1.	CTT (PubChem CID 5375838)	-5.69	-5.69	-0.7
2.	CPM (PubChem CID 75644)	-5.02	-5.02	-4.02

Table.2. The residue data for medicament, which interacted with CDK-1 molecule, are listed below.

S. No	Ligands	Mw	Human oral absorption	Percentage of human oral absorption
1	CTT	358.4	3	91.1 - 100
2	CPM	72.10	3	92.094

Table.3. ADMET properties of identified CDK-1 inhibitors are given.

S. No	Interacted ligands	Interacting residues	Bond length
1	CTT	ASP 146	2.68, 1.77
2	CPM	SER 189, SER 171 & TYR 160	2, 2.17, 2.50

Next, we have investigated the ADME/T properties of the two ligands which revealed an outstanding pharmacokinetic characteristic (Table 3).

IV. CONCLUSION

This present study has uncovered a dual CDK-1 inhibitor CTT and CPM from the *C. cainito* medicinal plants leaves. The subsequent scrutiny of ADME/T was excellent, which reinforces the medicament likeliness. Thus, we suggest that those two molecules could be used as an effective medicament in the future for stage III and IV paclitaxel resistant cases and tumor recurrent cancer patients. However, the mode of action of those two medicaments, side effects and pharmacokinetic characteristics should be studied further in the animal model beforehand of pre-clinical trials. The consumption of chemotherapeutic *C. cainito* leaves as an ingredient in food will destroy the cancer cells and prevent cancer formations.

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Conflict Of Interest:
The authors state that they have no conflicts of interest.

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