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IN SILICO INTERACTION ANALYSIS OF SELECTED 5 TROPANE ALKALOIDS AGAINST ORAL CANCER DRUG TARGETS

Type of article : Research article

Running Title : In silico interaction analysis of selected (5) tropane alkaloids against oral cancer drug targets

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ABSTRACT:

The aim is to study the interaction of Indole alkaloids against 2 oral carcinoma drug targets by in silico docking using iGemdock tool.In this generation, technology has become so advanced that we are able to now achieve what was believed 20 years ago to be impossible. One such advancement is in silico interactions. It is a virtual screening which enables us to bind two compounds and check the affinity of the binding. This helps us to first screen the activity of the two compounds before money, time and energy is spent in manually performing the activity and then arriving at a failure. We will be able to concentrate on the compounds which show us positive results in the in silico interactions, thus helping us in conserving time, expenditure and energy.Ajmalicine shows good interaction with both drug targets and possesses the best fitness energy of all 5 tropane alkaloids.

KEYWORDS*: docking, tropane, oral cancer, alkaloids, ajmalicine.*

I. INTRODUCTION:

Amongst the modern epidemics, oral cancer is the second most common cause of death[1]. In developing countries, oral cancer is one of the top ten most common causes of death [2]. India has one of the highest prevalence of oral cancer in the world. According to WHO, 40% of the diagnosed oral cancers across the world occur in India, Pakistan, Bangladesh and Srilanka [3]. WHO also estimated that 90% of Indian males who were diagnosed with oral cancer were attributed to tobacco counseling [4].

There has been a significant increase in the use of herbal substances in recent times. One such herbal substance is Tropane alkaloids. They are obtained from sources such as Atropa belladonna, Hyoscyamus niger, Datura stramonium, etc [5]. These poisonous Solanaceae family plants have been found to have abundant folk medicinal use in ethnic groups [6–11]. Tropane, alkaloids occur as carboxylic acid containing esters and tropic acid [12].

The aim is to study the interaction of Indole alkaloids against 2 oral carcinoma drug targets by in silico docking using iGemdock tool.

II. MATERIALS AND METHOD :

TARGET IDENTIFICATION AND RETRIEVAL:

The Oral carcinoma drug targets were identified by literature search and its 3D structure was downloaded from RCSB PDB (Protein Data Bank), which is acrystallographic database for the three-dimensional structural data of large biological molecules, such asproteins andnucleic acids[13–17]. The data was typically obtained byX-ray crystallography,NMR spectroscopy, or, increasingly,cryo-electron microscopy. The PDB ID of the targets are as follows,

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- **PDB ID: 3DCY (Crystal Structure a TP53-induced glycolysis and apoptosis regulator protein)**

ACTIVE SITE RESIDUES:
Residues showing Bonded interaction: HIS 198, ARG 61, GLY 199, ARG 10
Residues showing Non Bonded interaction: GLY 89, ASN 17, HIS 11

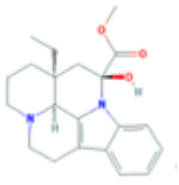
Figure 1- PDB ID: 3DCY (Crystal Structure a TP53-induced glycolysis and apoptosis regulator protein)

- **PDB ID: 5GGV (CTLA-4 in complex with tremelimumab Fab)**

Figure 2 - PDB ID: 5GGV (CTLA-4 in complex with tremelimumab Fab)

III. LIGAND RETRIEVAL:

The indole alkaloids with anticancer properties were identified by literature search and their 3D structure was retrieved from Pubchem, a database of chemical molecules [18,19] . The list of Indole alkaloids and its structures are as follows(figure1 and 2),

PUBCHEM ID	COMPOUND NAME	STRUCTURE
15376	Vincamine	

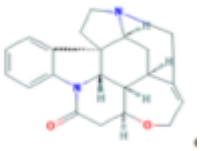
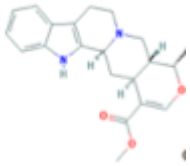
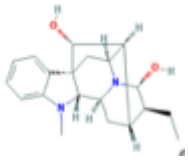
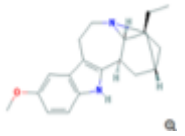
441071	strychnine	
441975	ajmalicine	
6100671	ajmaline	
197060	Ibogaine	

Table 1 - The following table provides the compound names along with the structures and the PUBCHEM ID.

IV. DOCKING:

The docking was carried out using iGEMDOCKv2.1, a Graphical-Automatic Drug Design System for Docking, Screening and Post-Analysis. Fitness is the total energy of a predicted pose in the binding site. The empirical scoring function of iGEMDOCK is estimates as:

Fitness = vdW + Hbond + Elec

Here, the vdW term is van der Waal energy. Hbond and Elect terms are hydrogen bonding energy and electro statistic energy, respectively.
To start docking protein file and ligand file was prepared. The active site was defined using “by bounded ligand” in case of cocrystal structure and “by current file” in case of non-cocrystal structure. The igemdock accepts ligand in mol2 format, so the ligands were converted from sdf to mol2 format.

V. RESULTS AND DISCUSSION:

PDB ID	COMPOUND	ENERGY	VDW	HBOND	ELEC
3DCY	Vincamine	-69.0957	-59.617	-9.47872	0

	strychnine	-66.7736	-61.9882	-4.78542	0
	ajmalicine	-74.8065	-67.898	-6.90847	0
	ajmaline	-67.211	-55.5155	-11.6955	0
	Ibogaine	-69.2264	-65.7264	-3.5	0
5GGV	Vincamine	-87.0853	-70.3446	-16.7407	0
	strychnine	-80.785	-78.285	-2.5	0
	ajmalicine	-88.5663	-81.5663	-7	0
	ajmaline	-75.0363	-67.7515	-7.28482	0
	Ibogaine	-89.9196	-80.423	-9.49655	0

Table 2 - The following table provides information on the interaction of the Tropane alkaloids.

- **Docked Structure of TP53-induced glycolysis and apoptosis regulator protein with Indole alkaloids:**

1. Protein docked with Vincamine:
2. Protein docked with strychnine
3. Protein docked with ajmalicine
4. Protein docked with Ajmaline:
5. Protein docked with Ibogaine:

- **Docked Structure of CTLA-4 in complex with tremelimumab Fab with Indole alkaloids:**

1. Protein docked with Vincamine:
2. Protein docked with strychnine:
3. Protein docked with ajmalicine:
4. Protein docked with Ajmaline:
5. Protein docked with Ibogaine:

VI. CONCLUSION:

From the above analysis, it shows that ajmalicine shows good interaction with both the receptors and also shows best fitness energy. Furthermore, in vitro studies can be done to analyse and understand the actions of the compounds before the studies can be shifted to in vivo studies. The establishment of the side effects of the drug has to be done before allowing the in vivo studies to be performed, thus giving the analysts an idea as to what adverse reactions can be expected during the time of the study.

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