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MOLECULAR DOCKING AND PASS PREDICTION FOR ANALGESIC ACTIVITY OF SOME ISOLATED COMPOUNDS FROM *ACALYPHA INDICA* L AND ADME/T PROPERTY ANALYSIS OF THE COMPOUNDS.

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ABSTRACT

Acalypha indica L. (Family - Euphorbiaceae) is commonly known as Indian Acalypha, is found in fallow lands throughout Bangladesh. This plant is used in the treatment of analgesicemetic, expectorant, laxative, diuretic, bronchitis, pneumonia, asthma and pulmonary tuberculosis. The aim of present study to investigate *in silico* molecular docking study used for four phytoconstituents 2-methylanthraquinone, β-Sitosterol, n-octacosanol and stigmasterol which are isolated from *Acalypha indica L.* to identify whether these compounds interact with the responsible protein (Cyclooxygenase 1 enzyme). *In silico* PASS prediction of the compounds measured with server. Also ADME/T properties of the phytoconstituents were analyzed using Qikprop 3.2 module. A wide range of docking score found during molecular docking by Schrodinger. 2-methylanthraquinone, β-Sitosterol, n-octacosanol and stigmasterol showed the docking score -5.918, -2.575, 0.049 and -2.397 respectively. Among all the compounds 2-methylanthraquinone showed best docking score. So, 2-methylanthraquinone is the best compounds for selective Cyclooxygenase (COX 1) enzyme inhibition, as it possessed higher value in Molecular docking. In the PASS prediction for their analgesic activity of the isolated

phytoconstituents, we found wide range of activity and all the compounds showed greater Pa than Pi value. From the ADME profiles of all the tested compounds, it cleared that they might safe for human. Further *in vivo* investigation need to identify whether isolated compounds from *A. indica* have Cyclooxygenase (COX 1) enzyme inhibitory activity or not.

KEYWORDS: *Acalypha indica L.*, Cyclooxygenase enzyme, Molecular docking, ADME/T properties, Pass prediction.

INTRODUCTION

Traditional knowledge concerning medicinal plants and their use by endemic cultures is not only helpful for maintenance of cultural traditions and biological diversity but also for community health aid and drug development within the gift and future.[1] Traditional medicinal observation has been famillier for hundred years in many parts of the world. Herbal medicines are interested due to their low cost and eco-friendly attributes.[2]

Plants and their preparations have been used as medicine since ancient time. The Ayurveda and various ancient Indian literatures have evidence the use of plants for various disorders. The plant *Acalypha indica* Linn. is commonly known as Indian *Acalypha*[3] and Muktajhuri, Swetbasanta, Biralhatchi in Bengali.[4] Plant has emetic, expectorant, laxative and diuretic; useful in bronchitis, pneumonia, asthma and pulmonary tuberculosis. Leaves are laxative and antiparasiticide.[5] Leaf extract possesses antifungal activities.[6] It belongs to the family Euphorbiaceae. the whole plant of *Acalypha indica Linn* possesses very good anti-inflammatory and anti-nociceptive activities, ascribable to high level of phytoconstituents for instance phenolic and flavonoid contents in the extract and also proved a natural safe remedy for the treatment of analgesia and inflammation.[7]

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue injury or described in terms of such damage and involves a psychological component that can modify its perception and integration in higher centers particularly in the brain.[8, 9] Analgesic compounds selectively relieves pain without significant alteration of consciousness by functioning on the CNS or PNS pain mechanism.[10]

Computational simulations of drug-target interactions using *in silico* molecular docking and molecular dynamics approaches are commonly used for the rational design and screening of drugs.[11,12] Molecular docking has become a major computational method for the prediction

of ligand–receptor interactions.[13] Over the last few years the number of new molecular targets has increased due to the completion of the human genome project, as well as the protein and protein–ligand complex structures isolated by high-throughput protein purification[14] and solved by crystallography and nuclear magnetic resonance spectroscopy techniques.[15,16] At the same time, the improvement of computational techniques for studying interactions of ligands with the biological targets at the atomic scale have increased and developed.

The aim of present study to investigate *in silico* molecular docking study used for four phytoconstituents 2-methylanthraquinone, β-Sitosterol, n-octacosanol and stigmasterol which are isolated from *Acalypha indica L.* to identify whether these compounds interact with the responsible protein (Cyclooxygenase 1 enzyme). *In silico* PASS prediction of the compounds measured with server. Also ADME/T properties of the phytoconstituents were analyzed using Qikprop 3.2 module.

MATERIALS AND METHODS

In silico Molecular Docking Analysis

Protein Preparation

Three dimensional crystal structure of COX 1 (PDB id:2OYE) was downloaded in pdb format from the protein data bank.[17] After that, structure was prepared and refined using the Protein Preparation Wizard of Schrödinger-Maestro v10.1. Charges and bond orders were assigned, hydrogens were added to the heavy atoms, selenomethionines were converted to methionines and all waters were deleted. Using force field OPLS_2005, minimization was carried out setting maximum heavy atom RMSD (root-mean-square-deviation) to 0.30 Å.

Ligand Preparation

Compounds were retrieved from Pubchem databases, i.e. 2-methylanthraquinone (CID 6773), β-Sitosterol (CID 222284), 1-Octacosanol (CID 68406) and stigmasterol (CID 5280794). The 3D structures for these were built by using Ligprep2.5 in Schrödinger Suite 2015 with an OPLS_2005 force field. Their ionization states were generated at pH7.0±2.0 using Epik2.2 in Schrödinger Suite. Up to 32 possible stereoisomers per ligand were retained.

Receptor grid generation

Receptor grids were calculated for prepared proteins such that various ligand poses bind within the predicted active site during docking. In Glide, grids were generated keeping the

default parameters of van der Waals scaling factor 1.00 and charge cutoff 0.25 subjected to OPLS 2005 force field. A cubic box of specific dimensions centred around the centroid of the active site residues (Reference ligand active site) was generated for receptor. The bounding box was set to 14 Å × 14 Å × 14 Å for docking experiments.

Glide Standard Precision (SP) ligand docking

SP flexible ligand docking was carried out in Glide of Schrödinger-Maestro v 10.1.[18,19] within which penalties were applied to non-cis/trans amide bonds. Van der Waals scaling factor and partial charge cutoff was selected to be 0.80 and 0.15, respectively for ligand atoms. Final scoring was performed on energy-minimized poses and displayed as Glide score. The best docked pose with lowest Glide score value was recorded for each ligand.

***In silico* Prediction of activity spectra for substances (PASS)**

Prediction of phytoconstituents namely 2-methylanthraquinone, β-sitosterol, 1-octacosanol, stigmasterol[20] for analgesic activity was done with the help of computer program, PASS. Software estimates predicted activity spectrum of a compound as probable activity (P_a) and probable inactivity (P_i). The prediction of activity is based on structure-activity relationship analysis of the training set containing more than 205,000 compounds exhibiting more than 3750 kinds of biological activities. The values of P_a and P_i vary between 0.000 and 1.000. Only activities with $P_a > P_i$ are considered as possible for a particular compound. If $P_a > 0.7$, the probability of experimental pharmacological action is high and if $0.5 < P_a < 0.7$, probability of experimental pharmacological action is less. If the value of $P_a < 0.5$, the chance of finding the activity experimentally is less, but it may indicate a chance of finding a new compound.[21-24]

ADME/T property analysis

Ligand based ADME/Toxicity prediction

The QikProp module of Schrodinger (Maestro, version 10.1) is a quick, accurate, easy-to-use absorption, distribution, metabolism and excretion (ADME) prediction program design to produce certain descriptors related to ADME. It predicts both physicochemical significant descriptors and pharmacokinetically relevant properties. ADME properties determine drug-like activity of ligand molecules based on Lipinski's rule of five. ADME/T properties of the compound (DIM) was analyzed using Qikprop 3.2 module.[25]

RESULTS AND DISCUSSIONS

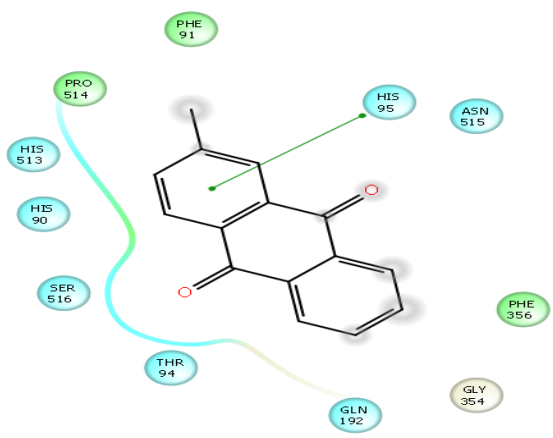
In silico analysis

Molecular docking analysis

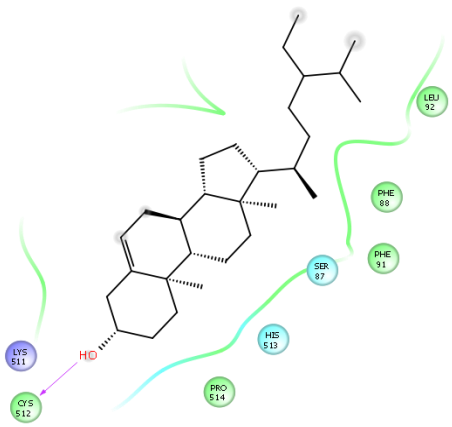
Advances in computational techniques have enabled virtual screening to have a positive impact on the discovery process. Virtual screening utilizes docking and scoring of each compound from a dataset and the technique used is based on predicting the binding modes and binding affinities of each compound in the dataset by means of docking to an X-ray crystallographic structure.[26] Grid based docking study was used to analyze the binding modes of molecules with the amino acids present in the active pocket of the protein.[27] To identify the potential analgesic lead molecule, we have subjected the docking analysis of the active compounds of *Acalypha indica* to the active site cyclooxygenase enzymes viz. In order to study the interaction of the compounds 2-methylanthraquinone, β-sitosterol, 1-octacosanol, stigmasterol with 2OYE, we performed Glide docking analysis by Schrodinger suite v10.1, where among of these compounds 2-methylanthraquinone shows highest docking score shown in Table 1. The negative and low value of free energy of binding demonstrates a strong favorable bond between 2OYE and 2-methylanthraquinone in most favourable conformations. The results of docking analysis were described in Table 1 and the docking figure showed in Figure 1.

Table 1: Docking results of 2-methylanthraquinone, β-Sitosterol, 1-Octacosanol and Stigmasterol with 2OYE (PDB: 2OYE).

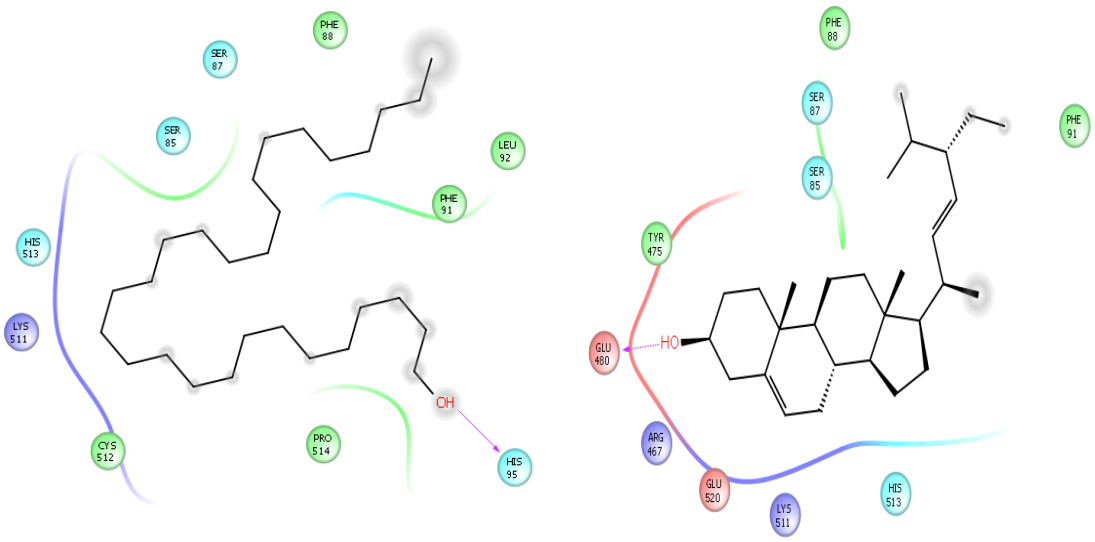
Compound Name	Docking Score	Glide emodel	Glide energy
2-methylanthraquinone	-5.918	-36.686	-25.474
b-Sitosterol	-2.575	-20.403	-19.348
1-Octacosanol	0.049	-17.181	-18.204
stigmasterol	-2.397	-19.423	-20.747



A. 2-methylanthraquinone



B. β-Sitosterol



C. 1-Octacosanol **D. Stigmasterol**

Figure 1: Docking results of 2-methylanthraquinone, β-Sitosterol, 1-Octacosanol and Stigmasterol with 2OYE (PDB: 2OYE).

In silico PASS prediction

Four constituents namely 2-methylanthra, β-sitosterol, 1-Octacosanol, stigmasterol were analyzed by the PASS for their analgesic activity and results were used in a flexible manner. All the compounds showed greater Pa than Pi (Table-1). Stigmasterol showed highest Pa for analgesic activity (Pa=0.601).

Table-2: Pass prediction of 2-methylanthra, β-sitosterol, 1-Octacosanol, stigmasterol for analgesic activity.

Phyto compound	Pass prediction of analgesic activity	
	Pa	Pi
2-methylanthraquinone	0.263	0.079
β-sitosterol	0.558	0.014
1-Octacosanol	0.318	0.027
stigmasterol	0.601	0.008

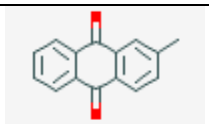
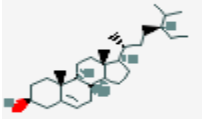
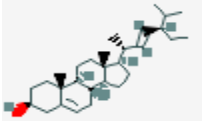
ADME and Toxicity analysis

Ligand based ADME/Toxicity prediction

The drug-like activity of the ligand molecule was categorized using ADME properties by QikProp module of Schrodinger. The ADME properties of the 2-methylanthraquinone, β-Sitosterol, 1-Octacosanol annd Stigmasterol were evaluated with QikProp module of Schrodinger, shown in Table 2. The selected properties are known to influence metabolism, cell permeation, and bioavailability. Only predicted properties of the 2-methylanthraquinone

was in the range for satisfying the Lipinski's rule of five to be considered as drug like potential. All other compounds were not satisfying the all five rules.

Table 3: ADME/T properties of 2-methylanthraquinone, β-Sitosterol, 1-Octacosanol and Stigmasterol by QikProp.

Name of molecules	Pubchem ID	Structure	MW[α]	HB donor[β]	HB accepter[€]	Log P[¥]	Molar refractivity[µ]
2-methylanthraquinone	6773		222	0	2	2.109	58.59
β-sitosterol	222284		414	1	1	8.62	129.21
1-Octacosanol	68406		410	1	1	6.079	107.83
stigmasterol	5280794		412	1	1	7.87	129.12

[α]Molecular weight (acceptable range: <500).

[β]Hydrogen bond donor (acceptable range: ≤5).

[€]Hydrogen bond acceptor (acceptable range: ≤10).

[¥]High lipophilicity (expressed as LogP, acceptable range: <5).

[µ]Molar refractivity should be between 40-130.

CONCLUSION

The present study revealed that *Acalypha indica* has the compound named 2-methylanthraquinone, may be this compound has the best analgesic activity among the tested phyto-compounds. Isolation of this compound will be imported to test the effectiveness of discovery of analgesic drug and also its ADME/T profile for safety, social benefit thus reducing the time and cost in drug discovery process.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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