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An *In-silico* Study on Thymoma with Inhibitors from Petiole and Tender Coconut Water from *Cocos nucifera*

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ABSTRACT

Thymoma is a tumor originating from the epithelial cells of the thymus. Thymoma is an unusual tumor, best known for its association with the neuromuscular disorder myasthenia gravis. When diagnosed, thymomas may be removed surgically. In the rare case of a dangerous tumor, chemotherapy may be used. Health and medicinal applications of tender coconut product get research interest in recent years. The application of edible coconut part is due to the different natural components present in it. This research paper aimed to know the main reported components of coconut i.e., tender coconut water and coconut Petiole for its inhibitory activity against Thymoma. We have chosen target proteins for Thymoma viz RasP21 protein (PDB ID: 4FSS), AKT-1 (PDB ID: 3O96) and BCL-2 (PDB ID: 4AQ3) for our study, it was predicted to be expressed in Thymoma. Docking is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets in order to in turn predict the affinity and activity of the small molecule. Docking study of the target protein was done with natural compounds derived from coconut. The coconut palm (also, cocoanut), *Cocos nucifera*, is a member of the family Arecaceae (palm family). It is the only accepted species in the genus *Cocos*. The term coconut can allude to the whole coconut palm, the seed, or the fruit, which, botanically, is a drupe, not a nut. Chemical constituents found in extracts of entire coconut palm. Phytochemicals screened for Glide HTVS docking showed good interaction with the target. The antitumor compound that yielded a fitness score of more than -5 and good toxicity value were further subjected to Molecular dynamics simulation (MDS). L-Histidine can be a good drug considering their binding affinity, glide energy, glide score and toxicity and that could be a potential target for Thymoma. The docking and ADME studies were performed using Schrödinger Suite.

Keywords: Thymoma, Docking, Glide, L-Histidine, Molecular dynamics simulation (MDS).

INTRODUCTION

We have selected Crystal structures of Ras p21 protein, AKT-1 and BCL-2. Crystal structure of RasP21 is a 3 chain structure was determined using X-ray diffraction at a resolution of 2.25 Å having length of 62 and deposited in 2012. Inhibitor inhibits the activity of the enzyme. Crystal structure of AKT-1 is a one chain structure was determined using X-ray diffraction at a resolution of 2.70 Å having length of 446 and deposited in 2010. [1] Crystal structure of BCL-2 is a 6 chain structure was determined using X-ray diffraction at a resolution of 2.40 Å having length of 169 and deposited in 2012. [2]

Docking is frequently used to predict the binding orientation of small molecule drug candidates to their protein targets in order to in turn predict the affinity and activity of the small molecule. Hence docking plays an important role in the rational design of drugs. [3] Geometric matching/ shape complementarity methods describe the protein and ligand as a set of features that make them dockable. [4] A binding interaction between a small molecule ligand and an enzyme protein may result in activation or inhibition of the enzyme. If the protein is a receptor, ligand binding may result in agonism or antagonism. Docking is most commonly used in the field of drug design; most drugs are small organic molecules.

Secondary metabolites are organic compounds that are not directly involved in the normal growth, development, or reproduction of an organism. [5] Humans use secondary metabolites as medicines, flavorings, and recreational drugs. Secondary compounds are complex chemicals made by plants that are not essential to the life of the plant. They are thought to be produced primarily as pesticides and anti-grazing agents, but they also used as pigments, hormones and chemical agents that can attack other plants (alleleopathy).

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These secondary metabolites can be unique to specific species or genera and do not play any role in the plants' primary metabolic requirements, but rather they increase their overall ability to survive and overcome local challenges by allowing them to interact with their environment. [6] Secondary metabolites, including antibiotics, are produced in nature and serve survival functions for the organisms producing them. The antibiotics are a heterogeneous group, the functions of some being related to and others being unrelated to their antimicrobial activities.

MATERIALS AND METHODS

PDB (Protein Data Bank), the single worldwide repository for the processing and distribution of 3D-structural data of large molecules of proteins and nucleic acids. The PDB archive contains information about experimentally determined structures of proteins, nucleic acids, and complex assemblies. (http://www.rcsb.org/pdb/home/home.do)

Ramachandran Plot

A Ramachandran plot originally developed in 1963 by G. N. Ramachandran, C. Ramakrishnan, and V. Sasisekharan, [7] is a way to visualize backbone dihedral angles ψ against φ of amino acid residues in protein structure.

PubChem is a database of chemical molecules and their activities against biological assays. The system is maintained by the National Center for Biotechnology Information (NCBI), a component of the National Library of Medicine, which is part of the United States National Institutes of Health (NIH). PubChem can be accessed for free through a web user interface. Millions of compound structures and descriptive datasets can be freely downloaded via FTP.

Maestro is the graphical user interface (GUI) for all of Schrödinger's computational programs: CombiGlide, Epik, Impact, Jaguar, Liaison, LigPrep, Macromodel phase, Prime, QikProp, Qsite, SiteMap and Strike. It contains tools for building, displaying and manipulating chemical structures for organizing, loading and storing these structures and associated data; and for setting up, submitting, monitoring and visualizing the results of calculations on these structures.

Glide 4.5 is used to perform high accuracy docking and ligand database screening. Conformational flexibility is handled in Glide by an extensive conformational search, augmented by a heuristic screen that rapidly eliminates unsuitable conformations, such as conformations that have long-range internal hydrogen bonds.

Receptor Grid Generation

Glide searches for favourable interactions between one or more ligand molecules and a receptor molecule, usually a protein. The shape and properties of the receptor are represented on a grid by several different sets of fields that provide progressively more accurate scoring of the ligand poses.

Toxicity prediction

The OSIRIS Property Explorer lets us to draw chemical structures and calculates on-the-fly various drug-relevant properties whenever a structure is valid. Prediction results are valued and color coded. Properties with high risks of undesired effects like mutagenicity or a poor intestinal absorption are shown in red. Whereas a green color indicates drug-conform behaviour. Toxicity of the Best compounds identified in *Cocos nucifera* is shown in Figure 5.

ADME Predictions

QikProp is used for Rapid ADME predictions of drug candidates. QikProp efficiently evaluates pharmaceutically relevant properties for over half a million compounds per hour, making it an indispensable lead generation and lead optimization tool.

The Advantages of ADME Properties Prediction

Nearly 40% of drug candidates fail in clinical trials due to poor ADME (absorption, distribution, metabolism, and excretion) properties. These late-stage failures contribute significantly to the rapidly escalating cost of new drug development. The ability to detect problematic candidates early can dramatically reduce the amount of wasted time and resources, and streamline the overall development process.

Accurate prediction of ADME properties prior to expensive experimental procedures, such as HTS, can eliminate unnecessary testing on compounds that will ultimately fail; ADME prediction can also be used to focus lead optimization efforts to enhance the desired properties of a given compound. Finally, incorporating ADME predictions as a part of the development process can generate lead compounds that are more likely to exhibit satisfactory ADME performances during clinical trials.

Pymol

PyMOL is an open-source, user-sponsored, molecular visualization system created by Warren Lyford DeLano and commercialized by DeLano Scientific LLC, which is a private software company dedicated to creating useful tools that become universally accessible to scientific and educational communities. It can produce high-quality 3D images of small molecules and biological macromolecules, such as proteins.

METHODS

Target proteins and its Retrieval

Target Proteins 4FSS, 3O96 and 4AQ3 were found to be highly expressed in Thymoma cancer. In order to find a marker of aggressiveness in thymomas, 21 cases (9 non-invasive, 8 invasive and 4 metastatic thymomas) were examined for expression of the ras oncogene product p21 by immunohistochemistry and immunoblot analysis. The increased amount of p21 in thymomas suggests that this protein has a role in the oncogenesis or progression of thymoma. The high incidence of a p21 molecular abnormality in metastatic thymomas indicates that the abnormality of this protein could be used as a possible marker of aggressive behaviour. [8]

The protooncogene bcl-2 encodes a protein that inhibits apoptosis. The protein is expressed in most epithelial cells of the fetal thymic medulla but, to the best of our knowledge, no data are available on bcl-2 expression in thymoma. Expression of bcl-2 protein was analysed in 30 cases of thymoma by immunohistological staining of paraffin-embedded tissue. [9]

AKT1 (v-akt murine thymoma viral oncogene homolog 1) is a protein-coding gene. Diseases associated with AKT1 include *Proteus syndrome*, and *thymoma.* AKT1 is one of 3 closely related serine/threonine-protein kinases (AKT1, AKT2 and AKT3) called the AKT kinase, and which regulate many processes including metabolism, proliferation, cell survival, growth and angiogenesis. AKT1 is more specifically involved in cellular survival pathways, by inhibiting apoptotic processes. [10]

Target proteins were retrieved from Pdb.

Prediction of stability of Proteins

Ramachandran Plot is used for predicting the stability of proteins. If the score is above 90%, the protein is stable.

These three targets were validated using the Ramachandran plot (Shown in Figure 1).

Protein preparation

The PDB is a key resource in areas of structural biology, is a key repository for 3D structure data of large molecules. The molecule which taken is Ras p21, AKT-1 and BCL-2 for our consideration. The PDB ID for Ras p21 is 4FSS, for AKT-1 is 3O96 and for BCL-2 is 4AQ3. Glide is a ligand docking program for predicting protein-ligand binding modes and ranking ligands via high-throughput virtual screening. Protein preparation wizard was used in Schrodinger 2009. All the water molecules and RNA were removed from the original crystal structure before protein preparation process, to analyse the structure and the bond order assigned, hydrogen atoms were added and the geometry of all the hetero groups were corrected. Hydrogen bonds assignment tool was used to optimize the hydrogen bond network. Finally, impref optimized the position of hydrogen bonds and keeping all the atoms in place. Energy minimization was carried out using default constraint of the 0.3 Å of RMSD and the OPLS_2005 force field. Glide utilizes two different scoring functions, SP and XP Glide Score, to rank-order compounds. Three modes of sampling ligand conformational and positional degrees of freedom are available to determine the optimal ligand orientation relative to rigid protein receptor geometry. Here it describes the protocols for flexible ligand docking with Glide, optionally including ligand constraints or ligand molecular similarities. [11]

The target proteins were prepared using Protein Preparation Wizard in Maestro. The ouput file generated was prepwizard-protassign-out.

Collection and Retrieval of Ligands

The coconut palm (also, cocoanut), *Cocos nucifera*, is a member of the family Arecaceae (palm family). It is the only accepted species in the genus *Cocos*. [12] The term coconut can refer to the entire coconut palm, the seed, or the fruit, which, botanically, is a drupe, not a nut. Many Phytochemicals obtained from *Cocos nucifera*. Constituents from petiole and tender coconut water of Cocos nucifera include 1-(1H-Pyrrole-2-yl), 1-(2-Pyrazinyl) -1-Ethanol, 2 (1H) -Naphthalenone, Cis-4-Hydroxy-2-Methyl-5-(1-Hydroxy-1-Isopropyl)-2-Cyclohexen-1-one, Citric Acids, Gibberellins, Histidine-Methyl-Ester, Indole-3-Acetic Acid, L-Histidine, Malic acid, Mannitol, Sorbitol, tannins and Zeatin. [13-14] Many others have found in extracts of the other parts of *Cocos nucifera*. For docking study we have used 14 chemical compounds obtained from extracts of the petiole and tender coconut water of this tree.

Structures of 14 compounds from both petiole and Tender coconut water from *Cocos nucifera* were obtained from PubChem database.

Ligand preparation

The three dimensional structure of compounds, that is 14 compounds from Cocos nucifera is taken for binding analysis were downloaded in .sdf format from PubChem database. Generate low energy conformations. These structures were used for docking and pharmacokinetic studies. Output file created after LigPrep was *ligandout.maegz*

The Bond orders were assigned, water molecules were deleted and Hydrogens were added. It optimizes the Hydrogen bonds and minimizes the energy of the structure. The LigPrep Process consists of a series of steps that perform conversions, apply corrections to the structures, generate variations on the structures, eliminate unwanted structures and optimize the structures. The output file generated was ligprep_out.mae.

Active site Prediction

In biology, the active site is the small portion of an enzyme where substrate molecules bind and undergo a chemical reaction. The active sites for the target proteins 4FSS, 3O96 and 4AQ3 were predicted using Sitemap of Schrödinger shown in Figure 2.

Receptor Grid Generation

The outputs from sitemap prediction were given as the input for Receptor Grid generation. Grid box generated for about 20 Angstrom within the DNA binding site of the proteins (4FSS, 3O96 and 4AQ3). Grids were generated by Receptor Grid Generation panel which defines receptor structure by excluding any other co-crystallized ligand that may be present, settle on position and size of the active site was represented by receptor grids. The out file generated was 1.*zip* and Ligprep (ligprep_out.mae) were loaded in the ligand docking panel. Output file generated after ligand docking was glide-dock_HTVS_pv.mae.

Docking studies

Ligand Docking

Output files generated from receptor grid generation (1.zip) and LigPrep (ligandout.mae) were loaded in the ligand docking panel. Output file generated after ligand docking was lig1.pv.maegz.

High throughput virtual screening

Virtual screening is the easiest method to identify and rank potential drug candidates from a set of compounds. Based on the active site of 4FSS, 3O96 and 4AQ3 high throughput virtual screening was performed using the 14 compounds from *Cocos nucifera*. The compounds were subjected to Glide based docking strategy in which all the compounds were docked by High Throughput Virtual Screening (HTVS). HTVS docking screens the ligands that are retrieved. Based on the glide score and glide energy, the protocol gives the leads in HTVS. Glide includes ligand-protein interaction energies, hydrophobic interactions, hydrogen bonds, internal energy, p-p stacking interactions and root mean square deviation (RMSD) and desolvation. After docking we will get good scores for the compounds Indole-3-Acetic acid, Zeatin and L-Histidine. Physico-chemical properties of Best compounds identified in *Cocos nucifera* was shown in Table 1.

The validation process consisted of two parts;

- Hydrogen bond details of the top-ranked docked pose.
- Prediction of binding energy between the docked ligand and the enzyme using various scores calculated using Schrodinger.

Interaction of target protein with 14 Ligands from *Cocos nucifera*

Out of 14 compounds, the best conformation generated was docked into the target proteins. Zeatin has shown the best score -6.19 but after toxicity prediction we got L-Histidine as better compound. The binding energy seems to be -26.29. It forms 2 Hydrogen bonds with the amino acids ASP 70 and GLU 73 and forms the hydrogen bond with H 28 and H 27.

Toxicity prediction

Using OSIRIS Property Explorer we found the better ligand. Ligand structures are drawn in OSIRIS Property Explorer. Toxicity Risks are shown in green colour so it is less toxic

and Drug likeness and Drug-Scores are more for the ligand L-Histdine.

ADME

ADME is predicted using QikProp module from Schrodinger. The results are shown in Table 4.

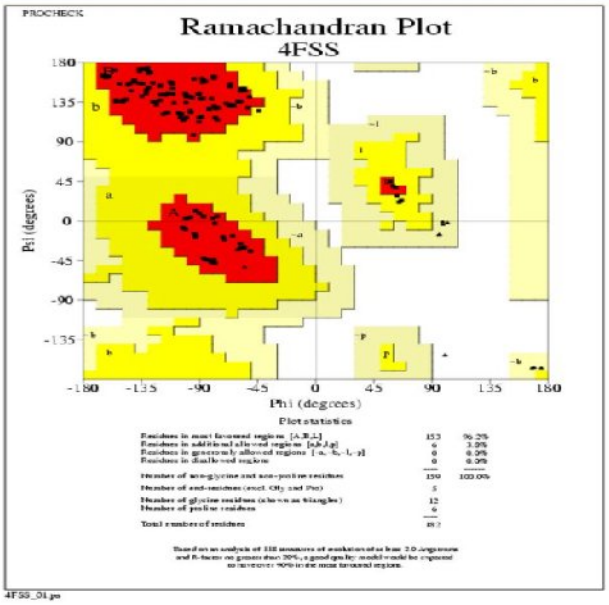
Pymol

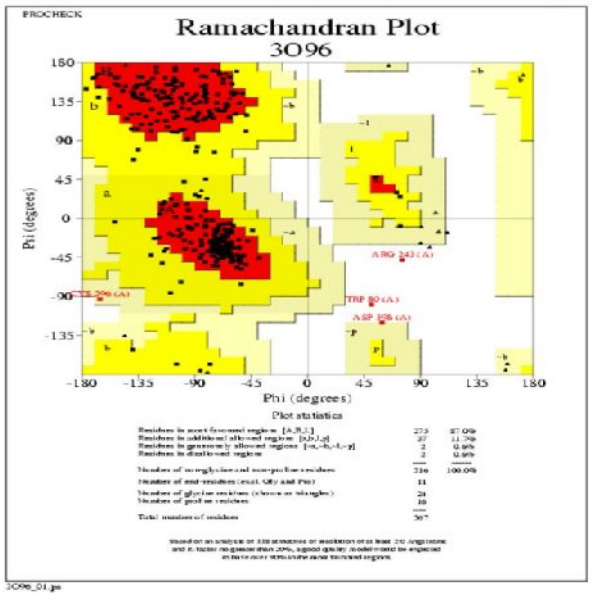
Image capturing was carried out using PyMol viewer.

RESULTS AND DISCUSSION

Docking and scoring processes were used for this study done with HTVS. Target proteins of Thymoma were docked with 14 chemical constituents from extracts of Petiole and tender coconut water of Cocos nucifera using Glide. HTVS selected compounds based on Glide score. Glide score criteria value (Glide score < -4.0 Kcal/mol) which led to 3 ligands for our target proteins. Three compounds were selected based on the Glide score. The ID's and H-Bond interactions of the top three scored compounds are shown in Figure 3 and Table 2. Docking results showed that CID 802, CID 449093 and CID 439224 and from Cocos nucifera got glide score of -5.03, -6.19 and -5.09 Kcal/mol.

Ramachandran Plot





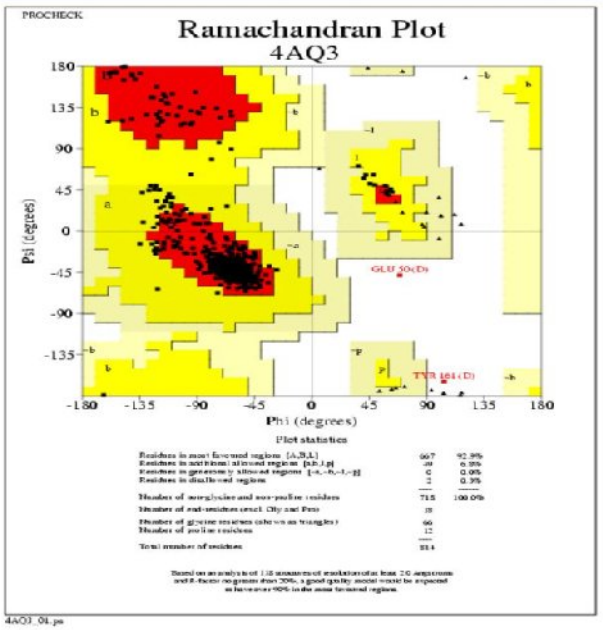
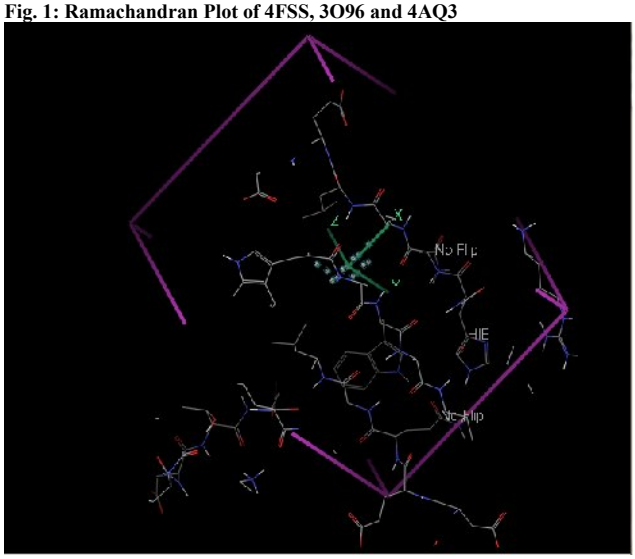
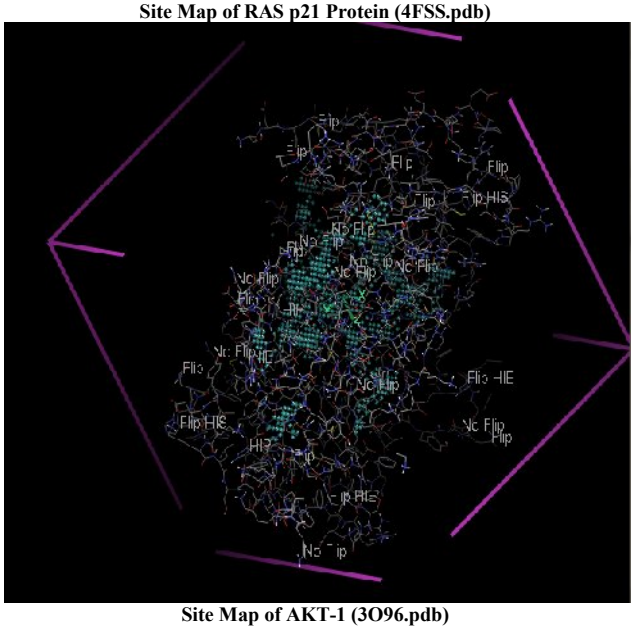


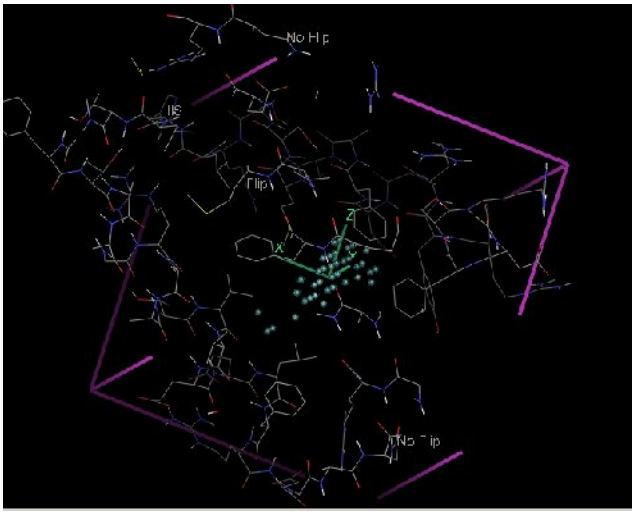
Fig. 1: Ramachandran Plot of 4FSS, 3O96 and 4AQ3



Site Map of RAS p21 Protein (4FSS.pdb)



Site Map of AKT-1 (3O96.pdb)



Site Map of BCL-2 (4AQ3.pdb)
Fig. 2: Predicted active sites of 4FSS, 3O96 and 4AQ3 using sitemap

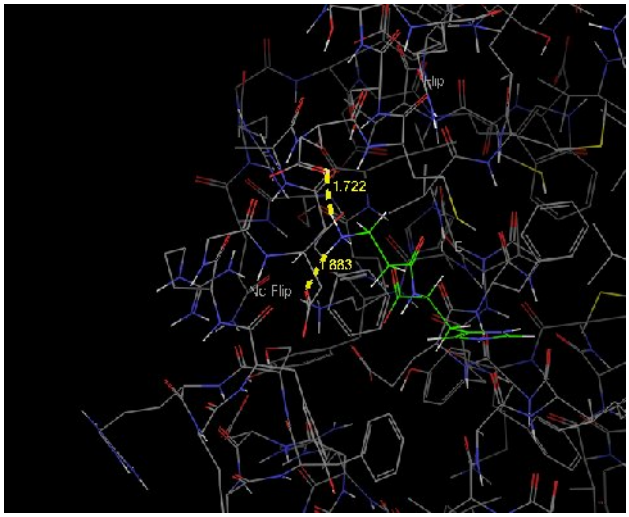


Fig. 3: Docking interaction of lead compounds with target proteins RAS P21 protein (4FSS), AKT-1 (3O96) and BLC-2 (4AQ3) proteins

Table 1: Physicochemical properties of best compounds identified in *Cocos nucifera*

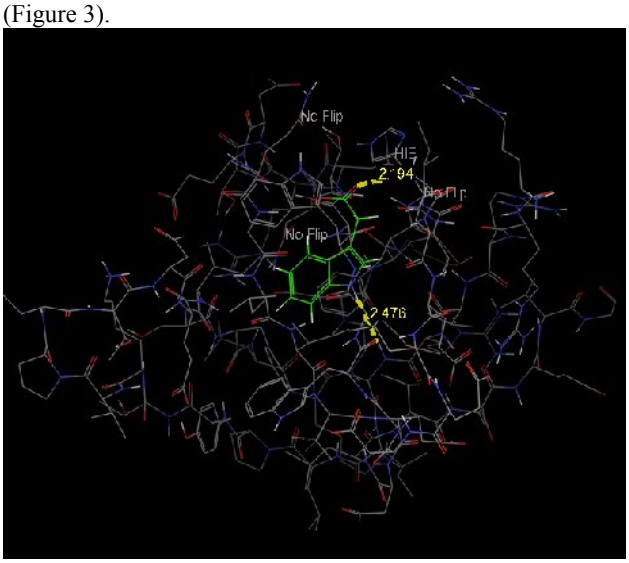
S. No	Compound Name	Compound ID	Mol. Wt	Xlogp	H-Bond donor	H-Bond acceptor
1	Indole-3-Acetic Acid	CID 802	175.18396 [g/mol]	1.4	2	2
2	Zeatin	CID 449093	219.24312 [g/mol]	0.7	3	5
3	L-Histidine	CID 439224	226.23246 [g/mol]	-4	4	5

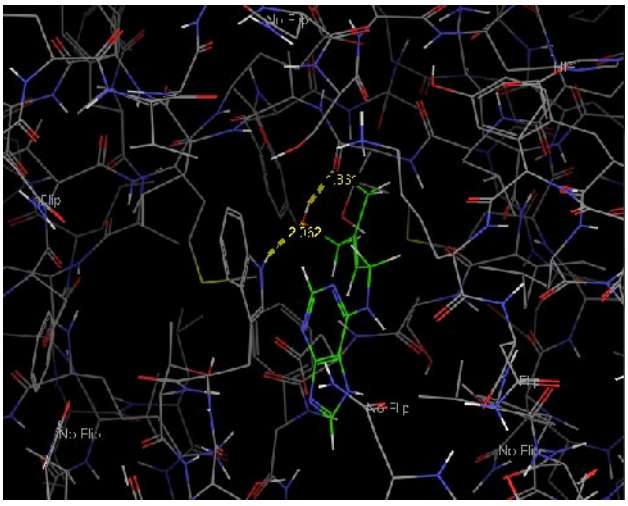
Table 2: Glide score and number of H bonds of best compounds identified in *Cocos nucifera*

Target Proteins	id	Compound Name	G score	No of H bonds	Distance	Protein Residues	Ligatm
4FSS	802	Indole-3-Acetic acid	-5.03	2	2.47 2.19	TRP 317: (O) ASN 311: (H)	H O
3O96	449093	Zeatin	-6.19	2	2.06 1.86	TRP 80: (H) THR 211: (O)	O H
4AQ3	439224	L-Histidine	-5.09	2	1.88 1.72	ASP 70: (O) GLU 73: (O)	H H

Binding mode of Indole-3-Acetic acid with 4FSS

Docking results showed that the ligand Indole-3-Acetic acid occupied the binding region of 4FSS with a Glide score of -5.03 and the Glide energy is -17.44 Kcal/mol. Two hydrogen bond interactions were identified with the amino acid residues Trp 317 and Asn 311 in the binding region of 4FSS (Figure 3).





Binding mode of Zeatin with 3O96

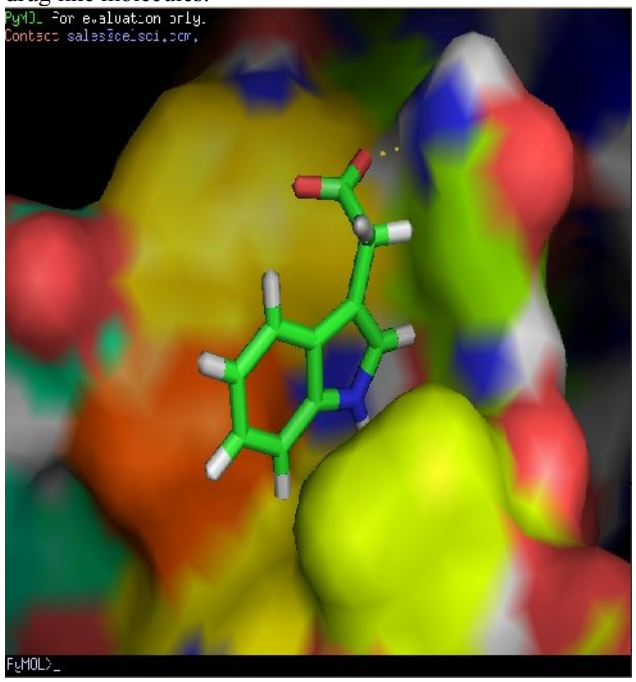
Docking results showed that the ligand Zeatin occupied the binding region of 3O96 with a Glide score of -6.19 and the Glide energy is -33.89 Kcal/mol. Two hydrogen bond interactions were identified with the amino acid residues Trp 80 and Thr 211 in the binding region of 3O96 (Figure 3).

Binding mode of L-Histidine with 4AQ3

Docking results showed that the ligand L-Histidine occupied the binding region of 4AQ3 with a Glide score of -5.09 and the Glide energy is -26.29 Kcal/mol. Two hydrogen bond interactions were identified with the amino acid residues Asp 70 and Glu 73 in the binding region of 4AQ3 (Figure 3).

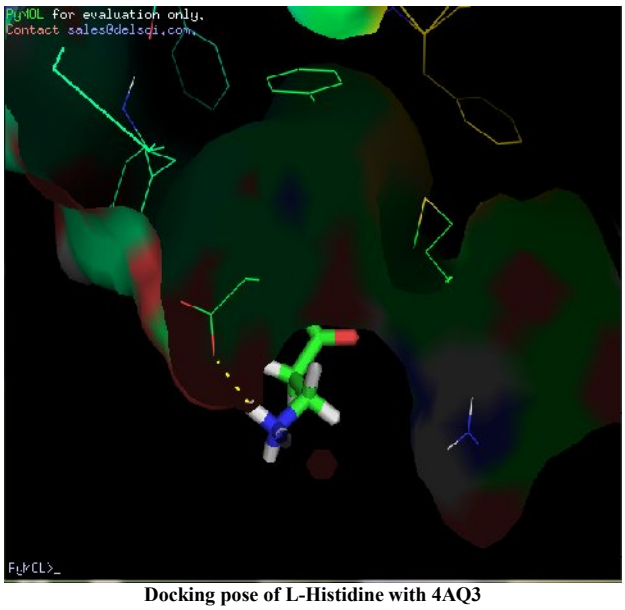
The structure of target proteins with PDB ID 4FSS, 3O96 and 4AQ3 is retrieved from PDB. The resolution factor is retrieved from PDB. The 14 chemical compounds from *Cocos nucifera* taken as a ligand for docking analysis with

Ras p21, AKT-1 and BCL-2 (4FSS, 3O96 and 4AQ3). The active site of the target protein determined using site map prediction. Docking done using Glide and the Receptor and ligand can browse for prepared output files. Docked pose of the compound with proteins is presented in Figure 4. The ligands Indole-3-Acetic acid, Zeatin and L-Histidine docked with protein Ras p21, AKT-1 and BCL-2 with -5.03, -6.19 and -5.09 dock score value (Shown in Table 3). Molecular docking is an efficient technique to predict the predominant binding modes of the ligand with the protein of known three-dimensional structure. Studies on binding modes are essential to elucidate key structural characteristics and interactions and they provide helpful data for designing effective inhibitors. The three selected compounds were in the acceptable range of Lipinski's rule of five, indicating their potential for use as drug like molecules. [15]



Docking pose of Indole-3-Acetic acid with Ras p21 (4FSS)

Docking pose of Zeatin with AKT-1 (3O96)



Docking pose of L-Histidine with 4AQ3

Fig. 4: Docking poses of best compounds identified in petiole and tender coconut of *Cocos nucifera*

Table 3: Glide score and glide energy of best compounds identified in *Cocos nucifera*

Target protein	Glide score	Glide energy
4FSS	-5.03	-17.44
3O96	-6.19	-33.89
4AQ3	-5.09	-26.29

Molecular dynamics simulations

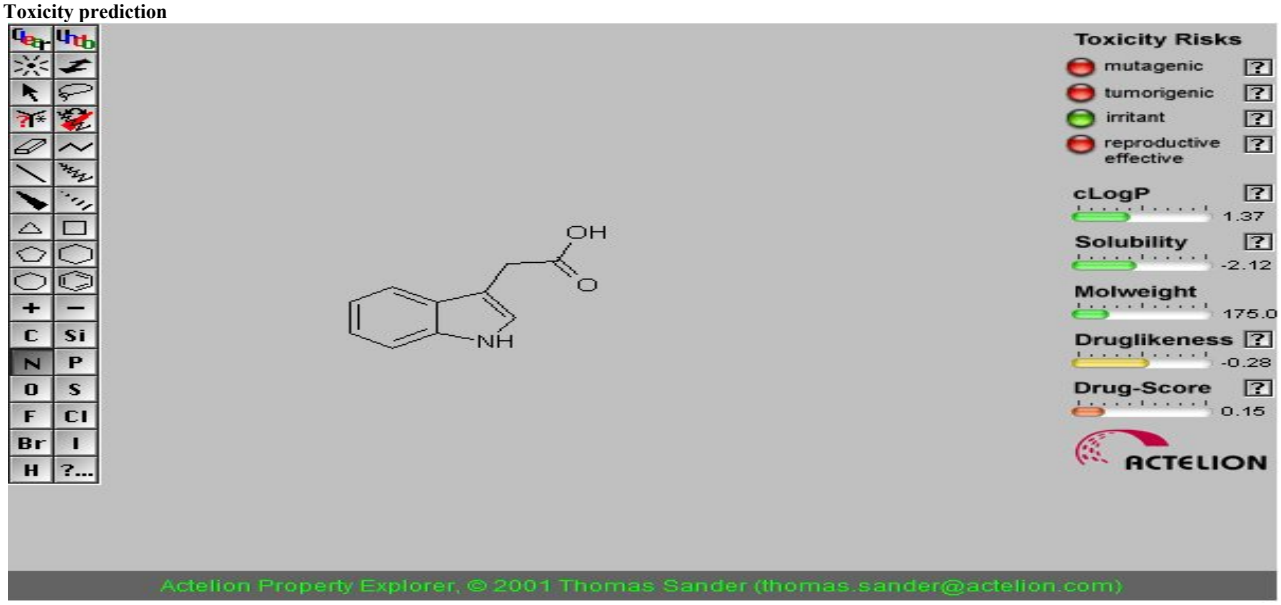
Molecular dynamics (MD) is a computer simulation of physical movements of atoms and molecules in the context of N-body simulation. The atoms and molecules are allowed to interact for a period of time, giving a view of the motion of the atoms. Molecular dynamics can be used to explain protein structure function problems, such as folding, conformational flexibility and structural stability. In the simulations, we monitored the backbone atoms and the C-α-helix of the modeled protein. The RMSD values of the modeled structure's backbone atoms were plotted as a time-dependent function of the MD simulation. The results support our modeled structure, as they show constant RMSD deviation throughout the whole simulation process. Graphs of potential energy, temperature, pressure and volume and time dependence of the RMSD (Å) of the backbone atoms of the modeled protein during a 5 ns simulation is shown in Figure. 6 & 7.

Molecular dynamics results

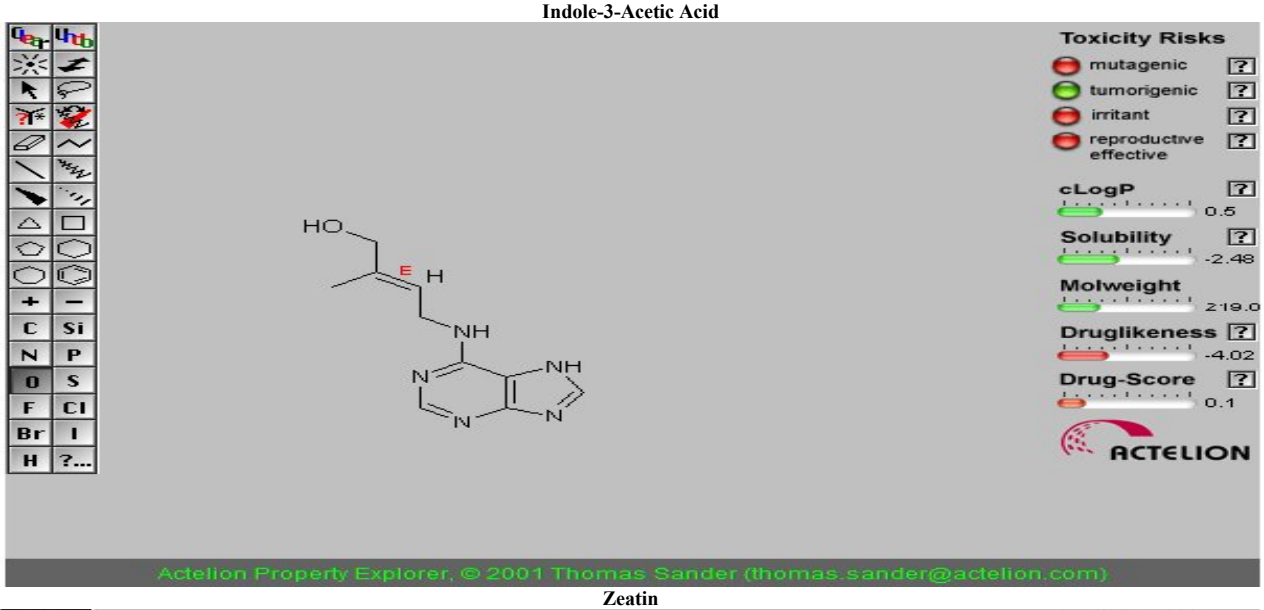
The RMSD values of the backbone atoms in the system tend to converge after 100 ps, showing fluctuations of around 1 Å. The low RMSD and the simulation time indicate that, as expected, the docked Structure of BCL-2 represents a stable folding conformation.

It is important to understand the role of chemical constituents found in petiole and coconut extracts of Cocos nucifera. Chemical compounds bind to specific receptors on target protein. *In silico* molecular docking is one of the most powerful techniques to discover novel ligand for proteins of known structure and thus play a key role in structure based drug designing. The ligand molecules were retrieved from pubchem. Investigators often use docking computer programs to find the binding affinity for molecules that fit a binding site on the protein.

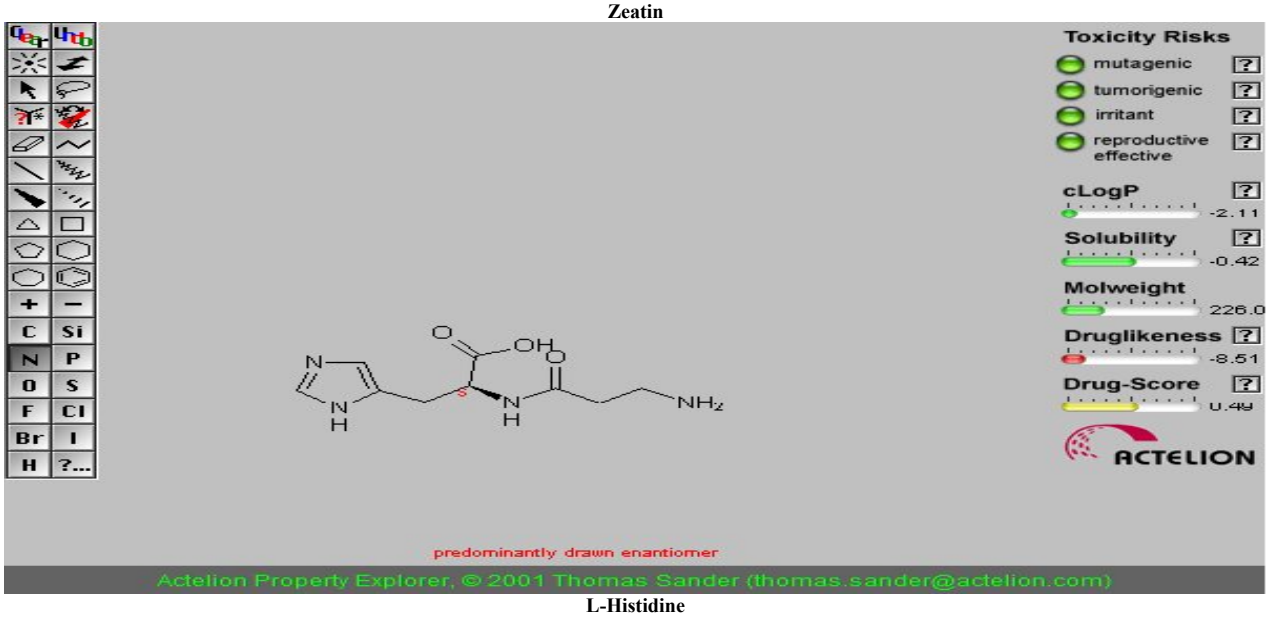
Toxicity prediction



Indole-3-Acetic Acid



Zeatin



L-Histidine

Fig. 5: Toxicity predicted for Indole-3-Acetic Acid, Zeatin and L-Histidine

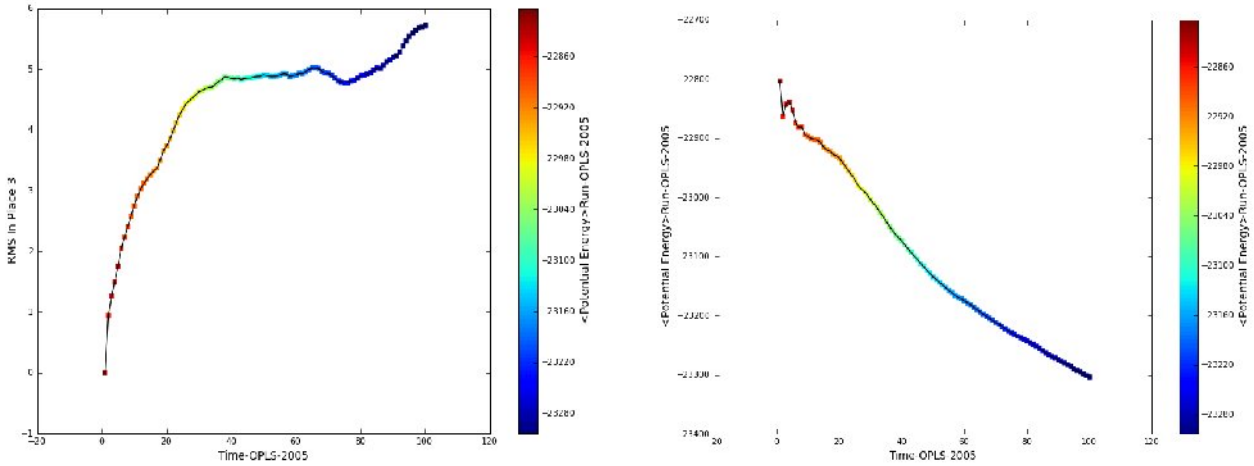


Fig. 6: RMSD of the backbone atoms of the docked 4AQ3 over a time period of 100 picoseconds

Table 4: Pharmacokinetic properties of L-Histidine

S. No	Pharmacokinetic Properties	Values
1	Molecular Weight	226.235
2	Total SASA	478.025
3	Donor-Hydrogen Bonds	3.250
4	Acceptor-Hydrogen Bonds	5.250
5	QP logP for octanol/gas	15.598
6	QP logP for octanol/water	-2.456
7	QP logS for aqueous solubility	-0.672
8	QP log K hsa Serum Protein Binding	-1.069
9	QP log BB for brain/blood	-1.766
10	HERG K+ Channel Blockage: log IC50	-1.948
11	Apparent Caco-2 Permeability (nm/sec)	1
12	Apparent MDCK Permeability (nm/sec)	1
13	QP log Kp for skin permeability	-7.186
14	Lipinski Rule of 5 Violations	0
15	Jorgensen Rule of 3 Violations	1
16	% Human Oral Absorption in GI (+-20%)	17

Hence in this present work we have carried out *in silico* molecular docking to analyze the binding properties of the Ras p21 protein, AKT-1 and BCL-2 with chemical constituents from *Cocos nucifera*. The docked structure was validated by molecular dynamics simulation. HTVS screened compounds from *Cocos nucifera* were subjected to HTVS docking which resulted in 3 best compounds. Using HTVS docking, based on the glide score, glide energy and H-bond interactions with the amino acid residues 3 compounds were shortlisted. 3 compounds were within the acceptable range of Lipinski's Rule of Five. CID 802, CID 449093 and CID 439224 has a good glide score and glide energy (-5.03 & -6.19 and -5.09 kcal/mol). The ligand Indole-3-Acetic acid has a good contact with the specific amino acid residues TRP 317 and ASN 311 with the hydrogen bond distances of 2.47 and 2.19Å respectively. The ligand Zeatin has a good contact with the specific amino acid residues TRP 80 and THR 211 with the hydrogen bond distances of 2.06 and 1.86Å respectively. The ligand L-Histidine has a good contact with the specific amino acid residues ASP 70 and GLU 73 with the hydrogen bond distances of 1.88 and 1.72Å respectively. Among the 14 ligands Zeatin showed the best Glide Score value of -6.19 with a binding energy of -33.89 but after toxicity prediction we got L-Histidine as better compound having Glide Score value of -5.09 with a binding energy of -26.29. Ligand's ADME properties were calculated using QikProp. So the present study may act as supportive evidence that substantiates property of *Cocos nucifera* petiole extract may be a good drug because of the inhibiting ability of L-Histidine identified from Cocos nucifera with BCL-2 protein (4AQ3). So, the search for phytochemical drugs from *Cocos nucifera* represents a good drug in curation of diseases due to its less side effects.

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