THE MODE OF ACTION OF PHYTOCOMPOUND FROM THE MEDICINAL PLANT *BIOPHYTUM SENSITIVUM* USING DOCKING STUDIES

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Abstract: Natural products with medicinal value are gaining importance in clinical research due to their therapeutic uses without side effects. *Biophytum sensitivum* is an important herb in ayurvedic system of medicine which contains more number of phytoconstituents. Molecular docking was performed on Cupressuflavone, which is isolated from ethanol extract of *Biophytum sensitivum* leaves with AKT1 protein. The protein sequence is retrived from SWISSPROT database. Docking study was performed by using iGMDOCK. From the result it was found to that binding energy is -9.4 kcal/mol with five hydrogen bonds and also shows binding energy of amino acids. It clearly proved that the isolated compound have great medicinal and pharmacological action towards curing breast cancer.

Indexing Terms: ***Biophytum sensitivum*, AKT1, Cupressuflavone, binding energy, breast cancer.**

I INTRODUCTION

Bioinformatics is an interdisciplinary research area at the interface between biological and computational sciences. Although the term 'Bioinformatics' is not really well defined, you could say that this scientific field deals with the computational management of all kinds of molecular biological information. Most of the bioinformatics work that is being done deals with either analyzing biological data or with the organization of biological information. The aim of bioinformatics is simplest bioinformatics organizes data in a way that allows researchers to access existing information and to submit new entries as they are produced. Eg. The Protein Data Bank for 3D macromolecular structure. While data-curation is an essential task, the information stored in these databases is essentially useless until analysed. Thus the purpose of second aim is to develop tools and resources that aid in the analysis of data. The third aim is to use these tools to analyse the data and interpret the results in a biologically meaningful manner (Attwood and Parry Smith, 1999; Arthur M Lesk, 2019; Dan E Krane and Michael L Raymer, 2002).

Computational structure prediction of ligand protein complexes using docking methods like DOCK, FLEXx and GOLD in combination with empirical scoring functions are used to predict ligand interactions in binding sites and binding affinities of ligands to proteins (Ewing *et al*., 2001; Jones *et al*., 1997; Karmer, Rareey and Lengauer, 1999). While the binding geometries depend on the binding affinities of ligands to proteins. While the binding geometries depend on the docking methods, binding energy estimates rely heavily on the potential functions used to calculate them. Knowledge based potentials follow rules based on statistical analysis of binding affinities and geometries of experimentally determined protein-ligand complexes. A concern with these methods is the dependence of the size, composition and generality of the training set used to derive the weights (Tame, 1999). Moreover, such methods can only interpolate and thus, are unable to identify new molecular scaffolds that are not present in the training set. Nevertheless, improvements in regression based methods have contributed to some encouraging examples demonstrating the potential of such techniques (Rognan *et al*., 1999).

1.1 Selected protein

The present investigation an attempt has been made to analyse the docking score of the isolated compounds with selected protein. Protein was choose against breast cancer.

1.1.1 AKT1

The AKT1 gene provides instructions for making a protein called AKT1 kinase. This protein is found in various cell types throughout the body, where it plays a critical role in many signaling pathways. AKT1 kinase helps regulate cell growth and division (proliferation), the process by which cells mature to carry out specific functions (differentiation), and cell survival and also helps control apoptosis, which is the self-destruction of cells when they become damaged or are no longer needed. The AKT1 gene belongs to a class of genes known as oncogenes. When mutated, oncogenes have the potential to cause normal cells to become cancerous.

UniProtKB/Swiss-Prot (AKT1_HUMAN, P31749)

AKT (Protein kinase B, PKB) is a serine/threonine kinase that plays a key in regulating cell survival, insulin signaling, angiogenesis and tumor formation. AKT is a downstream mediator of the PI 3-K pathway, resulting in the recruitment of AKT to the plasma membrane via the PH

(Plexstrin Homology domain) of AKT. AKT is fully activated by phosphorylation at two key sites: Ser308 (phosphorylated by PDK1) and Thr478 (phosphorylated by mTOR and DNA-PK) (ncbi).

II MATERIALS AND METHODS

2.1 UniProt

The universal protein resource provides a stable, comprehensive, freely accessible, central resource on protein sequences and functional annotation. The UniProt Consortium is a collaboration between the European Bioinformatics Institute (EBI), the Protein Information Resource (PIR) and the Swiss Institute of Bioinformatics (SIB).

2.2 PDB

The Protein Data Bank is a database for the three dimentional structural data of large biological molecules, such as proteins and nucleic acids. The data, typically obtained by X-ray crystallography, NMR spectroscopy or increasingly cryo-electron microscopy and submitted by biologists and biochemists from around the world, are freely accessible on the Internet via the websites of its member organizations. This resource is powered by the Protein Data Bank archive-information about the 3D shapes of proteins, nucleic acids and complex assemblies that helps students and researchers understand all aspects of biomedicine and agriculture from protein synthesis to health and diseases.

2.3 Protein sequence

The sequence of RAC – alpha serine/threonine-protein kinase was retrived from SWISSPROT database and sequence number is P31749. AKT1 sequence as follows.

>sp|P31749|AKT1_HUMAN RAC-alpha serine/threonine-protein kinase OS=Homo sapiens OX=9606 GN=AKT1 PE=1 SV=2
MSDVAIVKEGWLHKRGEYIKTWRPRYFLLKNDGTFIGYKERPQDVDQREAPLNNFSVAQC
QLMKTERPRPNTFIIRCLQWTTVIERTFHVETPEEREEWTTAIQTVADGLKKQEEEEMDF
RSGSPSDNSGAEEMEVSLAKPKHRVTMNEFEYLKLLGKGTFGKVILVKEKATGRYYAMKI
LKKEVIVAKDEVAHTLTENRVLQNSRHPFLTALKYSFQTHDRLCFVMEYANGGELFFHLS
RERVFSEDRARFYGAEIVSALDYLHSEKNVVYRDLKLENLMLDKDGHIKITDFGLCKEGI
KDGATMKTFCGTPEYLAPEVLEDNDYGRAVDWWGLGVVMYEMMCGRLPFYNQDHEKLFEL
ILMEEIRFPRTLGPEAKSLLSGLLKKDPKQRLGGGSEDAKEIMQHRFFAGIVWQHVYEKK
LSPPFKPQVTSETDTRYFDEEFTAQMITITPPDQDDSMECVDSERRPHFPQFSYSASGTA

III RESULT AND DISCUSSION

3.1 AKT1 (Cancer drug target)

The protein model of AKT1 was visualized by Discovery Studio Visualiser presented in Figure 1.

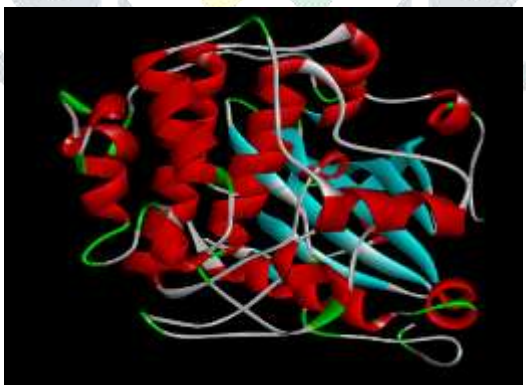

Fig.1 The protein model of AKT1

3.2 Structure of inhibitors

Selected inhibitors were isolated from *Biophytumsensitivum*. They have been confirmed by using different spectrometric methods which is shown in Figure 2 and 3.

3.2.1 *Cupressuflavone*

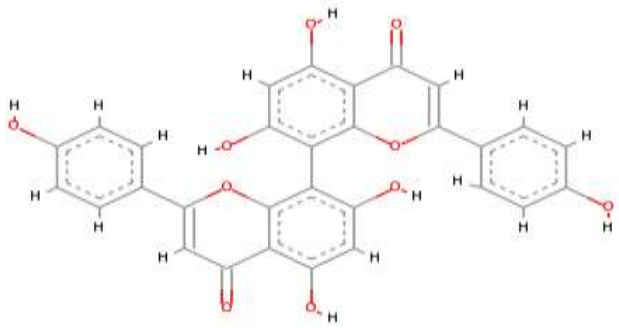

Fig. 2 2D structure of *Cupressuflavone*

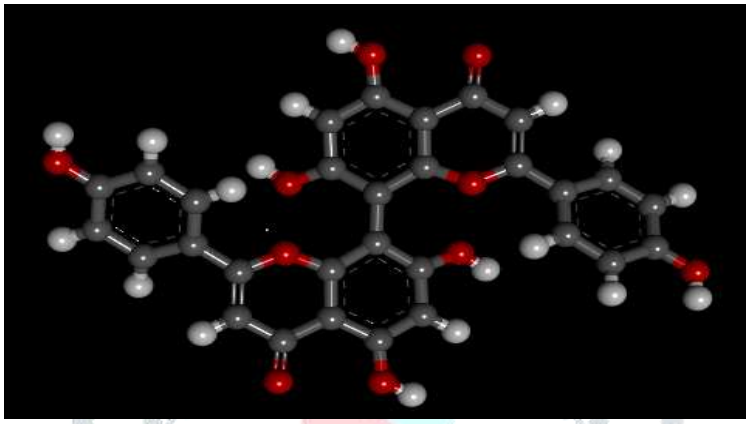

Fig. 3 3D structure of *Cupressuflavone*

3.3 Docking analysis between AKT1 and Cupressuflavone

The docking of protein AKT1 with the ligand *Cupressuflavone* exhibit binding energy corresponding to the cluster and element. The docking score are measured in terms of binding energy. Figure 4 to 6 describe the interaction of ligand with target protein AKT1.

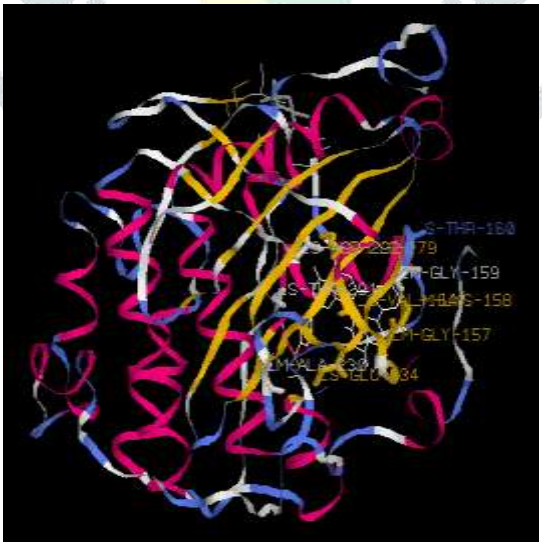

Fig. 4 3D structure of interaction between *Cupressuflavone* and AKT1 visualised by rasmol

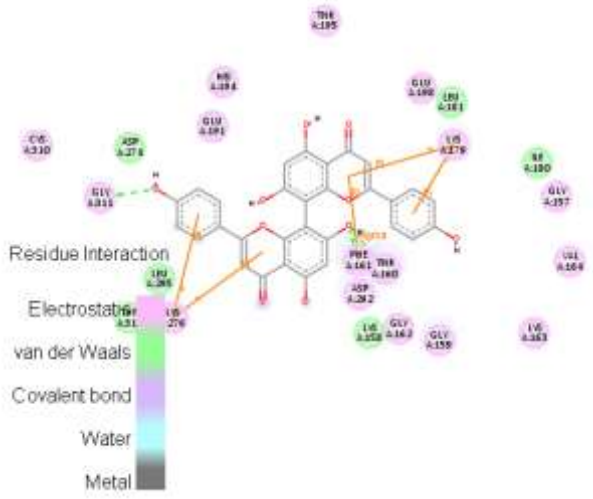

Fig. 5 2D structure of interaction between *Cupressuflavone* and AKT1 visualised by Accelrys Discovery Studio Visualizer

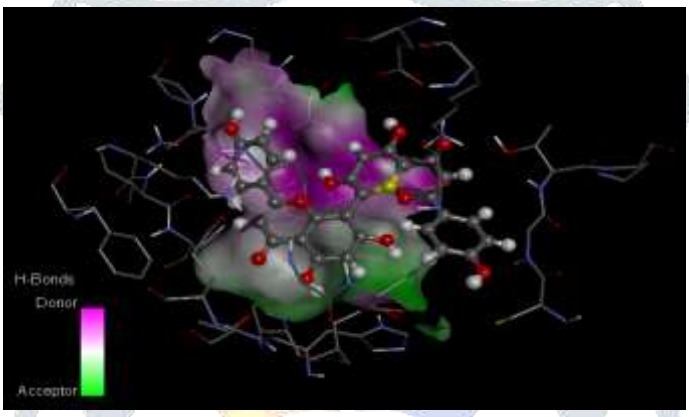

Fig. 6 Binding mode of *Cupressuflavone* in AKT1 represented in electrostatic potential solid surface

The Cupressuflavone interact with AKT1 protein with docking score -9.4 kcal/mol. The inhibitor Cupressuflavone fits the active site cavity making various close contacts with the residues including hydrogen bonding with main chain of Glycine at position 159 and alanine at position 230 were shows binding energy -3.5 kcal/mol. Hydrogen bonding with side chain of Threonine at position 160, Lysine at position 179 and Aspartate at position 292 shows binding energy value -2.5 kcal/mol, -7 kcal/mol and -2.5 kcal/mol. Vander Waals interaction with main chain of Glycine at position 157 and 159 with binding energy value -8.9 kcal/mol and 7.7 kcal/mol and Lysine at position 158 with binding energy-9 kcal/mol. Vander Waals interaction with side chain of Valine at position 164, Lysine at position 179, Glutamine at position234 and Threonine at position 291 with binding energy -8.2 kcal/mol, -5 kcal/mol, -9.4 kcal/mol and -4.7 kcal/mol respectively. Amino acid residue with binding energy is shown in Table 1.

Table 3.1- Amino acid residue with binding energy

Amino acid residue	Energy (kcal/mol)
H-M GLY 159	-3.5
H-S THR 160	-2.5
H-S LYS 179	-7
H-M ALA 230	-3.5
H-S ASP 292	-2.5
V-M GLY 157	-8.9
V-M LYS 158	-9
V-M GLY 159	-7.7
V-S VAL 164	-8.2
V-S LYS 179	-5
V-S GLU 234	-9.4
V-S THR 291	-4.7

IV DISCUSSION

The concept of complementary or alternative medicine is becoming widely accepted and there is an increasing belief in the efficacy of herbal remedies. Clinical researches show the value of herbal medicine in treatment and prevention of diseases. On analyzing the docked results, it was found that Cupressuflavone interact with AKT1 protein. *Biophytum sensitivum* extract exhibit breast anticancer activity using MCF-7 cell line (Saravanan *et al*., 2016). The result of docking phytocompound with AKT1 shows docking score -9.4 kcal/mol. Cupressuflavone can be used as lead structure in designing new drugs.

V CONCLUSION

The docking analysis of RAC-alpha serine/threonine-protein kinase (AKT1) with the ligands of isolated compounds was based on the measurement of binding energy and orientation of the docked compound within the active site. The best ligand is usually identified by evaluating the interaction energy for the ligand-receptor complex. The exact binding mode of the isolated compound based on computational approach is presented and various interacting residues within the protein were identified. Cupressuflavone have five hydrogen bonding with AKT1 with a docking score – 9.4 kcal/mol. It shows that compounds have inhibitory effect against cancer drug target and that it possibly posses anticancer activity.

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