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Comparative Docking Studies on Erlotinib (Synthetic drug) and Curcumin (Natural drug) Against the Lung Cancer (TCF21)

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ABSTRACT

Lung cancer is the second leading cause of death worldwide. In cancer, cells divide and grow uncontrollably, forming malignant tumors, and invade nearby parts of the body. The cancer may also spread to more distant parts of the body through the lymphatic system or bloodstream. A number of undesired side effects sometimes occur during chemotherapy. There has been a vast growth in the field of herbal medicine and these drugs popularly are increasing both in developing and developed countries because of their natural origin, more therapeutic effect and less side effects. Since ancient cultures, tribal people methodically collected information on herbs and developed well-defined herbal drugs for the treatment of many diseases. Mostly, cancer patients are gaining benefit from treatment with herbal medicine. In the present study the anti cancer activity of the existing drug (Erlotinib) and natural compound Curcumin (Curcuma longa) were compared based on the protein ligand interactions were carried out using bioinformatics software and tools. Protein ligand interactions in the present investigation revealed that curcumin is more effective to bind the gene TCF21 comparatively erlotinib.

Keywords: TCF21, Curcumin, Erlotinib, Autodock.

I. INTRODUCTION

Cancer known medically as a malignant neoplasm is a broad group of various diseases involving uncontrolled cell growth. In cancer, cell divide and grow uncontrollably, forming malignant tumors and invade nearby parts of the body. Cancer may also spread to more distant parts of the body through the lymphatic system of blood stream [1]. Many things are known to increase the risk of cancer, including uses of tobacco, radiation, lack of physical activity, obesity and environmental pollutants. This can directly damage genes or combined with existing genetic fault within cells to causes the disease. Approximately 5 to 10% of the cancers are entirely hereditary. Cancer can be detected in a number of ways, including the presence of certain signs and symptoms, screening test or medical imaging [2]. The main reason cancer can be difficult to cure is that it can spread to a different part of the body where it started. The cancer that grows where it first started in the body is called primary cancer. The place the cancer spreads to start growing is called secondary cancer or metastasis (Cancer research centre, UK. 2013). In 2007 about 15% of all cancer diagnosis and 29% of all cancer

death were due to lung cancer. It is the number one cause of death from cancer every year and the second most diagnosed after breast and prostate cancer [3]. Keeping in this view, lung cancer was assessed in the present investigation.

Lung cancer can be broadly classified into two main types based on the cancer appearance and a microscope: non-small cell lung cancer and small cell lung cancer. Non-small cell lung cancer accounts for 80% of the lung cancers, while small cell lung cancer accounts for the remaining 20% [4, 5]. Lung cancer usually found in older persons because it develops over a long period of time. Lung cancer occurs when a lung cells gene mutation makes the cell unable to correct DNA damage and unable to commit suicide. Mutation can occur for a variety of reasons most lung cancer are the results of inhaling carcinogenic substances [6]. Carcinogens are a class of substances that are directly responsible for damaging DNA, promoting or aiding cancer. Tobacco, asbestos, arsenic, radiation such as gamma and x-rays, the sun and compounds in car exhaust fumes are all examples of carcinogens. When our bodies are exposed to carcinogens, free radicals are formed that try to steal electrons from other molecules in the body. These free radicals damage cells and affect their ability to function and divide normally. About 87% of lung cancers are related to smoking and inhaling the carcinogens in tobacco smoke. Even exposure to second-hand smoke can damage cells so that cancer forms [7, 8]. Cancer can be the result of a genetic predisposition that is inherited from family members. It is possible to be born with certain genetic mutations or a fault in a gene that makes one statistically more likely to develop cancer later in life. Genetic predispositions are thought to either directly cause lung cancer or greatly increase one's chances of developing lung cancer from exposure to certain environmental factors [9].

Lung cancer symptoms may take years before appearing, usually after the disease is in an advanced stage [10]. Many symptoms of lung cancer affect the chest and air passages. These includes a persistent or intense coughing, pain in the chest shoulder or back from coughing, changes in color of the mucus that is coughed up from the lower airways (sputum), difficulty breathing and swallowing, hoarseness of the voice, harsh sounds while breathing (Stridor), chronic bronchitis or pneumonia, coughing up blood or blood in the sputum. Lung cancer spreads or metastasizes, additional symptoms an present themselves in the newly affected area. Swollen or enlarged lymph nodes are common and likely to be present early [11, 12]. Common imaging techniques include chest X-rays, bronchoscopy (a thin tube with a camera on one end), CT scans, MRI scans, and PET scans [13].

The main lung cancer treatments are surgery, chemotherapy and radiation. However, there also have been recent developments in the fields of immunotherapy, hormone therapy, and gene therapy. Chemotherapy utilizes strong chemicals that interfere with the cell division process- damaging proteins or DNA – so that cancer cells with commit suicide. These treatments target any rapidly dividing cells (not just cancer cells), but normal cells usually can recover from any chemical-induced damage while cancer cells cannot. Chemotherapy is considered systemic because its medicines travel throughout the entire body, killing the original tumor cells as well as cancer cells that have spread throughout the body [14]. Erlotinib hydrochloride is a drug used to treat non-small cell lung cancer, pancreatic cancer

and several other types of cancer. It is a reversible tyrosine kinase inhibitor, which acts on the epidermal growth factor receptor (EGFR). Erlotinib is an EGFR inhibitor. As this synthetic drug, causes many side effects, it is imperative to search for new, effective economical and eco-friendly drugs like phytotherapeutic drugs. One of the most frequently studied chemopreventive agents is a curcumin, a natural compound extracted from *Curcuma longa* (turmeric) that inhibits cell proliferation and induces apoptosis in human leukaemia, prostate cancer, and non-small cell lung cancer. Curcumin (diferuoylmethane) is a major yellow pigment in and is widely used as a spice. Curcumin exhibits a variety of pharmacological effects, and has been reported to have anti-inflammatory and anti-tumor activities.

Curcumin strikes at multiple targets in prostate malignancies, interfering with the spread of cancer cells and regulating inflammatory responses through the master regulator. Like certain breast cancers, prostate cancer is often dependent on sex hormones for its growth. Curcumin reduces expression of sex hormone receptors in the prostate, which speeds androgenic breakdown and impairs cancer cells' ability to respond to the effects of testosterone. It also inhibits cancer initiation and promotion by blocking metastases from forming in the prostate and regulating enzymes required for tissue invasiveness. Curcumin is equally powerful at preventing cancers it the stomach. It inhibits growth and proliferation of human gastric cancer cells in the laboratory and is particularly effective in stopping cancers that have become resistant to multiple drug treatment. Curcumin can prevent gastric cancer cells from progressing through their growth cycle, blocking further tumor growth [15].

In this study, Curcumin is a potential anticancer agent and that it achieves this by targeting TCF21. The gene TCF21 plays a major role in the disease lung cancer. TCF21 is a specific tumor suppressor gene associated with lung cancer. This gene is inactivated because of hypermethylation of the promoter region. Removal or inhibition of methylation could prevent metastasis. This work describes DNA-ligand docking for removal of methylation [16]. Hence in the present study anticancer activity of existing drug and natural compound were compared with TCF 21 gene based on the protein ligand interactions was investigated.

II. METHODS AND MATERIAL

The gene TCF21 which plays a main role in the disease cancer was taken as the target and the sequence was retrieved from NCBI. The related structure was found using BLAST similarity search of the sequence. Pfam database contains information about protein domains and families. Pfam database was used to find out protein domain. Modeler 9v1 was used for alignment of sequence. Ramachandran plot for the modeled protein was obtained from the database. The structure validation was performed using ProCheck (SAVS). Modeled TCF21 was visualized using Accelrys DS visualizer. Further by using the same tool, the structure of template and modeled protein was superimposed. Protein parameters of the modeled protein were obtained using PROSITE. GOR results were obtained for the modeled protein. Docking of TCF21 of *Homo sapiens* with ligands viz. Erlotinib and curcumin was done using autodock tools. Based on the docking energy, the efficacy of the ligand was predicted.

NCBI

NCBI refer to national centre of biotechnology information. The NCBI has had responsibility for making available the GenBank DNA sequence database since 1992. GenBank coordinates with individual laboratories and other sequence databases such as those of the European Molecular Biology Laboratory (EMBL) and the DNA Data Bank of Japan (DDBJ).

BLAST

In Bioinformatics, Basic Local Alignment Search Tool, or BLAST, is an algorithm for comparing primary biological sequence information, such as the amino-acid sequences of different proteins or the nucleotides of DNA sequences. A blast search enables a researcher to compare a query sequence with a library or database of sequences, and identify library sequences that resemble the query sequence above a certain threshold.

Pfam

Pfam database contains information about protein domains and families. Pfam-A is the manually curated portion of the database that contains over 9,000 entries.

PROSITE

PROSITE is a database of protein families and domains. It consists of documentation entries describing protein domains, families and functional sites as well as associated patterns and profiles to identify them. These are manually curated by a team of the Swiss Institute of Bioinformatics and tightly integrated into Swiss-Prot protein annotation. Prosite was created in 1988 by Amos Bairoch.

Brookhaven Protein DataBank (PDB)

The template structure thus chosen based on its similarity with the target protein is downloaded from the Brookhaven Protein DataBank .The Protein Data Bank (PDB) is the single worldwide depository of information about the three-dimensional structures of large biological molecules, including proteins and nucleic acids.

Modeling using Modeller 9v1

Modeller is a computer program used in producing homology models of protein tertiary structures as well as quaternary structures. It implements a technique inspired by nuclear magnetic resonance known as satisfaction of spatial restraints, by which a set of geometrical criteria are used to create a probability density function for the location of each atom in the protein. The method relies on an input sequence alignment between the target amino acid sequence to be modeled and a template protein whose structure has been solved.

ProCheck (SAVS)

SAVS refer to Stuctural Analysis and Verification Server. ProCheck is effective server which is used to plot the Ramachandran diagram. Ramachandran diagram is used to study the stability of the structure of the protein. These operating instructions describe how to run the procheck suite of programs for assessing the stereo chemical quality of a given protein structure.

ACD /Labs

ACD/Labs Online (I-Lab) is an Internet-based service for instant access to chemical databases and property predictions programs. With I-Lab access, one can obtain NMR spectra, get systematic chemical names, and predict properties such as pK_a, log*P*, or solubility for the chemical structures drawn either directly using Internet browser or using ACD/ChemSketch, a powerful structure drawing tool.

Docking using AutoDock

AutoDock is a suite of automated docking tools. It is designed to predict how small molecules, such as substrates or drug candidates, bind to a receptor of known 3D structure. AutoDock actually consists of two main programs namely docking of the ligand to a set of grids describing the target protein, autogrid pre-calculates these grids. In addition to using them for docking, the atomic affinity grids can be visualized. This can help, for example, to guide organic synthetic chemists design better binders.

III. RESULTS AND DISCUSSION

Anti cancer activity of the exiting drug and natural compounds were compared based on the protein ligand interactions in the present study. The protein helix-loop-helix protein 23 (TCF21) which plays a main role in the disease lung cancer was taken as the target and the sequence was retrieved from NCBI. The related structure was found using BLAST similarity search of the sequence and the template (2QL2) which is solved by X-Ray diffraction method and sharing an identity of 49% with human helix-loop-helix protein 23 proteins. The protein basic helix-loop-helix protein 23 (TCF21) from *Homo sapiens* was modeled using modeler9v1. The model structure was validated using procheck and was found to have 96.1% of the amino acids in the most favoured region and a good quality model would be expected to have over 90% (Fig.1). Q- site finder recommends the active sites of protein basic helix-loop-

helix protein 23. Fig.2 shows the super imposed structute of modeled protein. Structure of the Modeled Protein basic helix-loop-helix protein 23 was shown in Fig.3. The docking analysis was performed using Autodock. The results could provide useful insight in to the protein drug interactions. The docking results should that the binding property of the ligand was found to be more effective and can form active inhibition the protein basic helix-loop-helix protein 23 (TCF21). The docking analysis were performed for the target protein with ligands namely Curcumin (Natural drug) Erlotinib (Synthetic drug). Curcumin showed good binding affinity towards the target protein with a good docking score -6.44, -5.69 and -5.51 respectively which has good interactions between protein and the ligand (Fig.4). Erlotinib shows an energy value -5.05 and -5.0 (Fig.5).

Curcumin is a polyphenolic compound derived from turmeric. Its ability to affect gene transcription and induce apoptosis in various animal models with particular relevance to cancer chemoprevention and chemotherapy patients is well documented [17]. Curcumin is a functionally labile molecule with the potential to modulate the biological activity of a number of target molecules either indirectly or directly by binding through different bonding interactions. Various biophysical tools have been employed to show direct interaction of curcumin with target proteins. Some of these studies have utilized molecular docking as a computational tool to study the mode and site of binding. Curcumin's ability to bind directly to diverse proteins with high affinity stems from its molecular structure and functionality [18]. Curcumin has been reported to be an effective drug by preventing emergence of chemoresistance and eliminating CSCs in breast, glioblastoma, pancreatic and colon cancer [19, 20]. Curcumin can be considered as a good lead compound in the development of new inhibitors of dihydrofolate reductase, which is a potential target of anti-cancer drugs was reported [21]. Protein-ligand interactions in the present investigation revealed that Curcumin is more effective in binding with protein helix-loop-helix protein 23 (TCF21) of *Homo sapiens*. This results show a Curcumin has more potential with no side effects when compared to Erolotinib to cure Non small cell lung cancer.

Table 1. Docking Results for natural and Synthetic drugs against protein basic helix-loop-helix protein 23

S.NO	COMPOUND NAME	BINDING ENERGY
1.	Curcumin	-6.44
		-5.69
		-5.51
2.	Erlotinib	-5.05
		-4.87
		4.60

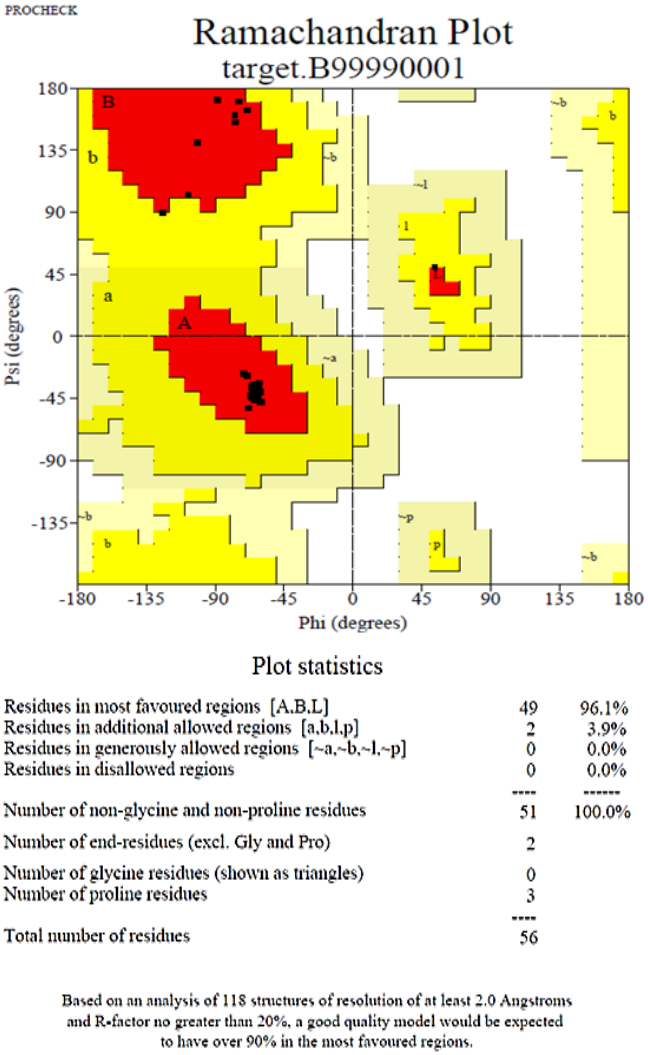

Figure 1. Ramachandran plot for the modeled protein

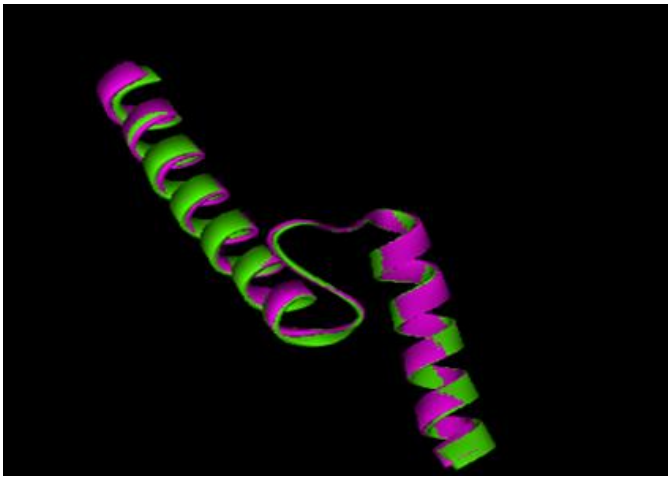

Figure 2. Superimposed Structure Protein basic helix-loop-helix protein 23

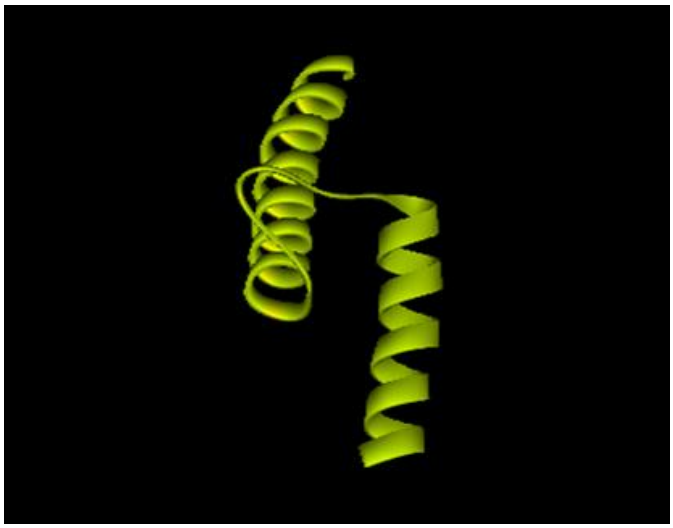

Figure 3. Structure of the Modeled Protein basic helix-loop-helix protein 23

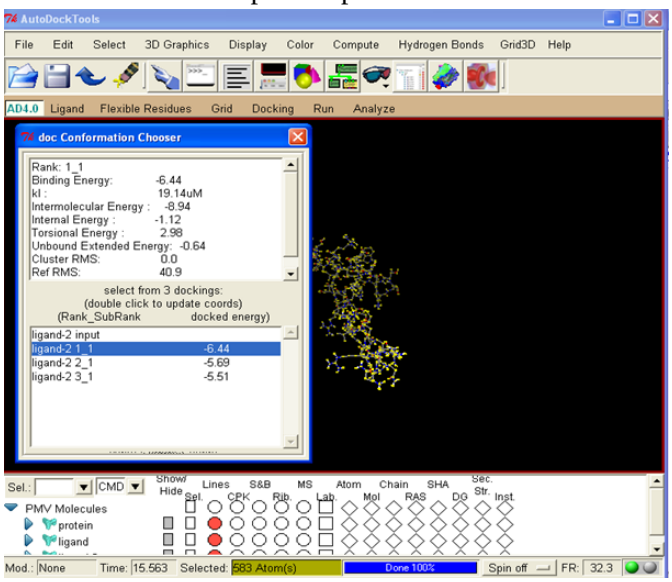

Figure 4. Energy Score of Curcumin (Turmeric)

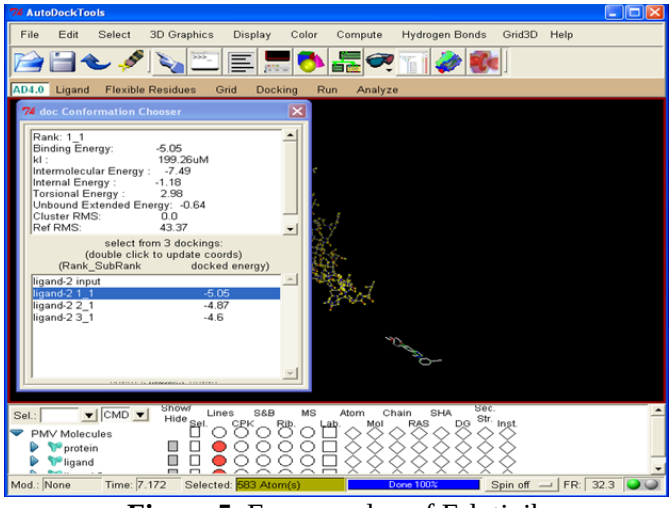

Figure 5. Energy value of Erlotinib

IV. CONCLUSION

In-silico experimentation modeling of lung cancer involved predictions from biological data with computer-based models to mimic biological system to have investigations based on entirely computer methods. In this paper, we have provided the concept of *in-silico* study and its importance in the field of providing the structures to enhance computational methodology. Protein-ligand interactions in the present investigation revealed that Curcumin is more effective in binding with protein helix-loop-helix protein 23 (TCF21) of *Homo sapiens*. Prediction of efficacy of protein-ligand interaction reduces the time and money spent on the scientific research. Further research works on these natural compounds can be extended to wet lab studies which can be proved as a novelled and efficient natural compound for the treatment of diseases.

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