Docking Studies On Phytochemical Derivatives As Tissue Transglutaminase-2 (TG2) Inhibitors Aganist Lung Cancer

Shivkumar B Madagi and Prachi P. Parvatikar.

***Abstract*— Lung cancer is one of the most threatening malignant cancers with a high metastatic rate and poor diagnosis. Tissue transglutaminase 2 (TG2) is a multidomain protein, which is up regulated in lung carcinoma and has been implicated in cancer progression and relapses. This study focuses on screening phytochemical drug for prediction of their good inhibitory activity aganist TG2 target. Total thirty drug target molecules were selected from class of phytochemicals; among the list of drug studies, six compounds showed suitable drug likeliness property. Binding efficiency of six compound was performed by PATCH dock server. Nobiletin and curcumin showed good activity compared to other. Interaction pattern analysis revealed that, Glu, Lys and Arg residues were involved in the hydrogen bond formation with drug.**

***Keywords*— Lung cancer, TG2, phytochemical, patchdock.**

I. INTRODUCTION

Lung cancer has become one of the remarkable threats to world healthcare, with death rate of one out of four mortality in both sexes. It is among one basis of cancer related deaths all over the world [1]. Globally lung cancer accounts for about 13% of new cancer cases and 19% fatality. In India, lung cancer accounts for 6.9% of new cases and 9.3% deaths in both men and women, it is the most common cause for cancer related death in men, and second most in women after breast and ovarian carcinoma [2]. Depending on tumour size and stages of lung cancer several therapeutic regimens are available for treatment of lung cancer. Yet current treatments like chemotherapy and radiation therapy are associated with several negative effects on the human. Inspite of the progress in development of several anticancer drugs, chemoresistance is still major obstacle that results in the failure of treatment [3]. Multiple factors are involved in development of chemoresistance such as inactivation of chemotherapy drug, alteration in tumor suppressor gene, anti and pro apoptotic proteins.

Understanding the moleculer role of tumor encoded gene in development of drug resistance has great significance in development of novel therapeutic target and also improve diagnosis[4].

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Tissue transglutaminase 2 (TG2) is one of ubiquitously expressed protein among the seven members of Tissue TG family. It is known to be involved in tumor metastasis [5]. It is distributed among major cell types and tissues and plays a significant role in several biological processes. It take part in post-translation modification transamidase activity it is involved in GTPase, ATPase, protein kinase, protein disulfide, and isomerase activity [6].

Overexpression of TG2 leads to various pathogencity such as Alzheimer's, Parkinson's disease, multiple sclerosis, celiac along with tumour development while over expression of TG2 is associated with malignant effects leading to tumorigenesis, invasion, cell differentiation, and failure in apoptosis [7]. As a consequence, TG2 is known to have a significant impact in lung carcinoma, especially towards non-small cell lung carcinoma [8]. Targeting TG2 protein may be valuable in identifying potential inhibitors against lung cancer. Numerous natural compounds have been reported to have many biological activities as antibacterial, antiviral and anti-cancer [9]. Natural products and their derivatives mimic over 50% of all the products that are being used. In current study, an attempt is made *in silico* investigation of natural inhibitors against TG2 from plant origin. The hit compounds obtained in this study could play an important role in designing personalized therapy against lung cancer patients.

II. METHODOLOGY

A. Retrieval of protein (Receptor) :

Co-crystallized structure of human TG2 protein was taken from RCSB protein data bank in .pdb format. Protein model with PDB I.D:4PYG was selected for further study(Fig.1). The retrieved protein structure was used for ligand docking.

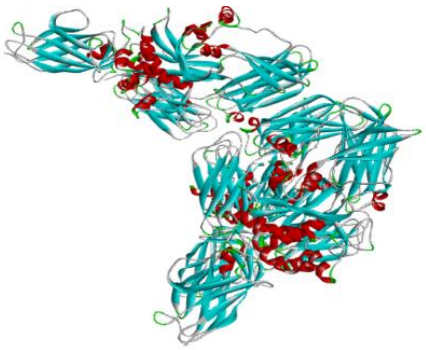

Fig 1. 3-D Structure of TG2 protein.

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B. Selection of ligands:

For present study natural origin drug from plants were selected. All compounds were reterived from NPACT [10] and pubchem database, in ".pdb" format. Properties and chemical structure of molecules are shown in (Table 1).

Table 1. Selected drug target for study.

Sl. No	Drug Name	Pubchem ID	Category
1.	Nobiletin	5280863	Flavonoid
2.	Curcumin	969516	Flavonoid
3	1,2,4-trihydroxynonadecane	10567452	Aliphatic natural
4	Artobiloxanthone	46887866	Flavonoid
5	4-Gingerol	5317596	Simple aromatic
6	3'-formyl-2',4',6'-trihydroxy-5'-methyldihydrochalcone	11033908	Flavonoid

A. ADME studies of compounds:

ADME study is essential and primary step of pharmacological drug screening. It includes properties of structural analogues, it predicts both physically significant descriptors and pharmaceutically relevant properties. It consists of principle descriptors and physiochemical properties with a detailed analysis of the log P (Octanol/Water), log S, molecular weight etc. It also calculate the analogues depending upon on Lipinski's rule of 5 (Lipinski 2001), which is important step for rational drug design. The properties were predicted using SWISS ADME tool [11].

A. Molecular docking studies:

Molecular docking studies and docking analysis was performed using Patchdock server. The server performs both protein-protein and protein- ligand docking. The PatchDock algorithm is based on shape complementarily principle [12]. The receptor and ligand surfaces are divided into concave, convex and flat surfaces and the complimentary patches are matched resulting in the possible complexes that are evaluated by a scoring function. The scoring function takes into account both geometric fit and atomic desolation energies. Analysis and visualization of interactions in docked complexes The binding interactions in the docked complexes obtained by Patchdock server were analyzed by Discovery studio visualizer[13].

III. RESULTS

A. Retrival of ligand :

The small molecular structures of 6 drug target molecule were retrieved in ".sdf" format from PubChem as well as NPACT database and then converted into ".pdb" format by using ViewerLite software (Fig 2).

B. ADMET studies of compounds

ADME analysis of six compounds predicted for Adsorption, Distribution, Metabolism and Excretion property by using SWISS ADME software. Allcompounds passes Lipinski rule of five. There is zero violation of rule shown by these molecules (Table 2). Hence these results may be used for generation of new drug targets against TG2.

C. Virtual screening and molecular docking:

Virtual screening by structure based drug designing (SBDD). It is crucial and essential to find out efficicacy of ligands by virtual screening carried out through molecular docking studies. Docking is process where two molecules fit together in 3D space. In present study Patchdock tool is used for molecular docking. This docking tool works on the basis of shape complementarily algorithm and calculates binding score of ligand with receptor. Molecular docking fits two molecules in favorable configuration using their topographical features. Practically molecular docking has been an important technique for the prediction of protein-ligand interactions and has been used in studies of the structural basis of biological functions. Binding interactions of all selected compounds and reference drug is shown in (Fig 3).

Binding scores of the compounds and reference molecules shows that all compounds showed interaction with receptor, Nobiletin is interacting with high binding energy of 6384 which is higher than the drug Curcumin showing 6290. These two compounds have high binding score compared with other drug molecule.(Table 3).

Table 3. Docking results of compounds with TG2.

Compounds	Interacting amino acids	Docking score	Area score
Nobiletin	Lys 54, GLU 47	6384	768.50
Curcumin	GLU 17,ASP 400, GLU 467	6290	741.50
1,2,4-trihydroxynonadecane	ARG 476, GLU 579, ARG 580,ILE 331.	5932	696.70
Artobiloxanthone	GLU400,VAL401,ALA391, LYS444,LYS464.	5850	741.50
4-Gingerol	ASP 405, GLU579,SER419, ARG 317,ASP581	5278	589
3'-formyl-2',4',6'-trihydroxy-5'-methyldihydrochalcone	LYS444, ILE416,SER 415,VAL422	5888	699

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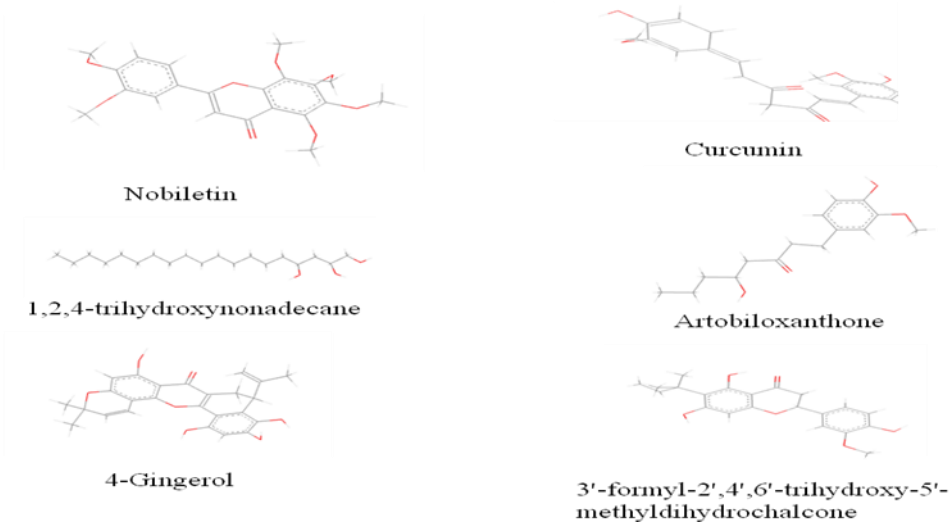

Fig 2. 3-D structure of selected drug target molecule.

Table 2. ADMET property of selected compound.

Sr No	Drug Name	Molecular Weight (g/mol)	HBond donar	Hbond acceptor	Lipinski Rule	Log P
1.	Nobiletin	402.39	0	8	Yes	3.96
2.	Curcumin	368.38	2	6	Yes	3.27
3.	1,2,4-trihydroxynonadecane	346.57	3	3	Yes	4.50
4.	Artobiloxanthone	434.44	4	7	Yes	3.49
5.	4-Gingerol	266.33	2	4	Yes	2.38
6.	3'-formyl-2',4',6'-trihydroxy-5'-methyldihydrochalcone	300.31	3	5	Yes	1.76

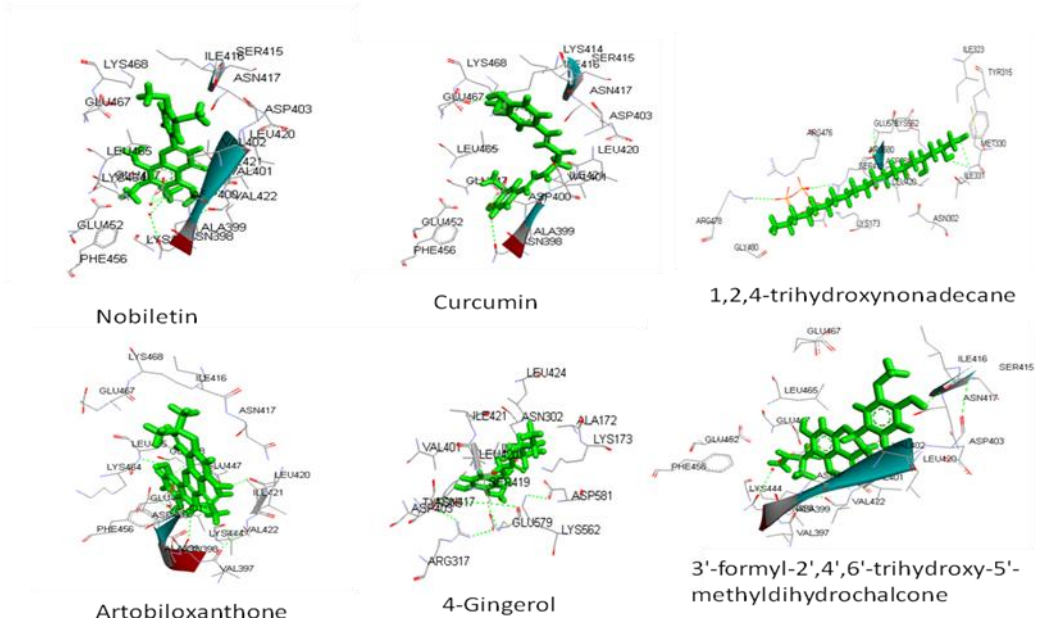

Fig 3. Docking interaction of receptor and ligands.

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IV. Conclusion

In this present, *in-silico* study various bioinformatics tools were used for docking the natural origin drug with the 3D structure of protein target tissue transglutaminase 2. The results of this study revealed that these phytochemicals molecules especially nobiletin and curcumin show potential inhibition of TG2 and thus can be implicated for treatment of lung cancer. The combined approach of ADME and docking used in this study, helps in expressing the binding affinity of drug on the target protein well and also validates as potential candidates for second generation drug target discovery. Development of effective and selective inhibitors of TG2 will make possible elucidation of TG2's role in a lung cancer, which may ultimately lead to effective clinical treatments against lung cancer. Further *in-vitro* studies could be undertaken to validate the present study.

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