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Molecular Docking of Phytochemicals Against Potential Drug Target in *Mycobacterium tuberculii*

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Abstract—*Tuberculosis still considered as one of the largest killer infectious disease , warranting the identification of newer targets and drugs. Identification and validation of applicable targets for designing drugs are critical steps in drug discovery, which are at present is the major bottle-neck. Computational approaches is powerful means of obtaining short- lists of potential targets and drugs for further experimental validation. In the present investigation , total of 30 targets proteins from Mycobacterium tuberculii have been screened. Many phytochemicals have been selected from different plants as a potential ligand. The Lipinski's screening was performed for all the phytochemical ligand to check its drug likeness. Based on Lipinski's filters analysis for drug likeness , 48 phytochemicals has been found to have drug like characteristics and these phytochemicals has been further considered for docking. In the present study a total of 1440 docking experiments were performed by considering each 30 potential drug target protein against 48 ligand using iGEMDOCK. Apigenin-7-O glucuronide gave the fitness value of –218.62 for 1LIE .We conclude that the ligand Apigenin-7-O glucuronide (CID6479876), the active compound of Ocimum sanctum (Tulasi) is effective in inhibiting the Mycobacterium tuberculosis. Hence Apigenin-7-O glucuronide can be selected for further analysis of ADME properties and the proceeding preclinical trials.*

1. INTRODUCTION

According to WHO reports , Tuberculosis (TB) is regarded as one of the most frequent infectious disease causing rapid increase in death and morbidity, thus affecting mostly young adults in their peak productive years[1,2] . *Mycobacterium tuberculosis* is the causative agent of tuberculosis and is considered to poses a serious threat to many tuberculosis control programmes worldwide[1,3] . One- third of the world's population is infected with *Mycobacterium tuberculosis* , accounting for 9.2 million new cases and about 1.7 million deaths in 2006. According to the research , there were 8.8 million new cases and 1.5 million deaths recorded in 2010 in developing countries[4]. Tuberculosis is among the top three , with HIV and malaria considered as leading causes of death from a single infectious agents , attributing to two million deaths annually[2] . Nowadays , many anti-tubercular drugs are available in market but due to the rapid emergence of multidrug-resistant TB (MDR-TB) , there is an immediate need to develop novel drugs to combat TB and new protocols to be implemented for efficacious clinical control of TB patients[5]. In the past decade , multidrug-resistant TB (MDR-TB) has been increasing predominantly in many areas , not only in developing countries but also affecting the industrialized countries as well[6]. Plant plays an eminent role in curing many diseases and offer a great hope as medication for past many centuries. Many plants have been investigated for their medicinal properties. They can be used as pure compounds or as a crude material[7]. Natural products including animals, plants and minerals have been the basis of treatment of human ailments[8]. India is among the few countries in world which has the unique diversity of medicinal plants and vast traditional knowledge of use of herbal medicine for curing various diseases. In India , the art of herbal healing has very deep roots in tribal culture and folklore. Medicinal plants have been used extensively as a source of medicine and many effective medicines such as atropine , aspirin , reserpine, morphine , digitoxin and ephedrine were developed from natural products[9]. The widespread use of herbal remedies and health care , as described in ancient texts have gained a wide acceptance over the years and is widely wide in formulation of novel drugs[10] . Anti-tubercular drugs available have several shortcomings despite having immense value in controlling the disease. So there is a need to develop novel drugs to cure TB. Identification and validation of applicable targets for designing drugs pave a way to drug discovery. Traditional drug discovery is considered to be laborious , time consuming and expensive experiments , thus sometimes resulting in very few drug targets. On the other hand , computational approaches has emerged as an attractive alternate way to identify potential drug targets, thus accelerating the drug discovery process in comparatively less time with more efficacy providing better treatment options and less drug failure rate during further clinical trails. . Current computational target discovery approaches include identification of pathogen-specific essential genes, host-pathogen interaction factors, proteins involved in persistence, chokepoint enzymes, resistance genes/resistance-associated proteins; characterization of pathogen-specific metabolic

pathways; prediction of gene expression levels etc[11-15]. The broad aim of the present study is to investigate and screen the phytochemical as possible drug candidate against potential therapeutic targets in *Mycobacterium tuberculii* and performing docking to find out ligand as a potential drug.

2. MATERIAL AND METHOD

2.1. Mining and screening of the potential protein drug targets

The potential targets for the present study are being identified . Proteins critical for the survival of *M.tuberculosis* are first identified , shortlisted targets have been further explored and targets that address mycobacterial persistence and drug resistance mechanism are also analysed . The crystal structure of the possible targets in *Mycobacterium tuberculii* has been obtained from RCSB Protein Data Bank under Brookhaven National Laboratories (BNL) (http://www.pdb.org).

2.2. Mining and preparation of ligand

The phytochemical molecules have been retrieved from from Pubchem and TIPdb (Taiwan Indigenous Plant databases) databases. The database, TIPdb is composed of a standardized format of published anticancer, antiplatelet, and antituberculosis phytochemicals from indigenous plants in Taiwan

2.3. Open babel

We have used open babel for converting sdf files into mol2 format of ligands as per the requirement of the iGEMDOCK software.

2.4. Lipinski screening

This screening methodology was implemented to analyze the Drug likeness of the proposed ligand. Lipinski's rule of 5 is an essential screening methodology for rational drug design . The ligand of the present study has well qualified in Lipinski's filter.

2.5. Docking

Molecular docking approaches are most commonly used in modern drug design in order to understand the three dimensional structure of the protein- ligand composite. The docking tool used in the present study is iGEMDOCK. The tool was developed by Jinn-Moon Yang, a professor of the Institute of Bioinformatics, National Chiao Tung University. It is a graphical automatic drug discovery system used for integrating docking, screening, post-analysis, and Generic Evolutionary Method for molecular docking.

3. RESULT AND DISCUSSION

A total of 30 targets proteins from *Mycobacterium tuberculii* have been screened through undergoing various research publications for finding out potential therapeutic target. Phytochemicals considered as a potential ligand have been selected from various medicinal plants whose anti-tubercular properties have been reported in various books , journals , databases and research papers. The phytochemicals are then screened for their drug-likeness characteristics by using Lipinski's rule of five , which resulted in total of 48 phytochemicals having a drug-likeness characteristics and were further considered for docking. A total 1440 docking experiments were done using iGEMDOCK. The selected target proteins have the properties to be considered as potential drug target for inhibiting *Mycobacterium tuberculii.* Apigenin-7-O glucuronide (CID6479876), the active compound of *Ocimum sanctum(Tulasi)* gave the highest fitness value for all the target proteins and the best fitness value of –218.62 was observed for 1LIE . It can be concluded that Apigenin-7-O glucuronide is effective against all the targets. Representing the fitness value in negative, which shows the formation of stable complex molecule between the ligand and target protein. 1LIE is involved in mycolic acid biosynthesis has also been shown to be a requirement for long-term mycobacterial persistence and virulence in mice model of tubercular infection.

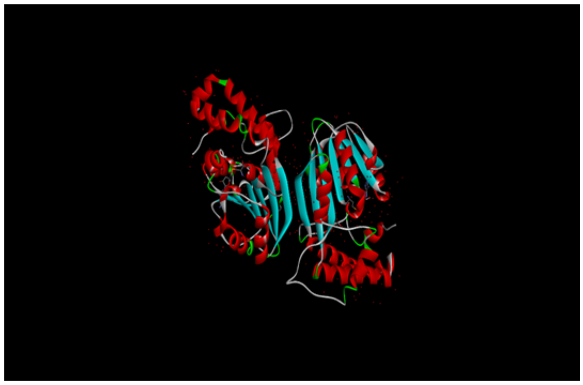

Fig. 1: Structure of 1LIE

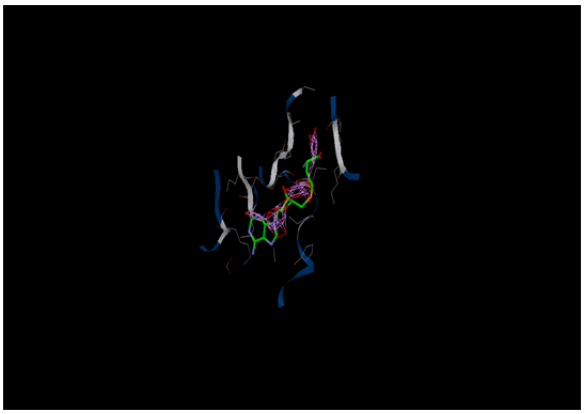

Fig. 2: CID6479876 is docked with 1LIE

Table 1: Fitness value of ligand CID6479876 in different targets

TARGET ID.	LIGAND ID NO.	ENERGY
1B1B	CID6479876	-168.92
1HKV	CID6479876	-205.6
1HZP	CID6479876	-179.24
1KLP	CID6479876	-155.9
1LIE	CID6479876	-218.62
1O6Y	CID6479876	-184.86
1SR9	CID6479876	-161.6
1SUR	CID6479876	-194.5
1YL5	CID6479876	-145.88
1ZAO	CID6479876	-178.16
1ZLJ	CID6479876	-135.31
1ZVW	CID6479876	-137.02
2GES	CID6479876	-145.3
2GWR	CID6479876	-139.72
2PZI	CID6479876	-148.95
2W3F	CID6479876	-194.66
2WGS	CID6479876	-176.22
2XWN	CID6479876	-207
2COY	CID6479876	-214.09
3OEY	CID6479876	-177.79
4B6C	CID6479876	-189.05
1F8M	CID6479876	-167.17
1OYO	CID6479876	-157.7
3G5F	CID6479876	-183.31
3ILW	CID6479876	-141.68
4KBJ	CID6479876	-181.02
4KNE	CID6479876	-156.93
1F8I	CID6479876	-149.13
3QBE	CID6479876	-167.72
1FX7	CID6479876	-154.49

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