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IN SILICO ANALYSIS OF MEDICINAL PLANTS AGAINST *MYCOBACTERIUM TUBERCULOSIS* (MTB)

R. Sathish Kumar[1]* and V.Sankaravel[2]

[1]Assistant Professor, Department of Botany, PSG College of Arts & Science, Coimbatore, Tamilnadu, India
[2]Department of Botany, PSG College of Arts & Science, Coimbatore, Tamilnadu, India.

***Corresponding Author Email: sathishbioinf@gmail.com**

ABSTRACT

Tuberculosis (TB) is a deadly infectious disease caused by the Mycobacterium tuberculosis (MTB). Tuberculosis mostly affects the lungs at later stages it also affects other organs. The protein epoxide hydrolase plays a major role in drug metabolism as well as signal processing molecule and therefore has been targeted in the present study. The medicinal plants being a solution for several human ailments, also act as a reservoir for secondary metabolites, has taken its credit as a cure from our ancient times. The compounds reported earlier in the plants Solanum torvum, Piper longum, Morinda citrifolia, Cocos nucifera, Dissotis rotundifolia, Curcuma longa, Aloe vera, Ocimum basillicum, Centella asiatica and Dipterocarpus sublamelatous were analyzed for its possible significant interaction with the target protein using molecular docking studies.The compounds from the plants Solanum torvum, Piper longum, Morinda citrifolia, Cocos nucifera, Dissotis rotundifolia, Curcuma longa, Aloe vera, Ocimum basillicum, Centella asiatica and Dipterocarpus sublamelatous were analyzed using the molecular docking studies ADME-properties, drug-likeness using the Schrodinger software.The docking results were observed which indicated that the compound catechin scored significant G.score of -8.74 Kcal/mol among the other compounds tested. The interactions were observed with amino acid residue tyrosine at two different positions 164 and 272, each of bond length of 2.1Å. The compound Catechin had significant interaction with the target protein, could be further analyzed for stability using molecular dynamics study and in vitro. The future perspective of the study is to determine the stability of the protein-compound complex through dynamics studies.

KEY WORDS

Mycobacterium tuberculosis, Medicinal Plants, in silico docking analysis, ADME-Toxicity, Epoxide Hydrolase B, catechin.

INTRODUCTION:

In the present era, everyone is aware of the infection tuberculosis (TB), caused by the *Mycobacterium tuberculosis*. Tuberculosis is a widespread, air borne infectious disease affects different parts of the body in later stages and finally leads to death (Sharma and Mohan in 2004). Symptoms of TB includes a persistent cough**,** fatigue, chest Pain or pain with breathing or coughing, weight loss, fever, night sweats, loss of appetite, etc. (Narwadiya *et al*., 2011). The two stages of TB are latent and active. In the former stage, bacteria remain inactive that is not contagious with nil symptoms. It is also known as latent TB and become active in favorable time, but it can become active. This phase can last for a very long time even decades. The TB bacteria that cause some symptoms and which can be transmitted to others (contagious) is known as Active TB. In this TB the microorganisms are reproduced and spreads from organ to organ and causes tissue damage.

In additional to the Active TB there is another type Miliary TB which passes through blood streams.

The prime intricacy of global effort to eradicate TB is the spread of multidrug-resistant (MDR) TB and extensively drug-resistant (XDR). Addition to that adequate and accurate diagnosis method for TB is still lacking (Tessema *et al*., 2017). So far, interferon-gamma release assays (IGRAs) and tuberculin skin test (TST) was the effective diagnosis for latent tuberculosis (LTBI) where both measure the response of T cells to TB antigens (Cruz-Knight et al., 2014; Anderson and Woodsworth, 2014). About 85% of MDR TB cases were reported in India, including other 27 countries worldwide (WHO, 2014; Tessema *et al*., 2017). Fogel, (2015) has reviewed and explained clearly the epidemiology, infection, treatment and diagnosis methods in detail about TB.

Treatments are based on an individual's probability of risk either the latent or active stage of infection (Fogel, 2015). Treatment includes the drug cocktail regimen as mentioned by Centers for Disease Control and Prevention (CDC) where the following drugs are used for chemotherapy, Isoniazid (INH), rifampin (RIF), pyraznamide (PZA), ethambutol (EMB) and streptomycin (SM) (Goldman and Schafer, 2011; Cruz-Knight et al., 2014). Though BCG vaccination has successful efforts to prevent MTB, it is evident for the need of a better vaccine due to its limited effect against adult (Thillai *et al*., 2014). Moreover, the capability of organism for fast and spontaneous mutation lead to the complexity called multiple drug resistance. WHO has reported that 17% of new resistance varieties from 2002 to 2007, especially for INH and RIF (WHO, 2014). Annual mortality rate also increases where most cases found in India, China and Russia according to 2013 report (WHO, 2014). In recent years, Cambodia shows evidence of reduction in TB prevalence by about 50%, whereas in India, the dropping rate is slow (WHO, 2014). Strategies like DOTS (Directly Observed Therapy Short-term), DOTS-Plus and Stop TB Strategy put forth to prevent and eradicate TB are aimed to be implemented at both local and national scales (WHO, 2014).

According to WHO, most of the developing and developed countries believe on herbal products for its medicinal availability, based on this methodology the following plants are used for the treatment of Tuberculosis *Solanum torvum* (Solanaceae), *Piper longum* (Piperaceae), *Morinda citrifolia* (Rubiaceae), *Cocos nucifera* (Arecaceae), *Dissotis rotundifolia* (Melastomataceae), *Curcuma longa* (Zingiberaceae), *Aloe vera* (Asphodelaceae), *Ocimum basillicum* (Lamiaceae), *Centella asiatica* (Apiaceae), *Dipterocarpus sublamelatous* (Diptreocarpaceae).

MATERIALS AND METHODOLOGY:

The 3D protein structure for Epoxide hydrolase B of *Mycobacterium tuberculosis* was retrieved from the Protein Data Bank database (PDB ID: 2ZJF) (https://www.rcsb.org/pdb/home/home.do). Active site region was predicted using LigSite online tool (http://projects.biotec.tu-dresden.de/pocket/). The chemical compounds from the mentioned plants were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The ADME properties were analyzed for the compounds to test its drug-likeness using QikProp, a Schrodinger module. Finally only chemical compounds exhibiting drug-likeness was taken to account for docking studies using Glide module. The interactions were observed using PyMol software.

RESULT AND DISSCUSSION:

The compounds were first subjected for analyzing Absorption, Distribution, Metabolism and Excretion properties. Prior ADME profiling of small molecules has significant contribution in the field of drug discovery by having impact on cost, labor-demand and duration (Jianling and Laszlo, 2004). Along with, the lipophilicity is calculated to determine the range of solubility and permeability of the molecule in octanol/water partition coefficient, brain/blood barrier in order to understand the transport mechanism. In the present study, palmitic acid alone violated Lipinski's rule of five, where the logP value was observed as 5.3 exceeding the limit of 5. Lipinski's rule of five otherwise called Pfizer's rule of five or rule of thumb to evaluate drug likeness indicates the following properties like molecular weight, octanol/water partition coefficient, hydrogen bond donor and acceptor. Since the rule has a limits in multiples of five, the name has been given as rule of five. Apart from the above properties, additional parameters such as surface area in square Armstrong (polar surface area, PSA), brain/blood barrier and percentage of human oral absorption were also predicted. It was observed that all the molecules shown in table 1 has values within the respective range mentioned, the

others were omitted (data not shown) and further were taken for docking analysis.

The results of docking studies were recorded (Table 2) and found the compound catechin from the plant *Solanum torvum* of Glide score (G.score) -8.74 Kcal/mol. The interactions were viewed in Pymol software and shown in figure 1. The interactions were observed with Tyr residue at the position 164 and 272, each with a bond length of 2.1Å. The compounds indole-3-butyric acid and ferulic acid also had G.score of -8.57 and -8.13 Kcal/mol, respectively. Caffeic acid, gallic acid and p-coumaric acid all had G.score in the range of -7Kcal/mol. Apart from Tyr164 and Tyr272, the residue Asp104 observed to interact with the plant compounds. Further, the interactions of plant compounds with the target would compared to the presently available drug molecule, in order to study its potency. As well as the simulation studies would provide an insight about the stability of protein-compound complex.

Table 1.1: **Analysis of ADME Properties for the Plant Compounds using QikProp**

Molecule Name	Rotatable bonds	Molecular Weight (Da)	Donor Hydrogen Bonds	Acceptor Hydrogen Bonds	Octanol / Water partition coefficient	Surface area in square Armstrong	Brain/Blood partition coefficient	Percent Human Oral Absorption	Rule of Five
Normal Range	**0 - 15**	**130 - 725**	**0 - 6**	**2 - 20**	**-2.0 - 6.5**	**300 - 1000**	**-3.0 - 1.2**	**(<25% is poor) (>80% is high)**	**Max .4**
Caffeic acid	5	180	3	4	0.6	393	-1.6	54	0
Camphor	0	152	0	2	1.9	361	0.3	100	0
Carvone	1	150	0	2	2.2	393	0.1	100	0
Catechin	5	290	5	6	0.5	510	-1.8	61	0
Curcumin	12	368	2	7	2.9	702	-2.1	85	0
Deconoic acid	8	172	1	2	3.0	479	-0.9	87	0
Ellagic acid	4	302	4	8	-1.3	447	-2.3	35	0
Fenchone	0	152	0	2	2.1	370	0.3	100	0
Ferulic acid	5	194	2	4	1.4	420	-1.2	67	0
Gallic acid	4	170	4	4	-0.6	342	-1.7	41	0
Indole-3-butyric acid	4	203	2	2	2.7	449	-0.9	80	0
l-arabinose	4	150	4	9	-1.7	303	-0.9	58	0
l-ascoric acid	6	176	4	8	-1.9	338	-1.7	45	0
Methyl succinic acid	3	132	2	4	-0.3	315	-1.0	43	0
Methyl tridecanoate	11	228	0	2	4.6	628	-0.8	100	0
Naringenin	3	272	2	4	1.7	502	-1.4	74	0
Octanoic acid	6	144	1	2	2.6	413	-0.7	85	0
p-coumaric acid	4	164	2	3	1.4	386	-1.1	67	0
Palmitic acid	14	256	1	2	5.3	677	-1.5	88	1
Pellitorine	9	223	1	3	4.1	594	-0.4	100	0
Pterostilbene	6	256	1	2	4.0	532	-0.3	100	0

Table 2: Docking of compounds from plants with epoxide hydrolase B of *Mycobacterium tuberculosis*

S. No.	Medicinal plants	Name of the ligand / PubChem ID	Glide score (Kcal/mol)	Residues Interaction	Bond length (Å)	No of Bonds
1	*Solanum torvum*	Catechin/ 9064	-8.74	TYR - 164 (O-H) TYR - 272 (H-O)	2.1 2.1	2
2	*Cocos nucifera*	Indole-3-butyric acid / 8617	-8.57	TYR - 164 (O-H) TYR - 272 (O-H) ASP - 104 (H-O)	2.0 2.3 2.3	3
3	*Aloe vera*	Ferulic acid/ 445858	-8.13	TYR - 164 (O-H) TYR - 164 (O-H) TYR - 272 (O-H)	2.1 2.4 2.0	3
4	*Solanum torvum*	Caffeic acid/ 689043	-7.94	TYR - 272 (O-H) TYR - 272 (O-H) TYR - 164 (O-H) ASP - 104 (H-O)	2.3 1.8 2.1	3
5	*Solanum torvum*	Gallic acid / 370	-7.50	ASP - 104 (H-O) ASP - 104 (H-O) TYR - 272 (O-H) TYR - 164 (O-H)	1.6 2.1 1.7	3
6	*Curcuma longa*	p-Coumaric acid / 637542	-7.41	TYR - 164 (O-H) TYR - 272 (O-H) ASP - 104 (H-O)	1.9 2.1 2.4	3
7	*Centella asiatica*	Naringenin/ 932	-6.32	TYR - 164 (O-H) TYR - 272 (O-H)	2.1 2.1	2
8	*Curcuma longa*	Octanic acid/ 379	-5.90	TYR - 164 (O-H) TYR - 272 (O-H)	2 2.1	2
9	*Ocimum basilicum*	Fenchone/ 14525	-5.11	TYR - 164 (O-H)	2.1	1
10	*Curcuma longa*	Camphor/ 2537	-5.01	TYR -164 (O-H)	2.2	1
11	*Curcuma longa*	l-arabinose/ 439195	-4.92	TYR - 164 (O-H) TYR - 272 (O-H) ASP - 104 (O-H)	1.9 2 1.7	3
12	*Dipterocarpus sublamelatus*	Pterostilbene / 5281727	-4.91	TYR - 164 (O-H) TYR - 272 (O-H)	2.0 2.2	2
13	*Moringa citrifollia*	Deconoic acid/ 2969	-4.89	TYR - 164 (O-H) TYR - 272 (O-H) TYR - 272 (O-H) ASP - 104 (H-O) ASP - 104 (H-O)	1.9 2.3 2.6 2.2 2.8	5
14	*Ocimum basilicum*	Carvone/ 439570	-4.66	TYR - 164 (O-H) TYR - 272 (O-H)	1.6 2.1	2
15	*Dissotic rotuntifolia*	Ellagic acid / 5281855	-4.62	TYR - 272 (O-H) TYR - 272 (O-H)	2.2 1.9	2
16	*Curcuma longa*	l-ascorbic acid / 54670067	-4.38	TYR - 164 (O-H) TYR - 272 (O-H) ASP - 104 (H-O) ASP - 104 (H-O)	2.4 2.5 2.0 1.9	4
17	*Aloe vera*	Methyl succinic acid / 10349	-4.09	ASP - 104 (H-O) ASP - 104 (H-O) TYR - 164 (O-H) TYR - 272 (O-H)	2.1 1.7 1.8 2.1	4
18	*Piper longum*	Pellitorine/ 5318516	-3.95	ASP - 104 (H-O) TYR - 164 (O-H)	2.2 2.5	2
19	*Curcuma longa*	Curcumin / 969516	-3.84	TRP - 105 (O-H)	2.5	1
20	*Aloe vera*	Methyl tridecanoate / 15608	-2.88	TYR - 272 (O-H)	1.7	1
21	*Aloe vera*	Palmitic acid / 985	-2.59	ASP - 104 (H-O)	2.2	1

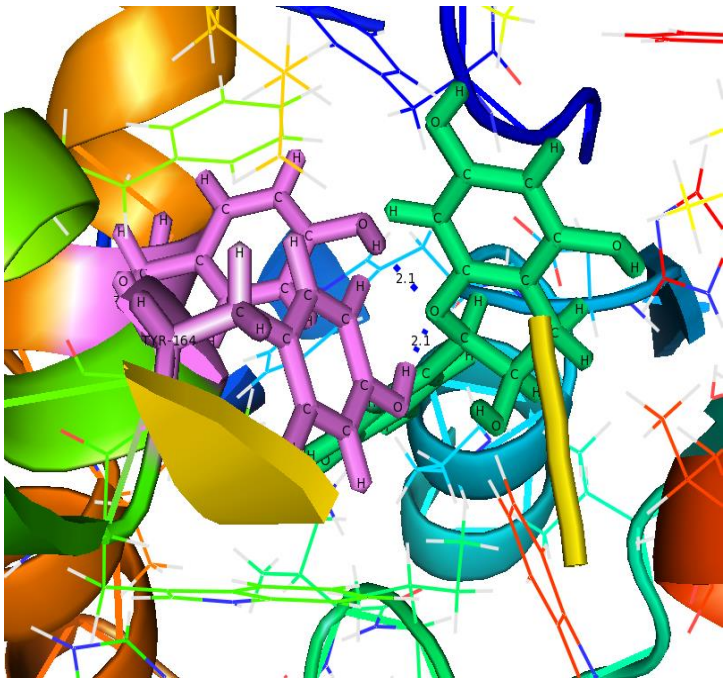

Fig. 1: Interaction of compound catechin with Epoxide Hydrolase B

CONCLUSION:

The chemical compound Catechin had significant G.score value and interactions with active site residues Tyr164 and Tyr272. Among the several compounds retrieved from the plants *Solanum torvum, Piper longum, Morinda citrifolia, Cocos nucifera, Dissotis rotundifolia, Curcuma longa, Aloe vera, Ocimum basillicum, Centella asiatica, Dipterocarpus sublamelatous*, only 25 showed drug-likeness in the ADME studies. The plant compounds should be explored more in order to identify an efficient and potential drug molecule.

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***Corresponding Author:**
R. Sathish Kumar*
Email: sathishbioinf@gmail.com