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Research Article

DOCKING STUDY ON MYCOBACTERIUM TUBERCULOSIS WITH PHYTOCHEMICALS OF ACALYPHA INDICA

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ABSTRACT

Considering the world- wide TB issues, there is an earnest need to develop moderately economical new medications to treat this destructive infection. Natural products isolated from plants have assumed a vital part in revelation of medications against irresistible ailments. In the present study, thirty ligand molecules which were present in the plant Acalypha indica were docked with the selected target proteins of Mycobacterium viz. 4RHU, 1W30, 2A7S, 1N2B, 1F0N. Among them Potassium Brevifolincarboxylate had a significant inhibitory activity with 1N2B protein forming bonds at a very low energy value, thus forming a stable complex. The other active compounds were found to be beta-Glucogallin and Caffeic Acid. The active substances from the extracts of Acalypha indica which exhibited promising activities is reported for the first time. These can serve as promising candidates to develop new drugs to combat M. tuberculosis.

INTRODUCTION

Microbial diseases are a developing issue in contemporary drug, yet just a couple of antimicrobial agents are utilized as a part of clinical practice. Mycobacterium tuberculosis (MTB) is a pathogenic bacterial species in the genus Mycobacterium and the causative agent of most instances of tuberculosis (Ryan K.J. *et al*., 2004). Tuberculosis (TB), a lung contamination and is one of the infectious and dangerous maladies which have added to the troubles of the humankind. The primary explanation behind across the board of this sickness is the populace development, rise of multi- drug resistant TB strains, budgetary weight in the growing nations and unsuccessful endeavor to orchestrate another medication with novel component of activity. Albeit one conceivable long haul answer for the issue is a superior immunization, for the time being, the significant dependence will be on chemotherapy (Tomioka H. *et al*., 2006) requiring the improvement of novel, viable and non- poisonous antitubercular agents (Berning, S.E., 2001; Reddy, V.M. *et al*., 1996 ; Barry C.E., 1997). The genome of M. tuberculosis encodes for around 4000 proteins (Cole ST *et al*., 1998). In this way, determination of a protein as a medication target is urgent for sedate disclosure for TB. Broad research, including bioinformatics based investigations has been completed to distinguish and organize tranquilize focuses for TB (Agüero F *et al*., 2008; Sundaramurthi JC *et al*., 2011).

Pantothenate (vitamin B5) is a basic forerunner for the biosynthesis of coenzyme A (CoA) and acyl bearer proteins (ACP). Since both CoA and ACPare basic in fattyacid biosynthesis that plays a key role in tenacious development and pathogenicity of MTB, pantothenate synthetase is a proper focus for creating new drugs against TB, and this comes under the classification of Ligase - an enzyme which joins two molecules (Wang S *et al*., 2003). Another potential target is hypoxanthine-guanine phosphoribosyltransferase (MtHGPRT), a key enzyme (transferase) of the purine salvage pathway (Wai Soon Eng *et al*., 2015). The Mycobacterium tuberculosis pyrR gene (Rv1379) encodes a protein that manages the expression of pyrimidine-nucleotide biosynthesis (pyr) genes in an UMP-dependent way. Since pyrimidine biosynthesis is a fundamental step in the progression of TB, the gene pyrR is an appealing antitubercular target, and this is an example of transferase (K. A. Kantardjieff *et al*., 2005). The Mycobacterium tuberculosis 30 kDa major secretory protein (antigen 85B) is the most copious protein sent out by M. tuberculosis, and in addition an intense immunoprotective antigen and a main medication target. A mycolyl transferase of 285 buildups, which is firmly identified with two other mycolyl transferases, each of molecular mass 32 kDa: antigen 85A and antigen 85C. All the three catalyze exchange of the fattyacid mycolate from one trehalose monomycolate then onto the next, bringing about trehalose dimycolate and free trehalose, in this way fabricating the bacterial cellwall, this

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transferase is expressed in the acid-fast bacterial species Mycobacterium smegmatis of the genus Mycobacterium (Daniel H.Anderson *et al*., 2001). Mycolic acids and multimethyl-branched fattyacid are discovered exceptionally in the cell envelope of pathogenic mycobacteria. These uncommonly long fattyacids are basic for the survival, virulence, and antibiotic resistance of Mycobacterium tuberculosis. Acyl-CoA carboxylases (ACCases) commit acyl-CoAs to the biosynthesis of these special fattyacids. Past investigations demonstrate that AccD5 is imperative for cell envelope lipid biosynthesis and that its interruption prompts pathogen passing; this also comes under the classification of ligase (Ting-Wan Lin *et al*., 2006). Vitality of protein for the pathogen and absence of homolog in eukaryotes are normally utilized criteria for drug target determination.

Acalypha indica is a traditional plant, understood by more established ages in numerous nations, especially in Asia and Africa. It develops well in many parts of upper east, west, and south of Africa including Ethiopia, Somalia and different areas (Aboubaker D. *et al*, 2013). Most worldwide manuscript on Acalypha indica were distributed from Indian region since this plant has a nearby association with Ayurveda (Lingaraju D. *et al*., 2013). Acalypha indica has been utilized by individuals in India to treat any sickness identified with the breathing framework (Jayaprakasam, R. *et al*., 2013). Gupta *et al*. conducted an experiment with several tuberculosis bacteria using an aqueous extract of Acalypha indica. As a result, the mycobacterium tuberculosis H37Rv and two multi-drug resistance mycobacterium tuberculosis isolates were hindered by aqueous extract of Acalypha indica (Gupta R. *et al*., 2010).

In molecular modeling, docking is a method which predicts the favoured orientation of one molecule to a second when bound to each other to form a stable complex. Knowledge of the favoured orientation in turn may be used to predict the strength of association or binding affinity between two molecules using for example scoring functions (Ewing T. *et al*., 2001; Bursulaya B. *et al*., 2003). Molecular docking algorithms fit molecules together in complementary fashions. The method has pulled in expanding consideration as an approach to foresee the geometries of bimolecular complexes (Irawin D. Kuntz *et al*., 1994). The present study has been carried out to report for the first time the efficiency of the naturally occurring compounds of the plant Acalypha indica against tuberculosis 4RHU, 1W30, 2A7S, 1N2B, 1F0N proteins using MOLECULAR DOCKING STUDIES with the objective to find antitubercular compounds.

MATERIALS AND METHODS

Preparation of Protein

Crystal structure of the target proteins were obtained from RCSB Protein Data Bank (PDB ID's : 4RHU, 1W30, 2A7S, 1N2B, 1F0N). The Proteins were automatically imported to the Schrödinger working interface. The unprepared protein was then subjected to alteration under the command Protein Preparation Wizard which was used to preprocess, erase the other chains of protein, advance all; the water particles that were as a team with the chains were additionally erased. At last metal binding states were produced and eventually protein structure was subjected to optimization and minimization. In the wake of experiencing every one of these means last protein was prepared for docking (Friesner R.A. *et al*., 2004; Friesner R.A. *et al*., 2006).

Ramachandran Plot

The Ramachandran Screen panel shows a graph of the dihedral angles φ and ψ for each residue in the protein that is displayed in the working area. The graph area shows a graph of protein dihedral for all residues in the protein. The red portion corresponds to the core which represents the most favorable combinations. Ideally, ninety percentage of residue should be in this region. The evaluated structure of the prepared proteins had the maximum residues in the central region. This showed that the alterations made had not aggravated the protein structure (Harsh Barua *et al*., 2017). (Results not Shown).

Ligand Preparation

Thirty phytochemicals present in Acalypha indica were selected to find out the inhibitory activity towards target proteins. Structure of the phytochemicals and 5 first line oral drugs recommended by WHO were downloaded from pubchem in the (.sdf) format. These ligands were subjected to ligand preparation using the ligand preparation wizard (Ligprep) of Schrödinger software in the Maestro interface. Ionization states were generated for the structures. The low energy conformation Ligprep ligands were used for the Docking analysis.

Docking Studies

The compounds were screened by Schrödinger docking software to study the inhibitors of target proteins. Grid generation was done. The rigid receptor docking using the Glide program was carried out against the target protein with the set of ligands. The mode of docking was selected as XP (Extra precision) for a high docking accuracy. The glide docking was carried out for the minimised proteins.

ADME & Toxicity studies

Almost 40% of drug candidates fail clinical trials due to the poor properties of ADME (absorption, distribution, metabolism and excretion). These late failures contribute significantly to the rapid increase in costs of developing new drugs. The ability to promptly identify problematic applicants can drastically reduce the amount of time and resources wasted and simplify the overall development process. Precisely predicting ADME properties prior to costly experimental procedures such as HTS can eliminate unnecessary tests; The ADME prediction can also be used to focus lead optimization efforts to improve the desired properties of a given compound. Finally, the incorporation of ADME predictions as part of the development process can generate lead compounds that are more likely to exhibit satisfactory ADME yields during clinical trials. QikProp provides the widest variety of pharmaceutically relevant properties: log octanol / water and water / gas Ps, log S, log BB, overall CNS activity, permeability of Caco-2 and MDCK cells, log Khsa for human serum albumin binding and access IC50 for HERG block of the K + channel - for decisions concerning the suitability of a molecule can be based on a complete analysis. QikProp bases its predictions on the complete 3D molecular structure; Unlike fragment approaches, QikProp can provide equally accurate results in predicting objects from molecules with new scaffolds as well-known drug analogs (QikProp, Schrödinger, LLC, New York, NY, 2015).

RESULTS

Table 1 Phytochemicals in Acalypha indica having good docking results with target protein (PDB ID: 1N2B)

Protein	Chain	PubChem CID	Name	Glide Score	Stars
1N2B	A	101933031	Potassium Brevifolincarboxylate	-12.145	1
		689043	Caffeic Acid	-11.221	0
		445858	Ferulic Acid	-10.513	0
		54678492	COUMARIN, 3,3'-(o-Chlorobenzylidene) BIS(4-HYDROXY-	-10.050	1
		370	Gallic Acid	-9.667	0
		124021	beta-Glucogallin	-9.506	4
		14052	Ethambutol*	-5.572	3
	B	101933031	Potassium Brevifolincarboxylate	-12.597	1
		49787014	Acalyphin	-11.098	1
		689043	Caffeic Acid	-10.710	0
		445858	Ferulic Acid	-10.495	0
		10742	Syringic Acid	-10.411	0
		1046	Pyrazinamide*	-3.768	3

* Indicates First line oral drugs recommended by WHO

Table 2 Phytochemicals in Acalypha indica having good docking results with target protein (PDB ID: 4RHU)

Protein	Chain	PubChem CID	Name	Glide Score	Stars
4RHU	A	5280343	Quercetin	-9.980	0
		124021	beta-Glucogallin	-9.572	4
		439246	Naringenin	-8.862	0
		72281	Hesperetin	-8.851	0
		49787014	Acalyphin	-8.686	1
		6323490	Rifabutin*	-5.389	-
	B	49787014	Acalyphin	-10.800	1
		689043	Caffeic Acid	-9.906	0
		185904	Aurantiamide	-9.722	1
		124021	beta-Glucogallin	-9.631	4
		445858	Ferulic Acid	-9.589	0
		6323490	Rifabutin*	-8.084	-
	C	124021	beta-Glucogallin	-10.846	4
		49787014	Acalyphin	-9.140	1
		3082704	3,7,8-Tri-O-methylellagic acid 4-glucoside	-9.051	0
		101933031	Potassium Brevifolincarboxylate	-8.709	1
		5280343	Quercetin	-8.481	0
		14052	Ethambutol*	-8.635	3
	D	124021	beta-Glucogallin	-8.148	4
		14052	Ethambutol*	-5.653	3
		124021	beta-Glucogallin	-12.180	4
		370	Gallic Acid	-10.275	0
	E	101933031	Potassium Brevifolincarboxylate	-9.976	1
		10742	Syringic Acid	-9.328	0
		439246	Naringenin	-9.266	0
		14052	Ethambutol*	-8.176	3
		370	Gallic Acid	-6.212	0
	F	124021	beta-Glucogallin	-6.085	4
		6323490	Rifabutin*	-7.824	-

* Indicates First line oral drugs recommended by WHO

Table 3 Phytochemicals in Acalypha indica having good docking results with target protein (PDB ID: 1W30)

Protein	Chain	PubChem CID	Name	Glide Score	Stars
1W30	A	124021	beta-Glucogallin	-11.582	4
		445858	Ferulic Acid	-9.092	0
		5280863	Kaempferol	-8.719	0
		3082704	3,7,8-Tri-O-methylellagic acid 4-glucoside	-7.474	0
		1046	Pyrazinamide*	-3.128	3
	B	124021	beta-Glucogallin	-11.463	4
		3082704	3,7,8-Tri-O-methylellagic acid 4-glucoside	-8.022	0
		5280863	Kaempferol	-7.927	0
		101933031	Potassium Brevifolincarboxylate	-7.838	1
		370	Gallic Acid	-7.440	0
		6323490	Rifabutin*	-4.831	-

* Indicates First line oral drugs recommended by WHO

Table 4 Phytochemicals in Acalypha indica having good docking results with target protein (PDB ID: 27AS)

Protein	Chain	PubChem CID	Name	Glide Score	Stars
2A7S	A	124021	beta-Glucogallin	-8.513	4
		1046	Pyrazinamide*	-3.832	3
	B	124021	beta-Glucogallin	-6.994	4
		14052	Ethambutol*	-5.429	3
	C	124021	beta-Glucogallin	-8.794	4
		6913622	Rifampin*	-4.185	-
	D	124021	beta-Glucogallin	-9.574	4
		370	Gallic Acid	-6.985	0
		6913622	Rifampin*	-4.953	-
	E	689043	Caffeic Acid	-6.314	0
		445858	Ferulic Acid	-5.915	0
		151108	Quebrachitol	-5.777	1
		3767	Isoniazid*	-4.288	1
	F	5280343	Quercetin	-7.558	0
		124021	beta-Glucogallin	-7.428	4
		439246	Naringenin	-6.921	0
		14052	Ethambutol*	-5.312	3

* Indicates First line oral drugs recommended by WHO

Table 5 Phytochemicals in Acalypha indica having good docking results with target protein (PDB ID: 1F0N)

Protein	Chain	PubChem CID	Name	Glide Score	Stars
1F0N	A	124021	beta-Glucogallin	-8.745	4
		5280343	Quercetin	-8.546	0
		5280863	Kaempferol	-7.938	0
		72281	Hesperetin	-7.024	0
		3767	Isoniazid*	-3.652	1

* Indicates First line oral drugs recommended by WHO

Table 6 Top 11 ranked Phytochemicals in Acalypha indica among all target proteins.

Name	Protein	Chain	Glide Score	Glide Rank	Interacting Aminoacid residues
Potassium Brevifolincarboxylate	1N2B	B	-12.597	1	38 PRO, 158 GLY, 47 HIE, 160 LYN, 197 SER, 44 HIE
beta-Glucogallin	4RHU	E	-12.180	2	176 VAL, 176 VAL, 188 ARG, 182 ASP, 65 LEU
Caffeic Acid	1N2B	A	-11.221	3	47 HIE, 44 HIE, 195 MET, 187 VAL
Acalyphin	1N2B	B	-11.098	4	72 GLN, 503 GOL, 160 LYN
Ferulic Acid	1N2B	A	-10.513	5	197 SER, 44 HIE, 47 HIE, 46 GLY
Syringic Acid	1N2B	B	-10.411	6	160 LYN, 158 GLY
Gallic Acid	4RHU	E	-10.275	7	188 ARG, 188 ARG, 66 LYS, 64 VAL
COUMARIN, 3,3'-(o-CHLOROBENZYLIDENE)BIS(4-HYDROXY-	1N2B	A	-10.050	8	198 ARG, 164 GLN
Quercetin	4RHU	A	-9.980	9	176 VAL, 182 ASP, 130 THR, 127 SER
Aurantiamide	4RHU	B	-9.722	10	64 VAL, 124 VAL, 130 THR
Naringenin	4RHU	E	-9.266	11	188 ARG, 176 VAL

3D & 2D Docking Interaction of Ligands

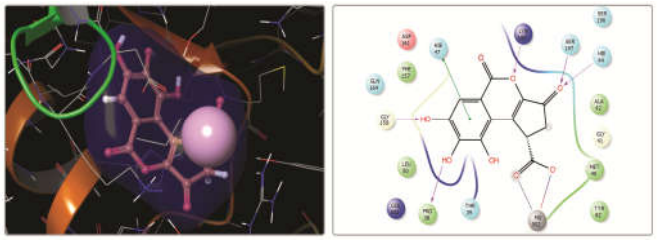

Figure 1 Potassium Brevifolincarboxylate with Chain B of Protein 1N2B

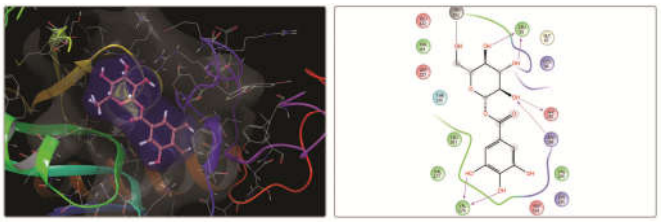

Figure 2 beta-Glucogallin with Chain E of Protein 4RHU

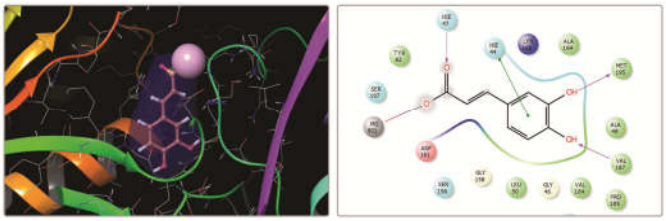

Figure 3 Caffeic Acid with Chain A of Protein 1N2B

DISCUSSION

Among the ligands docked with target protein 1N2B, the Compound Potassium Brevifolincarboxylate showed an excellent glide score of -12.145 kCal/mol followed by Caffeic Acid (-11.221 kCal/mol). All the first line oral drugs showed scores below 6 Kcal/mol. Among the phyotchemicals docked with target protein 4RHU, the Compound beta-Glucogallin showed a glide score of -12.180 kCal/mol followed by Acalyphin (-10.800 kCal/mol). The first line oral drugs also showed good scores the highest among them was for Ethambutol (-8.635 KCal/mol) at the Chain C.

Among the ligands docked with target protein 1W30, the Compound beta-Glucogallin showed a glide score of -11.582 kCal/mol followed by Ferulic Acid (-9.092 kCal/mol). The first line oral drugs showed only poor glide scores (below 5KCal/mol). Among the phyotchemicals docked with target protein 2A7S, the Compound beta-Glucogallin showed a glide score of -9.574 kCal/mol. All the first line oral drugs showed scores below 6 Kcal/mol. Among the ligands docked with target protein 1F0N, the Compound beta-Glucogallin showed a glide score of -8.745 kCal/mol. The first line oral drugs showed only poor glide scores (below 4KCal/mol).

Table -6 illustrates the top 11 phytochemicals in Acalypha indica. Among the 30 compounds selected from literature, sixteen of them satisfied the ADMET conditions predicted by Qik prop option. Least star value indicates more drug likeness of the compound. The accepted range of star is 0-5.

From the results obtained, it has been observed that there exist excellent binding interactions between phytochemicals of Acalypha indica and target proteins compared to the first line oral drugs. The phytochemical Potassium Brevifolincarboxylate shows a docking score -12.597 kCal/mol and forms five hydrogen bonds with the aminoacid residues. Oxygen in the ring and Carbonyl group forms side chain hydrogen bonds with 160 LYN (Bond Length-2.440 and Donor angle-95.497) & 44 HIE (Bond Length-2.237 and Donor angle-96.067). Two of the hydroxyl groups forms a back bone hydrogen bonds with 38 PRO (Dist - 4.893, Acceptor angle 157.73, Donor angle 166.955) & 158 GLY (Dist - 1.676, Donor angle 121.825). A Pi-Pi stacking Edge to face interaction at a distance of 5.35, angle - 63.54 exist between the ring and residue 47 HIE. The carboxylate group has a Metal coordination (Dist - 1.903, Acceptor angle 136.352) and a salt bridge (Dist - 3.755) with the 907 MG.

The phytochemical beta-Glucogallin shows a docking score -12.180 Kcal/mol and forms six hydrogen bonds with the aminoacid residues. Four hydroxyl groups froms back bone H-bonds with 176 VAL (Dist - 1.8177, Acceptor angle - 174.197, Donor angle - 133.578), 176 VAL (Dist - 1.911, Acceptor angle - 156.666, Donor angle - 156.385), 65 LEU (Dist - 2.456, Acceptor angle - 126.164, Donor angle - 102.462), 65 LEU (Dist - 1.962, Acceptor angle - 178.743, Donor angle - 138.315). One hydroxyl group forms two side chain hydrogen bonds with 182 ASP (Dist-1.965, Acceptor angle -142.8, Donor angle - 126.977) & 188 ARG (Dist-2.163, Donor angle - 100.094). Another hydroxyl form metal corordination with 302 MG (Dist-2.158, Acceptor angle-161.542).

Caffeic Acid shows a docking score -11.221 Kcal/mol and forms three hydrogen bonds with the aminoacid residues. Two hydroxyl groups froms back bone H-bonds with 187 VAL (Dist - 2.0633, Donor angle - 113.585), 195 MET (Dist - 1.911, Acceptor angle - 172.054, Donor angle - 130.741). The carboxylate group forms a side chain H-bond with 47 HIE (Dist-2.189, Donor angle-128.4) and a salt bridge (dist-1.8651) with 901 MG. A Pi-Pi stacking Edge to face interaction at a distance of 5.2.17, angle - 79.574 exist between the ring and residue 44 HIE.

On comparing the ligand interaction of Potassium Brevifolincarboxylate with Chain B of 1N2B and Chain B of 1W30 the glide score difference is about -4.759 kcal/mol. This may be due to the pi-pi stacking with the ring, metal coordination and salt bridge formation with the MG. The Potassium Brevifolincarboxylate docked at 5 different chains of target proteins 1N2B, 4RHU and 1W30 with good docking scores. Interestingly, the beta-Glucogallin docked at 16 different chains of all target proteins with docking score ranging form -7 to -12 Kcal/mol. The Caffeic Acid docked at 5 different chains of target proteins 1N2B, 4RHU and 27AS with good docking scores.

CONCLUSION

A thorough study was carried out over thirty phytochemicals of Acalypha indica with the goal of identifying potential lead molecules that bind to the potential target proteins of *mycobacterium tuberculosis* relying on computational docking and pharmacological properties prediction with GLIDE of Schrodinger 2015 and QikProp respectively. The top 11 phytochemicals showed excellent glide score on comparison with the first line oral drugs recommended by WHO. The Potassium Brevifolincarboxylate ranked first followed by beta-Glucogallin and Caffeic Acid. Eventhough Potassium Brevifolincarboxylate has the highest score the beta-Glucogallin docked with all the target proteins. This outweighs all other factors. Thus, it is hoped that these 11 phytochemicals identified in this study if synthesized and tested in animal models would hold promising results for new drug discovery.

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