JOURNAL OF NATURAL REMEDIES
DOI: 10.18311/jnr/2022/30194

RESEARCH ARTICLE

Computational Investigation of Plant-based Bioactive Compounds as Inhibitors against Tuberculosis

L. S. Dhivya[1], M. K. Mohan Maruga Raja[2] and M. K. Kathiravan[1,3]*

[1]Dr. APJ Kalam Research Lab, Department of Pharmaceutical Chemistry, SRM College of Pharmacy, SRM Institute of Science and Technology, Kattankulathur – 603203, Kancheepuram, Tamil Nadu, India
[2]Department of Pharmacognosy and Phytochemistry, Parul Institute of Pharmacy and Research, Parul University, Vadodara – 391760, Gujarat, India
[3]Department of Pharmaceutical Chemistry, SRM College of Pharmacy, SRM Institute of Science and Technology, Kattankulathur – 603203, Kancheepuram, Tamil Nadu, India; drmkkathir@gmail.com

Abstract

The objective of the work is to identify a natural origin compound that could have an anti-tubercular effect, thereby preventing the infection in humans using computational approach. Our focus was to find a inhibitor for Enoyl-acyl carrier reductase enzyme and hence chemically diverse scaffolds from plants origin were selected. Admet parameters were performed for the compounds, and the top nine compounds among 50 compounds were found to be non-carcinogenic. The pharmacological predicted activity (Pa) of few compounds such as 14-Deoxy-11,12 didehydroandrographolide, Terflavin B, and Liquirtin was found to be more active when compared with that of the standard reference. Further more the synthesis of these active compounds derivatives can be investigated theoretical followed by its synthesis and evaluation by *in vitro* activity against the *InhA* could be of interest.

Keywords: *InhA*, Liquirtin, *Mycobacterium tuberculosis,* Molecular Docking, Terflavin B

1. Introduction

Tuberculosis (TB) is a historical disease that has harmed humans for over 4,000 years and is caused by the bacillus Mycobacterium Tuberculosis. When the World Health Organization (WHO) recognized tuberculosis (TB) as a global medical emergency in 1992, the infection has been already spread to many countries. According to WHO, in 2020, more than 10 million people are estimated to have fallen ill with TB, while 1.6 million people died of the disease. India continues to bear the heaviest global burden of tuberculosis, accounting for more than one-third of all TB cases worldwide[2]. TB is described in the Vedas and ancient Ayurvedic writings of India. Historically, the struggle against tuberculosis in India can be divided into three periods: the early period, before the discovery of x-rays and chemotherapy; after independence, when state-wide TB control programs were launched and executed; and now, the ongoing WHO-assisted TB control programs in place. TB can infect anybody, anywhere, but the majority of individuals affected are adults. Men are infected more than women, and thirty countries with high TB prevalence are responsible for around 90%[3]. People suffering from tuberculosis find it difficult due to poverty, economic hardship, vulnerability, marginalization, stigma, and discrimination. It is a long-term disease induced by the bacillus Mycobacterium tuberculosis that spreads through the air from person to

*Author for correspondence

Article Received on: 05.05.2022 Revised on: 06.06.2022 Accepted on: 16.06.2022

person. Tuberculosis primarily damages the lungs, but it can also damage the brain, intestines, renal, and spine[4]. The symptoms of tuberculosis vary depending on where the microorganisms are developed in the body. In case of pulmonary tuberculosis, symptoms may include chronic cough, chest pain, hemoptysis, weakness or weariness, weight loss, fever, and night sweats. The use of Directly-Observed Therapy Short courses (DOTS) has been described as a "breakthrough" in tuberculosis treatment. It's become the backbone of tuberculosis treatment in many nations. Over the years, the number of countries and the availability of DOTS inside those countries has increased[5]. Mycobacterium TB showed resistance to both first-line and second-line treatments. As a result, Multi-Drug Resistance (MDR) and widely resistant (XDR) strains of M. tuberculosis are emerging all over the world, including India[6]. Medicinal herbs, which have been used for years to cure diseases, provide a great deal of hope in fulfilling these requirements. These have been widely employed as chemical constituents or as raw materials. A few species of plants have been extensively studied for possible therapeutic benefit[7]. In India has a distinct variety of herbal medicines as well as extensive traditional awareness of the use of herbal medicine for the treatment of various diseases, and latent tuberculosis is mostly found in developing countries[8]. We ended up choosing plants for our study based on two principles: the first is oral efficacy, which means that the majority of Indian traditional plants should be likely to be absorbed through the oral route; the second is traditional use compatibility; and eventually, using molecular docking to select potential compounds that could have an anti-tubercular agent.

2. Materials and Methods

2.1 Data Set

A data set of 50 molecules derived from various aromatic and medicinal plants was considered for the study. Molecular docking, ADME properties, toxicity, and pharmacological activity of these compounds were analysed

2.2 Receptor Identification and Preparation

The X-ray crystal structure of Mycobacterium tuberculosis InhA bound with ETH-NAD adduct (PDB Accession code : 2H9I) was retrieved from RSCB Protein Data Bank. Crystal complexes were created using the clean protein tool and imported in Autodock tools 1.5.6. The protein preparation was performed using Autodock tools 1.5.6 on removing the original ligand and water molecules from .pdb file, addition of polar hydrogen and kollman charges, assigning Autodock atom type to the protein structure and finally the prepared protein were saved in .pdbqt format[9].

2.3 Preparation of Ligands

The 2-dimensional (2D) structure of the 50 selected chemical compounds were obtained from the PubChem database in the structure-data file format. The 2D structures of ligands were converted to its 3D format by using ChemBioDraw Ultra 12.0 and saved as .pdb format for carrying out molecular docking.

2.4 Molecular Docking

To predict the binding affinity of the ligand molecule, molecular docking was performed, which further determines the scoring function by evaluating protein-ligand interactions. The ligands bioactive binding poses at the active site of the InhA were docked using the Autodock® 1.5.6 program. The area of interaction between the protein and the ligand is defined by the receptor grid. This was done using Autodock 1.5.6's receptor grid generation tool, which describes the area around the active site in terms of x, y, and z coordinates. The resolution of the receptor grid box was centered at coordinates 3.245, 36.896, and 18.276 on the x, y, and z-axis, respectively. The binding site was defined using the protein coordinates of 2H9I bound ligand and the scoring function was generated using the Lamarckian genetic algorithm. The energy minimized poses were determined by using the binding score and the lowest binding scores are considered as the best docked pose for each ligand. The RMSD value which is the difference between the observed X-ray crystallography of the protein and the predicted confirmation of input ligand geometry were calculated. The results of Hydrogen and hydrophobic interactions at the inhibitor site of 2H9I were modeler using Biovia Discovery Studio 2019. The docking interactions were determined by using Pymol[10].

2.5 Toxicity Prediction

The Osiris Property Explorer was used in the toxicity prediction to determine the features of mutagenicity, carcinogenicity, irritability, and reproductive impact, and the results are summarized in Table 4[11].

2.6 ADME Prediction

A new online admetSAR-2.0 webserver was also used to predict adsorption, distribution, metabolism, and elimination[12]. Human ether-a-go-go-related gene inhibition, AMES toxicity, acute oral toxicity (c), and carcinogenicity (Class-3) were all evaluated for all the 50 compounds[13].

2.7 Pharmacological Activity Prediction

The PASS web tool can predict 3678 pharmacological effects as well as the molecule's mechanisms and particular toxicities, such as mutagenicity, carcinogenicity, teratogenicity, and embryotoxicity. As previously reported, activity estimation is done by utilizing PASS online. For prediction, structures in.mol format were uploaded to PASS online. The predicted activities were tested for anti-bacterial activity, and 50 compounds were chosen for further processing. Pa (probability of being active) and Pi (probability of being passive) values were calculated[14].

3. Results

3.1 Molecular Docking

To find a promising candidate for anti-tubercular activity, molecular docking was performed on bio-active components identified from several Indian traditional plants on the binding site of (PDB ID: 2H9I). In total, 50 components have been docked. Table 1. demonstrates natural compound binding affinity for the InhA target, while Table 2. lists the top 9 docking results based on binding energy.

The virtual screening binding affinity values of the 50 selected compounds were in the range from -3.59 to-12.05 kcal/mol. It should be noted that a hit molecule that binds to the target can be a impact is the best contender against tuberculosis. These compound with the highest conceivable binding energy represented in Gibbs free energy variation (ΔG) are according to thermodynamics. The top nine compounds are Columbin (-12.05 kcal/mol), Tinosporon (-11.51 kcal/mol), 14-Deoxy-11,12-Dihydroandropholide

Table 1. Docking results of selected chemical constituents and their binding energy

Sl. No	Compounds	Binding Energy (Kcal / mol)
1.	14-Deoxy-11,12-didehydroandrographolide	-11.38
2.	Chebulinic acid	-6.96
3.	Alpha-Santalol	-7.89
4.	1-Octacosanol	-8.74
5.	Gama vetiverene	-8.18
6.	Anaferine	-7.04
7.	Papaverine	-7.42
8.	Rosmarinic acid	-7.89
9.	Glycyrrhizin	-7.69
10.	Terpinyl acetate	-7.12
11.	Chebulagic acid	-6.87
12.	Withanolide	-7.09
13.	Thymol	-5.46
14.	P-Cymene	-5.53

15.	Liquiritic acid	-7.32
16.	Tetrahydropiperine	-8.46
17.	Terflavin B	-9.67
18.	Camphor	-7.6
19.	Linalool	-6.28
20.	1,4-Cineole	-6.65
21.	Menthol	-5.42
22.	Chavibetol	-5.42
23.	Carveol	-4.85
24.	Quinidine	-5.87
25.	Diallyl Sulfide	-3.97
26.	Diallyl Di- Sulfide	-3.74
27.	Diallyl Tri- Sulfide	-3.59
28.	Estragol	-6.98
29.	Limonene	-7.01
30.	Fenchone	-5.85
31.	Trans-Anethole	-5.63
32.	Vasicine	-6.77
33.	Vasicinone	-7.05
34.	Quinazoline	-5.43
35.	Zingiberene	-6.47
36.	Beta-Bisabolene	-6.02
37.	Alpha-Farnesene	-5.98
38.	Gingerol	-4.97
39.	Shoagoal	-7.09
40.	Tinosporon	-11.51
41.	Limonate	-6.34
42.	Columbin	-12.05
43.	Piperine	-7.78
44.	Sitoindoside IX	-7.28

45.	Sitoindoside X	-7.48
46.	Codeine	-9.56
47.	Furanoendesma 1,3-diene	-8.53
48.	Menthofuran	-6.6
49.	Liquirtin	-8.7
50.	Isopelletierine	-6.1
	Isoniazid	-4.8

Table 2. Top nine compounds docking results

S.No.	Compounds	Hydrogen Bond Interaction	Binding Energy (Kcal / mol)
1.	Columbin	GLY 14, THR 39	-12.05
2.	Tinosporon	GLY 96, LEU 63	-11.51
3.	14-Deoxy-11,12-didehydroandrographolide	GLY 96, LEU 63	-11.38
4.	Terflavin B	GLY14, SER94, ILE 21	-9.67
5.	Codeine	THR 39	-9.56
6.	Octacosanol	ILE 15,PHE 42	-8.74
7.	Liquiritin	GLY 14, THR 39, GLY 96, MET 98	-8.7
8.	Furanoendesma-1,3-Diene	VAL 65	-8.53
9.	Tetrahydropiperine	ASP 150	-8.46
	Isoniazid	GLY 96, ASP 234	-4.8

(-11.38 kcal/mol), Terflavin B (-9.67 kcal/mol), Codeine (-9.56 kcal/mol), Octacosanol (-8.74 kcal/mol), Liquiritin (-8.7 kcal/mol), Furanoendesma -1,3-Diene (-8.53 kcal/mol) and Tetrahydropiperine (-8.46 kcal/mol) are the best docked molecules when compared with the reference standard and co-crystal ligand (Isoniazid-4.80 kcal/mol). The active site of the pocket is predominantly lined by hydrogen groups from the side chains of Gly 97, ILeE 194 and is adjacent and partly overlapped with the fatty acyl substrate-binding site. The interaction analysis of the nine best well-docked compounds (FIG.1-3) were examined in detail. Glycine is a major requirement and three active constituents showed interactions with Glycine 96 in hydrogen bond interactions. The interaction energies were examined, and found to have H bond interactions. The first level of interactions was considered the most important. The presence of hydrogen bond interactions in the selected compounds explains a good interaction between the three compounds and the protein.

3.2 Toxicity Prediction

Currently, several approaches have been developed to assess the drug-likeness of bio-active compounds based on topological descriptors, fingerprints of molecular structure, or other properties such as molecular weight, water solubility, and cLogP. In this work, the open-source programme OSIRIS Property Explorer was used to predict the fragment-based drug-likeness of title compounds and compare them with Isoniazid. The OSIRIS programme

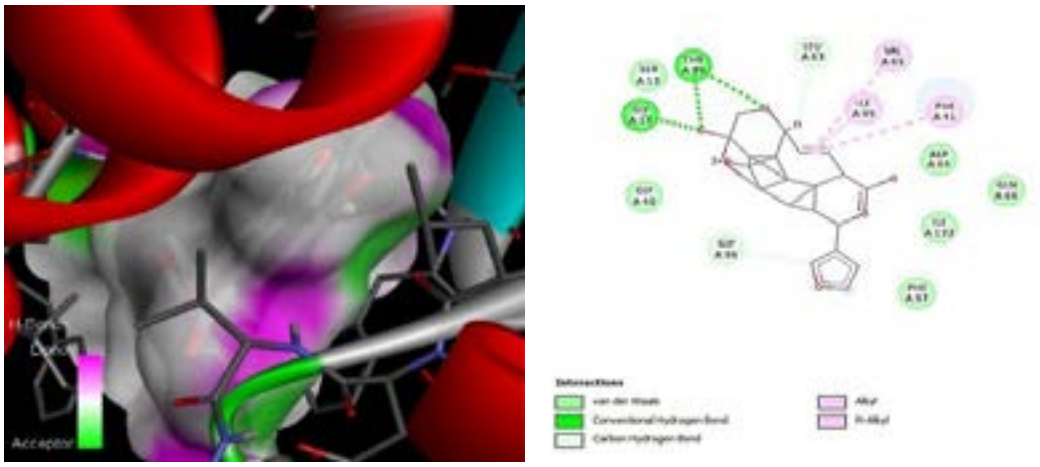

Figure 1. 2D and 3D View of the Binding Conformation of Columbin Inhibitor at the active site of *InhA*.

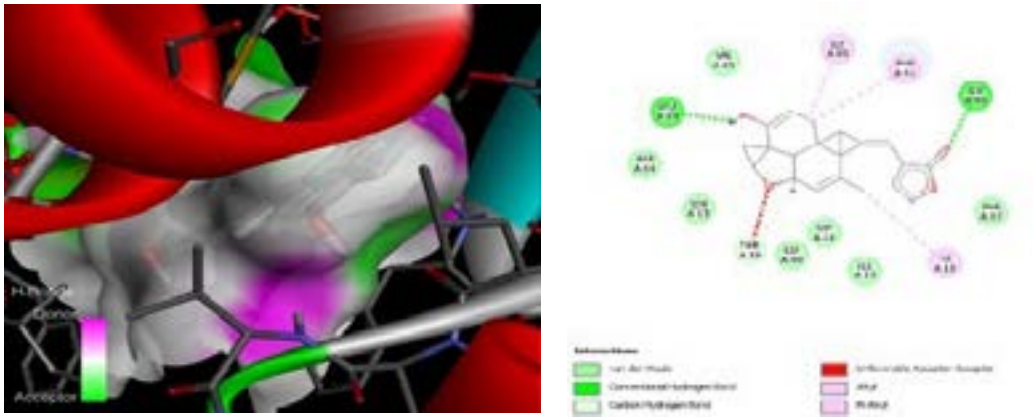

Figure 2. 2D and 3D View of the Binding Conformation of 14-Deoxy-11,12-didehydroandrographolide Inhibitor at the active site of *InhA*.

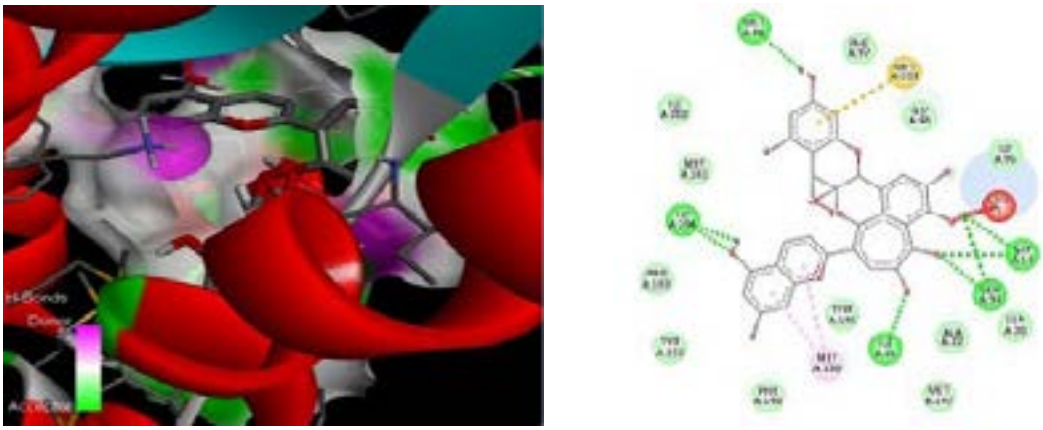

Figure 3. 2D and 3D View of the Binding Conformation of Terflavin B Inhibitor at the active site of *InhA*.

involves a database of traded drugs and commercially available compounds assumable as a non-drug-like data set to assess the occurrence frequency of each fragment in the individual structure. The programme estimated the risks of side effects, such as mutagenic, tumorigenic, irritant, and reproductive effects, as well as drug-relevant properties, including drug-likeness. The drug - likeness value should be within the range of 0 -1. Moreover, the overall drug-score was estimated by combining the outcomes of toxicity risks and drug-likeness. A compound's drug-score is a measure of the compound's potential to meet the criteria of a possible drug candidate. The results are represented in Table 3.

3.3 ADME Properties

Admetsar is a commercial database that specializes in pharmacokinetics information. It provides comprehensive data on drug-metabolizing enzymes and drug transporters that are specific to humans. The data has been widely used in drug research and development, such as ADME prediction and drug-drug interactions. Users can search for classification, metabolic reactions, and kinetics-related information about compounds by structure or substructure. However, the database currently limits large-scale downloads of user data as well as public dissemination of some models. From the results, it is clear

Table 3. Toxicity Profile of Chemical Constituents

S. No	Compounds	Mutagenicity	Carcinogenicity	Irritant	Reproductive Effect	Drug-Likeness
1.	14-Deoxy-11,12-didehydroandrographolide	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	-1.00
2.	Chebulinic acid	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	1.19
3.	alpha-Santalol	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	-3.58
4.	1-Octacosanol	Non-Toxic	Non-Toxic	Toxic	Non-Toxic	-32.17
5.	Gama vetiverene	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	-3.92
6.	Anaferine	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	-0.69
7.	Papaverine	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	3.37
8.	Rosmarinic acid	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	-2.07
9.	Glycyrrhizin	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	--4.29
10.	Terpinyl acetate	Non-Toxic	Non-Toxic	Toxic	Non-Toxic	-7.68
11.	Chebulagic acid	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	1.19
12.	Withanolide	Non-Toxic	Non-Toxic	Non-Toxic	Toxic	0.14
13.	Thymol	Toxic	Non-Toxic	Non-Toxic	Toxic	-3.02
14.	P-Cymene	Non-Toxic	Toxic	Toxic	Non-Toxic	-5.63

15.	Liquiritic acid	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	-2.36
16.	Tetrahydropiperine	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	-3.57
17.	Terflavin B	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	0.36
18.	Camphor	Toxic	Toxic	Toxic	Toxic	-3.71
19.	Linalool	Toxic	Non-Toxic	Toxic	Non-Toxic	-6.68
20.	1,4-Cineole	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	-6.07
21.	Menthol	Toxic	Toxic	Toxic	Non-Toxic	-10.47
22.	Chavibetol	Non-Toxic	Toxic	Toxic	Non-Toxic	-1.90
23.	Carveol	Non-Toxic	Non-Toxic	Toxic	Non-Toxic	-18.48
24.	Quinidine	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	1.09
25.	Diallyl Sulfide	Toxic	Non-Toxic	Non-Toxic	Non-Toxic	-3.93
26.	Diallyl Di- Sulfide	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	-4.70
27.	Diallyl Tri- Sulfide	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	-4.70
28.	Estragol	Toxic	Toxic	Toxic	Non-Toxic	-3.75
29.	Limonene	Toxic	Toxic	Toxic	Toxic	-21.85
30.	Fenchone	Non-Toxic	Non-Toxic	Toxic	Non-Toxic	-3.72
31.	Trans-Anethole	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	-3.42
32.	Vasicine	Non-Toxic	Non-Toxic	Non-Toxic	Toxic	3.95
33.	Vasicinone	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	4.61
34.	Quinazoline	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	-1.89
35.	Zingiberene	Toxic	Non-Toxic	Toxic	Toxic	-3.02
36.	Beta-Bisabolene	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	-6.41
37.	Alpha-Farnesene	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	-7.39
38.	Gingerol	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	-7.78

39.	Shoagoal	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	-14.48
40.	Tinosporon	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	-0.41
41.	Limonate	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	-3.41
42.	Columbin	Non-Toxic	Non-Toxic	Toxic	Non-Toxic	1.35
43.	Piperine	Non-Toxic	Non-Toxic	Non-Toxic	Toxic	0.60
44.	Sitoindoside IX	Non-Toxic	Non-Toxic	Non-Toxic	Mild-Toxic	-2.40
45.	Sitoindoside X	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	-27.51
46.	Codeine	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	5.96
47.	Furanoendesma 1,3-diene	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	1.02
48.	Menthofuran	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	-1.42
49.	Liquirtin	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	-5.98
50.	Isopelletierine	Non-Toxic	Non-Toxic	Toxic	Non-Toxic	-2.19
	Isoniazid	Toxic	Toxic	Toxic	Toxic	-5.06

*Non-Toxic - Green ; Toxic – Red

that none of the top 9 compounds were carcinogenic. Tetrahydropiperine and Furanoendesma 1,3-diene were found to be positive for AMES toxicity, while others were found to be negative. Table 4. lists the compounds' BBB, P-gpi, Acute Oral Toxicity, and CYP450 Inhibitory values.

3.4 Pharmacological Activity Prediction

The biological activity spectra of previously identified phyto-constituents were obtained by the online PASS version. These predictions were interpreted and used in a flexible manner. The predicted probable activity (Pa) of 14-Deoxy-11,12 didehydroandrographolide, Terflavin B,

Table 4. ADMET Parameters of Chemical Constituents by admetSAR

S. No.	ChemicalConstituents	BBB	P-gpi	Carcinogens	AMES Toxicity	Acute Oral Toxicity	CYP450 Inhibitory
1.	Chebulinic acid	-	+	-	+	3.232	-
2.	14-Deoxy-11,12 -didehydroandrographolide	+	-	-	-	2.353	-
3.	Alpha-Santalol	+	-	-	-	2.274	-
4.	1-Octacosanol	+	-	-	-	1.401	-
5.	Gama vetiverene	+	-	+	-	2.664	-

6.	Anaferine	+	-	-	-	2.517	-
7.	Papaverine	-	-	-	-	1.725	+
8.	Rosmarinic acid	-	-	-	-	1.801	-
9.	Glycyrrhizin	-	+	-	-	2.132	-
10.	Terpinyl acetate	+	-	-	-	1.952	-
11.	Chebulagic acid	-	+	-	+	2.986	-
12.	Withanolide	+	-	-	-	3.660	-
13.	Thymol	+	-	-	-	2.202	-
14.	P-Cymene	+	-	-	-	1.883	-
15.	Liquiritic acid	-	-	-	-	2.793	-
16.	Tetrahydropiperine	+	-	-	-	1.895	+
17.	Terflavin B	-	+	-	-	1.870	-
18.	Camphor	+	-	-	-	1.031	-
19.	Linalool	+	-	-	-	2.338	-
20.	1,4-Cineole	+	-	-	-	1.448	-
21.	Menthol	+	-	-	-	2.223	-
22.	Chavibetol	+	-	-	-	1.266	+
23.	Carveol	+	-	-	-	1.896	-
24.	Quinidine	+	+	-	-	3.010	-
25.	Diallyl Sulfide	+	-	+	-	1.606	-
26.	DiallylDi-Sulfide	+	-	+	-	2.727	+
27.	Diallyl Tri- Sulfide	+	-	+	-	2.448	-
28.	Estragol	+	-	-	-	2.211	+
29.	Limonene	+	-	-	-	1.856	-
30.	Fenchone	+	-	-	-	2.223	-
31.	Trans-Anethole	+	-	-	-	2.206	-
32.	Vasicine	+	-	-	-	1.974	-

33.	Vasicinone	+	-	-	+	2.614	-
34.	Quinazoline	+	-	-	-	2.485	-
35.	Zingiberene	+	-	-	-	1.827	-
36.	Beta-Bisabolene	+	-	-	-	2.216	-
37.	Alpha-Farnesene	+	-	+	-	1.598	-
38.	Gingerol	+	-	-	-	2.290	-
39.	Shoagoal	+	-	-	+	2.267	-
40.	Tinosporon	+	-	-	-	2.135	-
41.	Limonate	+	-	-	-	3.701	-
42.	Columbin	+	-	-	-	2.735	-
43.	Piperine	+	-	-	-	2.200	+
44.	Sitoindoside IX	+	+	-	-	3.812	-
45.	Sitoindoside X	+	+	-	-	3.273	-
46.	Codeine	+	-	-	-	3.496	-
47.	Furanoendesma 1,3-diene	+	-	-	-	3.139	+
48.	Menthofuran	+	-	-	-	1.938	-
49.	Liquirtin	-	-	-	-	2.667	-
50.	Isopelletierine	+	-	-	-	2.641	-
	Isoniazid	+	+	-	-	1.167	-

and Liquirtin was found to be more active when compared with that of the standard reference. The results are shown in Table 5.

4. Discussion

Mycobacterium tuberculosis (M.tb) kills more people than any other infection in the world, and it's becoming increasingly resistant to antibiotics. New prevention techniques are required to end the tuberculosis (TB) epidemic. The lack of validated preclinical models and human immunological correlates of protection to provide evidence for progressing candidates into late-stage trials stymies the development of novel tuberculosis vaccines[15]. M.tb exposure can result in early bacterial clearance by innate or adaptive immunity, or infection, which can be asymptomatic (latent) in most people or lead to active disease in others. As a result, evaluating a traditional medicine by screening for a newer phytochemical component could be beneficial in treating the mycobacterium species. By selecting Indian traditional herbs and their primary components, we performed molecular docking to find new lead compounds against tuberculosis[16]. Natural plant compounds have previously been found to effectively treating pathogenic diseases in several investigations, and plants have also been utilized

Table 5. Pharmacological Activity of Chemical Constituents by PASS Prediction tool.

S. No	Molecule Name	Pa>Pi		Pa>0.3		Pa>0.7	
		Pa	Pi	Pa	Pi	Pa	Pi
1	Chebulinic acid	0.491	0.017	0.491	0.017	-	-
2	**14-Deoxy-11,12 dide-hydroandrographolide**	**0.481**	**0.018**	**0.481**	**0.018**	**-**	**-**
3	alpha-Santalol	0.179	0.016	0.179	0.016	-	-
4	**1-Octacosanol**	**0.278**	**0.069**	-	-	-	-
5	Gama vetiverene	0.298	0.061	-	-	-	-
6	Anaferine	0.250	0.005	-	-	-	-
7	Papaverine	0.032	0.005	-	-	-	-
8	Rosmarinic acid	0.222	0.100	-	-	-	-
9	Glycyrrhizin	0.569	0.011	0.569	0.011	-	-
10	terpinyl acetate	0.315	0.055	0.315	0.055	-	-
11	Chebulagic acid	0.425	0.025	0.425	0.025	-	-
12	Withanolide	0.392	0.032	0.392	0.032	-	-
13	Thymol	0.336	0.047	0.336	0.047	-	-
14	P-Cymene	0.248	0.084	-	-	-	-
15	Liquiritic acid	0.352	0.043	0.352	0.043	-	-
16	**Tetrahydropiperine**	-	-	-	-	-	-
17	**Terflavin B**	**0.568**	**0.011**	**0.568**	**0.011**		
18	Camphor	0.191	0.126	-	-	-	-
19	Linalool	0.385	0.034	0.385	0.034	-	-
20	1,4-Cineole	0.274	0.070	-	-	-	-
21	Menthol	0.473	0.019	0.473	0.019	-	-
22	Chavibetol	0.325	0.051	0.325	0.051	-	-
23	Carveol	0.494	0.017	0.494	0.017	-	-
24	Quinidine	0.266	0.074	0.417	0.002	-	-
25	Diallyl Sulfide	0.374	0.037	0.374	0.037	-	-
26	Diallyl Di- Sulfide	0.397	0.031	0.397	0.031	-	-

27	Diallyl Tri- Sulfide	0.486	0.018	0.486	0.018	-	-
28	Estragol	0.264	0.075	-	-	-	-
29	Limonene	0.405	0.029	0.405	0.029	-	-
30	Fenchone	0.219	0.102	-	-	-	-
31	Trans-Anethole	0.323	0.052	0.323	0.052	-	-
32	Vasicine	0.151	0.056	-	-	-	-
33	Vasicinone	0.134	0.088	-	-	-	-
34	Quinazoline	0.213	0.011	-	-	-	-
35	Zingiberene	0.416	0.026	0.416	0.026	-	-
36	Beta-Bisabolene	0.413	0.027	0.413	0.027	-	-
37	Alpha-Farnesene	0.459	0.021	0.459	0.021	-	-
38	Gingerol	0.262	0.076	-	-	-	-
39	Shoagoal	0.268	0.073	-	-	-	-
40	**Tinosporon**	**0.394**	**0.032**	**0.394**	**0.032**	**-**	**-**
41	Limonate	0.191	0.127	-	-	-	-
42	**Columbin**	**0.358**	**0.041**	**0.358**	**0.041**	**-**	**-**
43	Piperine	0.160	0.156	-	-	-	-
44	Sitoindoside IX	0.728	0.004	0.728	0.004	0.728	0.004
45	Sitoindoside X	0.488	0.017	0.488	0.017	-	-
46	**Codeine**	-	-	-	-	-	-
47	**Furanoendesma 1,3 -diene**	**0.159**	**0.156**	-	-	-	-
48	Menthofuran	0.253	0.092	-	-	-	-
49	**Liquirtin**	**0.565**	**0.011**	**0.565**	**0.011**	**-**	**-**
50	Isopelletierine	0.183	0.134	-	-	-	-
	Isoniazid	0.371	0.038	0.371	0.038	-	-

*Pa - Probability of Active, Pi – Inactive

for therapeutic purposes since ancient times[17]. When compared to standard anti-tubercular drugs, the majority of the biactive constituents have higher activity in the current study[18]. Molecular docking was performed to assess the activities of phytochemicals obtained from Indian traditional plants against target proteins under in silico environments. Molecular docking, a structure-based computer-aided virtual screening technique, accomplishes a distinct amalgamation of positions, orientations, and conformations by evaluating the interaction between a

protein and a plausible drug molecule. Protein pliability is significant for ligand binding in the computational drug development process. In docking studies, binding to the active areas of proteins inhibits the targeted protein. In this study, the complexes Columbin, Tinosporon, 14-Deoxy-11,12- Dihydroandropholide, and Terflavin B had non-bonded contacts with the active points Gly 96, as well as numerous interactions around the protein's active points, which could be responsible for the target protein's inhibition with higher binding affinity[19]. Furthermore, a number of descriptors generated from simulated trajectories for docked structures revealed that the complexes and hydrogen bonds of the systems had tight conformations. Furthermore, the top nine potential candidates were toxic-free, had positive BBB (less than one) within limitations, were permeable, and free from AMES toxicity[20]. As a result, bioactive constituents from Indian traditional herbs may block the target protein's receptor domain. Additional wet-lab in vitro and in vivo studies are required to support these findings.

5. Conclusion

At present, the search for new molecules from natural products is based on ethnological studies, which assist inventories of plants in a zone or country, preceded by phytochemical and pharmacological studies, as well as other scientific aspects, such as the importance of the use of these medicinal plants, which pushed us to seek and find molecules that can prevent tuberculosis. Based on the results of molecular docking, we have identified nine compounds among 50 compounds as inhibitors of the InhA target. All the compounds were found to be non-carcinogenic and the pharmacological predictable activity (Pa) of 14-Deoxy-11,12 didehydroandrographolide, Terflavin B, and Liquirtin was found to be more active when compared with that of the standard.

6. Acknowledgment

We are thankful to the Research Council of SRMIST for constant encouragement and support.

7. References

1. Zaman K. Tuberculosis: A global health problem. J Health Popul Nutr. 2010; 28(2):111–3. https://doi.org/10.3329/jhpn.v28i2.4879. PMid:20411672. PMCid:PMC2980871
2. Chandir S, Hussain H, Salahuddin N, Amir M, Ali F, Lotia I, et al. Extrapulmonary tuberculosis: A retrospective review of 194 cases at a tertiary care hospital in Karachi, Pakistan. J Pak Med Assoc. 2010; 60(2):105–9. PMID: 20209695.
3. Sandhu GK. Tuberculosis: Current situation, challenges and overview of its control programs in India. J Glob Infect Dis. 2011; 3(2):143–50. https://doi.org/10.4103/0974-777X.81691. PMid:21731301. PMCid:PMC3125027
4. Chadha VK. Progress towards millennium development goals for TB control in seven Asian countries. Indian J Tuberc. 2009; 56(1):30–43.PMID: 19402270.
5. Smith KC, Armitige L, Wanger A. A review of tuberculosis: Reflections on the past, present and future of a global epidemic disease. Expert Rev Anti Infect Ther. 2003; 1(3):483–91. https://doi.org/10.1586/14787210.1.3.483. PMid:15482144
6. Singh MM. XDR-TB--danger ahead. Indian J Tuberc. 2007; 54(1):1–2. PMID: 17455416.
7. Gupta R, Thakur B, Singh P, Singh HB, Sharma VD, Katoch VM, et al. Anti-tuberculosis activity of selected medicinal plants against multi-drug resistant Mycobacterium tuberculosis isolates. Indian J Med Res. 2010; 131:809–13.PMID: 20571171.
8. Houben RM, Dodd PJ. The global burden of latent tuberculosis infection: A re-estimation using mathematical modelling. PLoS Medicine. 2016; 13(10). https://doi.org/10.1371/journal.pmed.1002152. PMid:27780211. PMCid:PMC5079585
9. Suresh AJ, Nandini S, Sangeetha K, Dhivya LS, Surya PR. Design, synthesis and invitro biological evaluation of pyridine, thiadazole, benzimidazole and acetyl thiophne analogues as anti tubercular agents targeting enzyme InhA. Curr Comput-Aided. 2020. https://doi.org/10.2174/1573409916666200724152827. PMid:32713342
10. Suresh J, Baek SC, Ramakrishnan SP, Kim H, Mathew B. Discovery of potent and reversible MAO-B inhibitors as furanochalcones. Int J Biol Macromol. 2018; 108:660–4. https://doi.org/10.1016/j.ijbiomac.2017.11.159. PMid:29195801
11. Sander T, Freyss J, von Korff M, Reich JR, Rufener C. OSIRIS, an entirely in-house developed drug discovery informatics system. J Chem Inf Model. 2009; 49(2):232–46. https://doi.org/10.1021/ci800305f. PMid:19434825
12. Sabarathinam S, Vijayakumar TM. Assessment of herb-drug interactions based on the pharmacokinetic changes of probe drug, midazolam. Drug Metab Lett. 2021; 14(1):5–8. https://doi.org/10.2174/1872312814666201112122110. PMid:33183217
13. Sabarathinam S, Vijayakumar TM. A short exploration of selected sensitive CYP3A4 substrates (probe drug). Drug Metab Lett. 2021; 14(1):2–4. https://doi.org/10.2174/1872312814666200811110024. PMid:32781977

14. Mittal M, Goel RK, Bhargava G, Mahajan MP. PASS-assisted exploration of antidepressant activity of 1,3,4-trisubstituted-beta-lactam derivatives. Bioorganic Med Chem Lett. 2008; 18(20):5347–9. https://doi.org/10.1016/j.bmcl.2008.09.064. PMid:18835165
15. Tucker EW, Dooley KE. Preclinical tools for the evaluation of tuberculosis treatment regimens for children. Int J Tuberc Lung Dis. 2018; 22(5):7–14. https://doi.org/10.5588/ijtld.17.0354. PMid:29665948. PMCid: PMC7577428
16. Maiolini M, Gause S, Taylor J, Steakin T, Shipp G, Lamichhane P, et al. The war against tuberculosis: A review of natural compounds and their derivatives. Molecules (Basel, Switzerland). 2020; 25(13). https://doi.org/10.3390/molecules25133011. PMid:32630150. PMCid:PMC7412169
17. Aanouz I, Belhassan A, El-Khatabi K, Lakhlifi T, El-Ldrissi M, Bouachrine M. Moroccan Medicinal plants as inhibitors against SARS-CoV-2 main protease: Computational investigations. J Biomol Struct Dyn. 2021; 39(8):2971-9. https://doi.org/10.1080/07391102.2020.1758790. PMid:32306860. PMCid:PMC7212546
18. Gutierrez-Lugo MT, Bewley CA. Natural products, small molecules, and genetics in tuberculosis drug development. J Med Chem. 2008; 51(9):2606–12. https://doi.org/10.1021/jm070719i. PMid:18393405. PMCid:PMC6260804
19. Borad MA, Jethava DJ, Bhoi MN, Patel CN, Pandya HA, Patel HD. Novel isoniazid-spirooxindole derivatives: design, synthesis, biological evaluation, in silico ADMET prediction and computational studies. J Mol Struct. 2020; 1222. https://doi.org/10.1016/j.molstruc.2020.128881
20. Guan L, Yang H, Cai Y, Sun L, Di P, Li W, et al. ADMET-score - a comprehensive scoring function for evaluation of chemical drug-likeness. Medchemcomm. 2018; 10(1):148–57. https://doi.org/10.1039/C8MD00472B. PMid:30774861. PMCid:PMC6350845