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In silico Evaluation of Indian Medicinal Plants to Find the Potential Remedy for *Mycobacterium tuberculosis*

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Research Article

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ABSTRACT

Tuberculosis (TB) is a disease caused by *Mycobacterium tuberculosis* bacterium. The bacterium primarily affects the lungs, but they can also harm other organs. The goal of this study was to identify potential phytocompounds from Indian medicinal plants that could be used to treat Tuberculosis. IMPPAT and the PubChem database were used to determine the 3D structure of phytocompounds. SwissADME was used to test the Lipinski rule of five for all phytocompounds. The target protein's 3D structure was downloaded from the PDB library. PyRx was used to conduct the docking studies, and Discovery Studio 2021 was used to analyse the results. The phytocompounds Diosgenin, Agapanthagenin, and Liquiritic acid showed very strong binding affinity of -9.6, -9.6, and -9.2 Kcal/mol, respectively, according to the results.

Keywords: *Mycobacterium tuberculosis*, Phytocompounds, Molecular Docking, PyRx, Discovery Studio, ADMET properties.

INTRODUCTION

One of the oldest and deadliest diseases to ever affect humans, tuberculosis (TB) is still a major global health, social, and economic burden, especially in low- and middle-income countries [1]. *Mycobacterium tuberculosis* (Mtb) infection starts when a few tubercle bacilli dispersed in the air from a patient with active pulmonary TB reach the host's alveoli. Professional alveolar macrophages quickly phagocytize Mtb, and because of the innate immune response, they can typically eradicate the invasive bacteria [2].

Based on new knowledge of Mtb biology, its various metabolic states, the dynamic host immune responses that take place during infection, and the spectrum of conditions observed during infection, it has been proposed that most bacilli persist in a dormant state during latent infection, with fewer Mtb found in an active replicating state. The host immune system processes and eliminates these proliferating bacteria, known as "scouts," which activates a sizable number of effector/memory T lymphocytes that are directed against Mtb antigens found in the peripheral blood [3].

A conclusive diagnosis of tuberculosis requires the confirmation of Mtb from a biological sample using at least one of the available microbiological methodologies: microscopy, isolation in culture, or molecular methods. Based on the individual symptoms, doctors may require Mtb detection in one or more specimens during these tests to make a microbiological diagnosis of tuberculosis[4]. High sensitivity and specificity have been noted in the detection of Mtb in samples such sputum, bronchoalveolar lavage, or induced sputum for the diagnosis of pulmonary TB [5].

India has the most tuberculosis patients among the global population, accounting for more than a quarter of all cases [6]. Drug-resistant *Mycobacterium TB*, the tuberculosis causative agent, is aggressively growing in India. As a result, India has the second largest number of multi-drug conferring resistance tuberculosis cases in the world (MDR-TB) [6], both isoniazid and rifampicin tolerant. Despite the fact that India has over 2 million tuberculosis infections, nothing is known about the genetic variety of the disease [7].

Our study, which focused on lineage 1 and 3 strains prevalent in India, a country where all genome sequencing-based *M. tuberculosis* analyses have been restricted [8, 9], adds to the body of knowledge regarding the genetic diversity of the *M. tuberculosis* complex. Within particular rehabilitation centers, we identified highly localised incidences of patient-to-patient propagation of strains (10 SNP changes). This could indicate a need to focus on nosocomial transmission prevention, which is consistent with prior research in India [10].

Every year, about 1⁄2 a million Indians died of tuberculosis (TB) [11]. The 5300 patients examined comprise less than 0.2 percent of the 2.8 million TB cases diagnosed each year. Furthermore, the 120 TB

units sampled represent 1.3 percent to 2.5 percent of the total population; because drug resistance is not evenly distributed throughout the country. This sampling technique may have missed locations with high incidence of DR-TB. The scarcity of primary MDR-TB cases in the assessment in Haryana, Jammu & Kashmir, Karnataka, Meghalaya, Orissa, and Telangana illustrates this [12].

Over the last 20 years, the economic consequences of tuberculosis have been extensively researched [13, 14]. Tuberculosis has a negative impact on the workforce [15] federal health finances are depleted [16], family savings are reduced [17, 18, 19] and wreaks havoc on local economies [20]. Nevertheless, without the need for a critical appraisal of the expense of the tuberculosis pandemic on economic wellbeing, the overall data on the finances of terminating tuberculosis has remained varied [14].

Firms and families in India and Nigeria, two of the eight nations with the huge financial losses, bear 43.8 percent and 51.6 percent of total tuberculosis spending, respectively [16]. Due to tuberculosis, 36 percent of Indonesian families endure devastating expenses [21]. Throughout southern India, 31 percent of families are affected by these expenditures [22]. *M. tuberculosis* is mostly a lung infection, but it can cause disease anywhere in the body. Moreover, tuberculosis can manifest itself in a variety of ways, ranging from microbial infections to life-threatening disease [23].

Latent tuberculosis infection (LTBI), which is asymptomatic and non-transmittable, or active tuberculosis infection (in active pulmonary TB), which is transmissible and detectable using conventional or molecular technologies, are the two conditions that constitute patients with tuberculosis. While those with pulmonary illness can have a persistent cough and haemorrhages (coughing up blood) in progressive disease, those with chronic tuberculosis can have similar signs and symptoms such as fever, fatigue, lack of appetite, and fat loss. On the other hand, asymptomatic patients with persistent, culture-positive illness may also be classified as having subclinical TB [23].

Modern tuberculosis medications are desperately needed to treat these resistant *M. tb* strains. In the last fifteen years, there has been steady progress in the development of new medications to treat tuberculosis, with several of these agents currently under investigation as part of standard treatment protocols [24]. Squaramides have been reported recently [25], tetrahydroisoquinolines [26] Pyrazolo[1,5-a] pyrimidines and 2,4-diaminoquinoline as possible blockers of Mtb's ATP production cycle [27].

Medicinal herbs, which have been used to treat ailments for millennia, provide a great hope for meeting these demands. As pure compounds or as a raw substance, these have been widely used. As active compounds or as a raw component, these have been widely used. Merely some few species of plants have had their therapeutic properties properly explored [28]. One of the few nations in the world with a unique wealth of medicinal plants and extensive traditional knowledge of using herbal medicine to treat a variety of disorders is India [29]. As of now, only a few numbers of plants have been studied in relation to mycobacteria, with *Salvia hypargeia, Euclea natalensis,* and other plants displaying anti-TB effect [30]. The rising global prevalence of *Mtb* highlights the urgent need for novel anti-tuberculosis chemicals and treatments.

Several Indian medicinal herbs, including *Glycyrrhiza glabra*, *Adhatoda zeylanica*, *Allium cepa*, *Allium sativum*, *Aloe vera*, *Acalypha indica* and *Zingiber officinale* were taken based on the previous report [29]. Currently, there is no ayush formulation is available with these plants for treating *Mtb.* Hence, in the present study, these plants were selected to find the potential phytocompounds for treating the infection caused by *M. tuberculosis* using *in silico* docking and ADMET studies.

MATERIALS AND METHODS

Ligand selection

Using literature & IMPPAT database [31] around 350 phytochemical compounds were selected from various Indian medicinal herbs, including *Glycyrrhiza glabra*, *Adhatoda zeylanica*, *Allium cepa*, *Allium sativum*, *Aloe vera*, *Acalypha indica* and *Zingiber officinale* [29] for treating Tuberculosis (Tb). The 3D structures of these compounds were obtained from the PubChem database [32] and Lipinski Rule of Five was tested using SwissADME [33]. The Lipinski Rule of Five was observed in 329 compounds, and these compounds were chosen for further study.

Target protein selection

From the literature, it was determined that the target protein, Serine/Threonine Protein Kinase, is a product of the Pkna gene [34]. The target protein's 3D structure was obtained from the PDB library (https://www.rcsb.org). This target protein's UniProt ID was retrieved from the Uniprot database [35].

Docking studies

PyRx software (Version 0.8, with Virtual Screening and Drug discovery features) was used to conduct docking experiments for the target protein Serine/threonine-protein kinase and the phytocompounds (ligands) [36]. Using this software, the target protein was further prepared for docking studies. The Open Babel option in PyRx was used to upload all of the ligands. Using the Vina wizard feature in PyRx, the grid was built and docking studies were performed. The binding affinity values were recorded in an Excel file. Discovery Studio (Version 2021 with enabling drug & ligand interaction and Visualisation features) was used to evaluate the results, and docked photos in 2D and 3D were collected. An outstanding outcome in the results is indicated by the lowest binding affinity.

ADMET and CYP properties

SwissADME was used to examine the ADMET and CYP characteristics of all the phytocompounds that interacted the best [33]. All the compounds with the best interactions were assessed using Lipinski, BBB (Blood-Brain Barrier), HIA (Human Intestinal Absorption), PGP (P-glycoprotein), XLogP3, TPSA (Topological Polar Surface Area), LogS, Fraction Csp3, Rotatable bonds, CYP enzyme inhibitor properties, Skin permeation, and Bioavailability score.

RESULTS

Ligand and Target Protein Selection

The PubChem database was used to get the 3D structure of ligands (phytocompounds). The 3D structure of target protein Serine/threonine-protein kinase was taken from the PDB database,

and its PDB ID is 4OW8. Figure 1 depicts the target protein's three-dimensional structure.

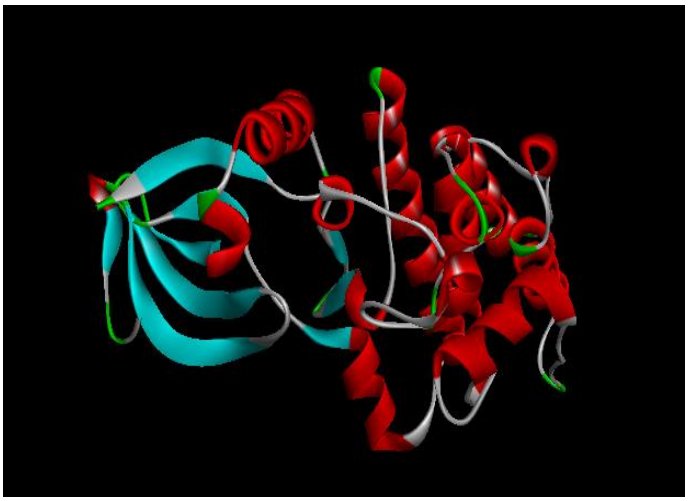

Figure 1: The 3D Structure of Target Protein Serine/threonine-protein kinase.

Docking Studies

PyRx 0.8 software was used to conduct docking experiments for the target protein Serine/threonine-protein kinase and the phytocompounds (ligands). From the results (Table 1) the following ten compounds showed very good interaction with the target protein and the target protein's interactions with phytocompounds in 2D and 3D are displayed in figure 2-9.

Table 1: Interaction of Phytocompounds with the target protein

S. No.	PubChem (CID)	Compound Name	Plant Name	Binding Affinity (Kcal/mol)	No. of Bonds	Interacting Residues	Bond Length (Å)
1.	99474	Diosgenin	*Allium cepa*	-9.6	8	LYS143 VAL98 VAL98 PRO102 ALA20 ALA40 LEU148 LEU148	2.98 5.18 2.19 5.28 4.07 5.00 5.16 5.10
2.	15558507	Agapanthagenin	*Allium sativum*	-9.6	4	LYS143 GLU96 VAL98 VAL98	3.06 2.61 1.24 1.86
3.	112111	Liquiritic acid	*Glycyrrhiza glabra*	-9.2	2	VAL98 GLU29	2.39 2.69
4.	442774	Hispaglabridin A	*Glycyrrhiza glabra*	-9.2	13	ALA20 ALA40 ALA163 VAL27 VAL98 LEU97 LEU148 MET24 LYS42 ASP159 ASP159 ILE19 GLY22	4.38 3.62 4.49 5.32 4.11 5.14 5.06 2.16 3.88 4.63 2.43 5.02 3.94
5.	5742590	Daucosterol	*Acalypha indica* and *Adhatoda zeylanica*	-9	11	ALA20 ALA40 VAL27 VAL98 LEU97	4.64 5.17 4.86 5.14 5.09

						LEU97 ILE19 ILE19 PRO102 TYR183 GLN182	5.00 3.85 4.88 5.29 2.64 2.51
6.	12310283	Glycyrrhetol	*Glycyrrhiza glabra*	-9	2	VAL98 GLU29	2.29 2.21
7.	107905	(-)-Epicatechin gallate	*Allium cepa* and *Glycyrrhiza glabra*	-8.9	9	ALA20 ALA40 LYS42 LYS143 GLU96 GLU96 VAL27 MET95 PRO102	4.00 4.57 2.34 2.66 2.44 2.29 4.60 5.33 4.31
8.	162350	Isovitexin	*Glycyrrhiza glabra*	-8.8	10	ALA20 ALA20 ASN146 LYS143 ASP159 MET24 VAL27 LEU148 ILE19 PRO102	4.11 3.62 2.20 3.31 3.25 1.93 4.95 5.06 5.31 5.46
9.	10494	Oleanolic Acid	*Allium cepa*	-8.7	2	GLY100 VAL98	2.62 2.46
10.	124052	Glabridin	*Glycyrrhiza glabra*	-8.7	9	ALA168 ALA194 ALA194 ALA194 ARG140 LYS164 LYS164 VAL166 ASP193	5.14 5.16 1.95 5.22 3.45 4.22 4.76 2.70 3.33
Synthetic Drug							
11.	5388906	Bedaquiline	Synthetic Drug	-7.8	8	ALA20 LEU97 LEU148 LEU148 ILE19 ILE19 VAL98 VAL98	4.71 4.34 3.86 5.36 3.62 3.75 5.48 2.95

From the results (Table 1), among other compounds, 10 compounds showed very good results with the target protein. Of which, the phytocompound Diosgenin shown excellent binding affinity (-9.6 Kcal/mol) with the amino acid residues LYS 143, VAL 98, PRO 102, ALA 20, ALA 40 and LEU 148 of the target protein. The phytocompound Agapanthagenin also provided a strong binding affinity of -9.6 Kcal/mol with the amino acid residues LYS 143, GLU 96 and VAL98. The binding affinity -9.2 Kcal/mol was observed between the phytocompound Liquiritic acid and the amino acid residues VAL 98 And GLU 29 of target protein. The phytocompound Hispaglabridin A gave good binding affinity of -9.2 Kcal/mol with the amino acid residues ALA 20, ALA 40, ALA 163, VAL 27, VAL 98, LEU 97, LEU 148, MET 24, LYS 42, ASP 159, ILE 19 and GLY 22 of the target protein. The phytocompound Daucosterol gave good binding affinity of -9 with the amino acid residues ALA 20, ALA 40,VAL 27,VAL 98,LEU 97,ILE 19,PRO 102,TYR 183 and GLN 182 of the target protein.

Further, the phytocompound glycyrrhetol demonstrated strong binding affinity with the target protein's amino acid residues VAL 98 and GLU 29 at -9 Kcal/mol. The target protein's amino acid residues ALA 20, ALA 40, LYS 42, LYS 143, GLU 96, VAL 27, MET 95, and PRO 102 were well-bound by the phytocompound (-)-Epicatechin gallate with a binding affinity of -8.9 Kcal/mol. The target protein's amino acid residues ALA 20, ASN 146, LYS 143, ASP 159, MET 24, VAL 27, LEU 148, and PRO 102 have a good binding affinity with the phytocompound isovitexin of -8.8 Kcal/mol.

Oleanolic Acid, a phytocompound, demonstrated strong binding affinity for the amino acid residues GLY 100 and VAL 98, measuring -8.7 Kcal/mol. The amino acid residues of the target protein that the phytocompound Glabridin had the lowest binding affinity for were ALA 168, ALA 194, ARG 140, LYS 164, VAL 166, and ASP 193. Moreover, the binding affinity of the Synthetic drug Bedaquiline with the target protein was -7.7 Kcal/mol and the interacted the amino acid residues were GLY100, ALA20, LEU97, LEU148, ILE19, VAL98. Besides, the binding affinity of all the ten compounds are high when compared to Synthetic drug Bedaquiline.

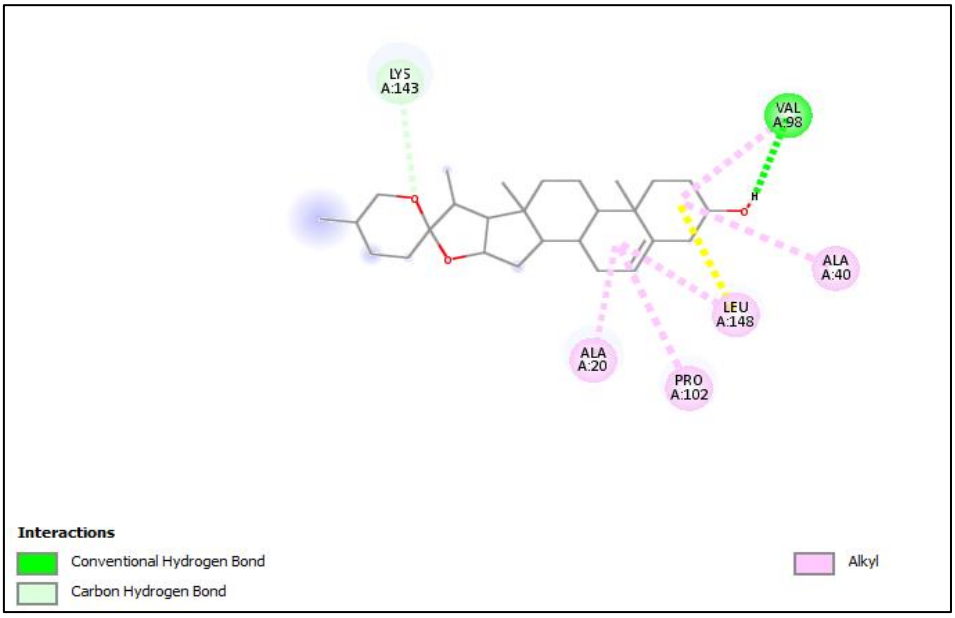

Figure 2: The 2D interaction of phytocompound Diosgenin with the target protein.

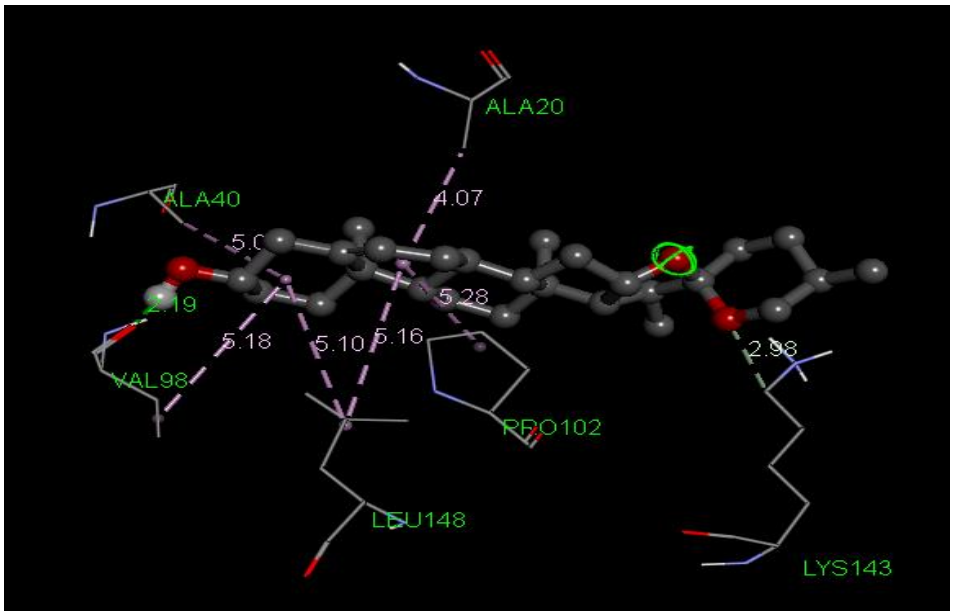

Figure 3: The 3D interaction of phytocompound Diosgenin with the target protein.

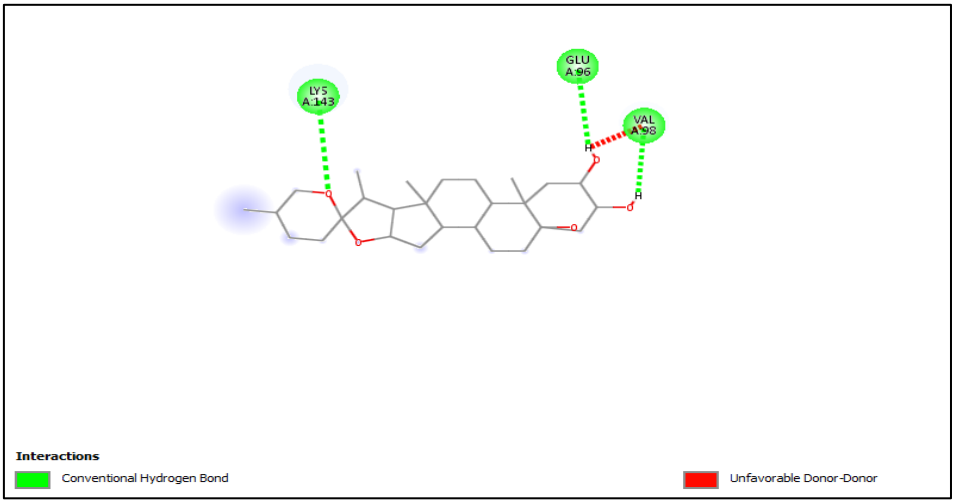

Figure 4: The 2D interaction of phytocompound Agapanthagenin with the target protein.

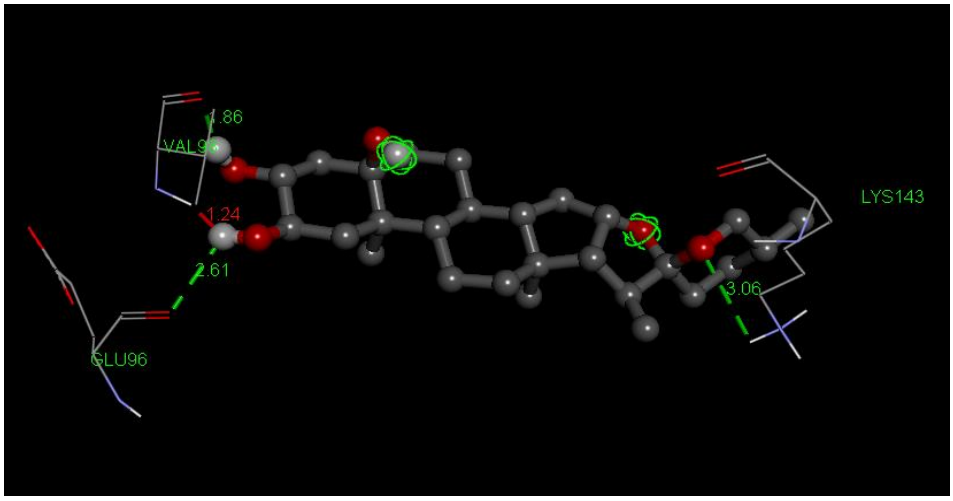

Figure 5: The 3D interaction of phytocompound Agapanthagenin with the target protein.

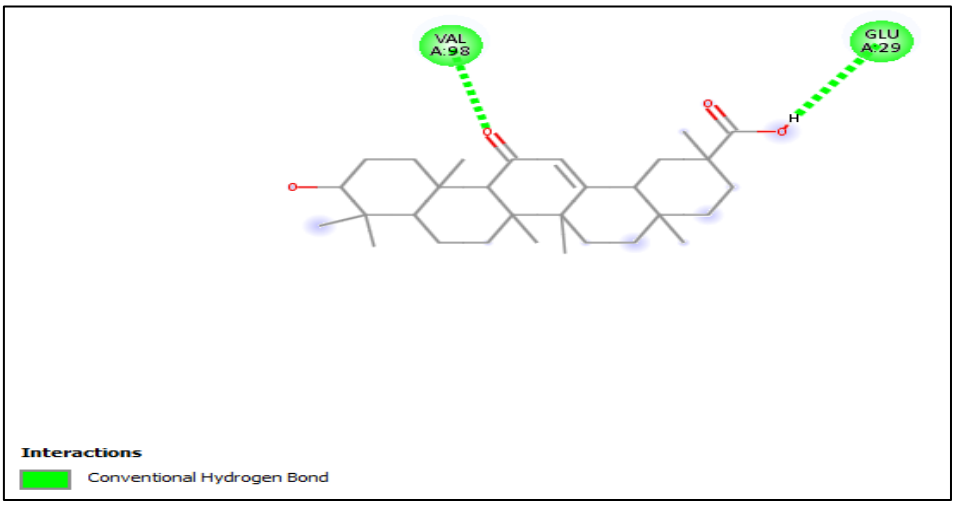

Figure 6: The 2D interaction of phytocompound Liquiritic acid with the target protein.

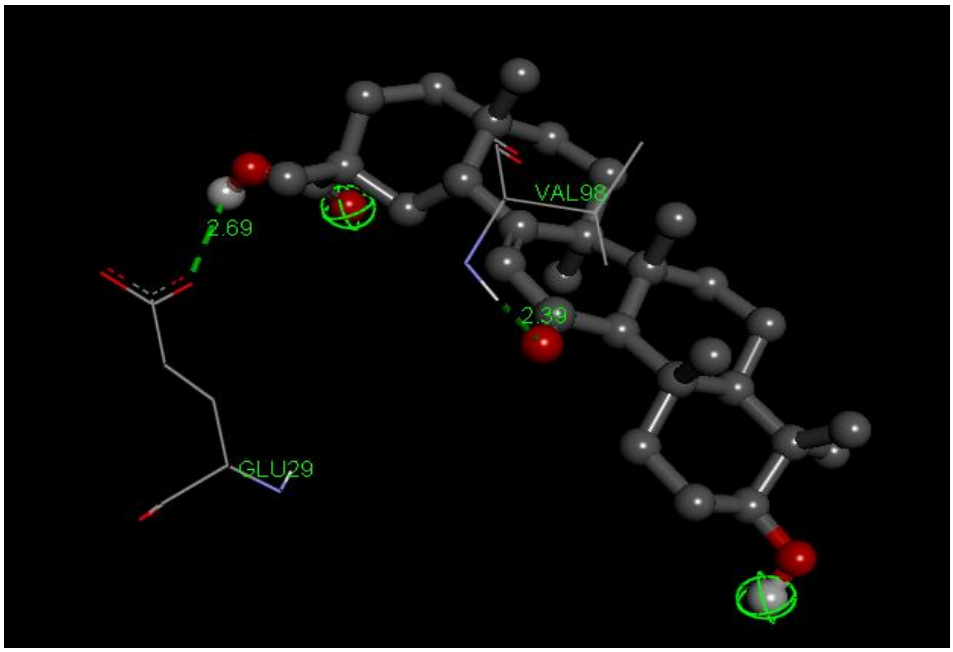

Figure 7: The 3D interaction of phytocompound Liquiritic acid with the target protein.

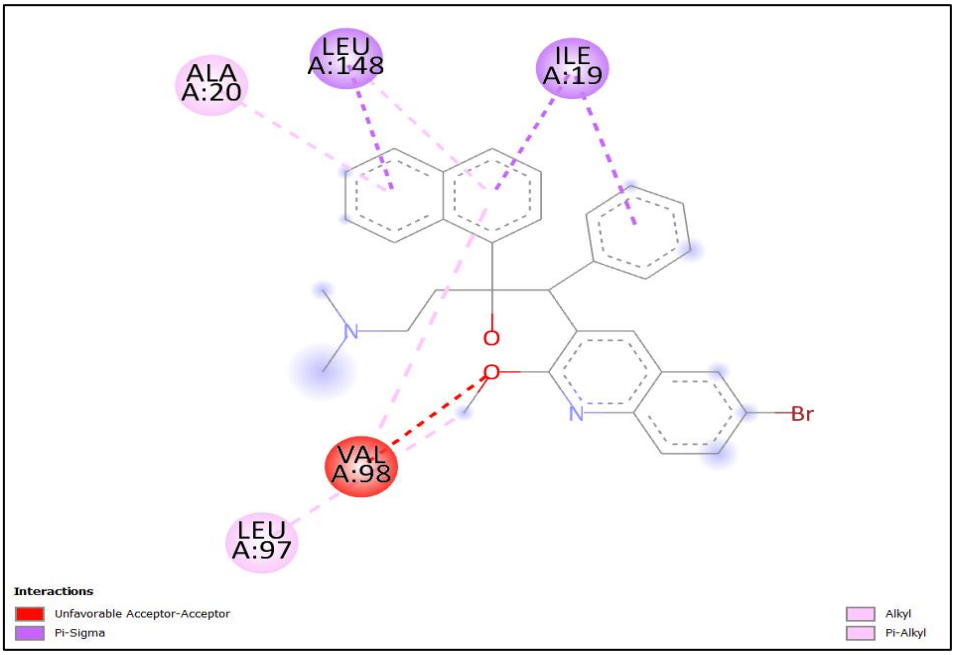

Figure 8: The 2D interaction of synthetic drug Bedaquiline with the target protein.

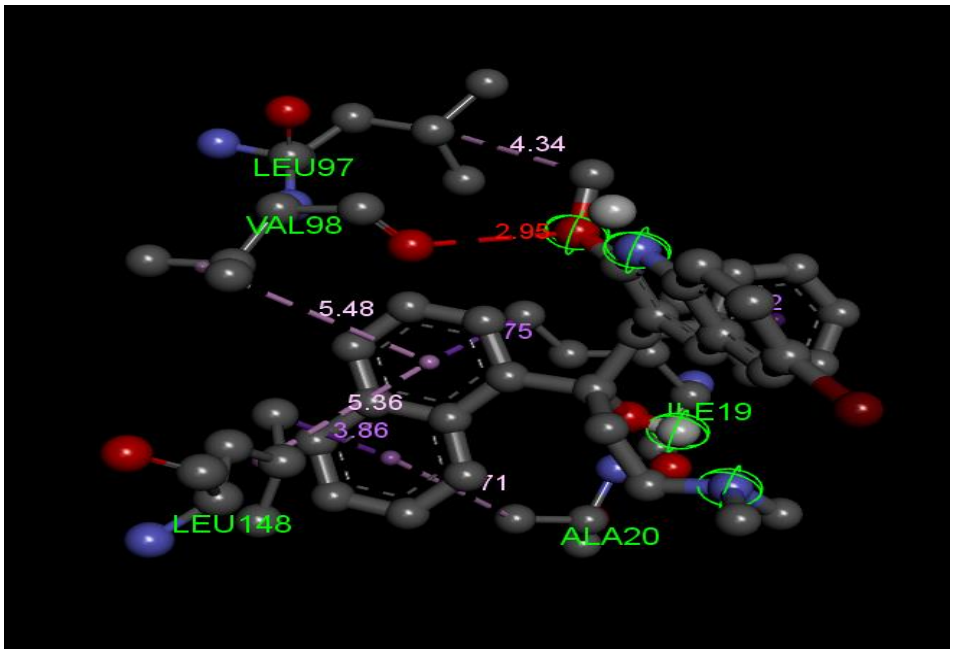

Figure 9: The 3D interaction of synthetic drug Bedaquiline with the target protein.

ADMET and CYP Properties

SwissADME was used in the current investigation to examine the ADMET qualities for the best phytocompounds and synthetic medication bedaquiline interactions, and the results were tabulated (Table 2). According to the findings, all of the best interacting phytocompounds follow the Lipinski rule of five, however the synthetic medication bedaquiline did not. The majority of the substances had high intestinal absorption and did not pass the blood-brain barrier (BBB). P-glycoprotein predicted that a large number of phytochemicals would be excreted from the CNS. Four of the ten compounds' XLogP3 values fell inside the acceptable range. The majority of the compounds' TPSA (Topological Polar Surface Area) and Log S values were within the permitted range. Two compounds' fraction Csp3 values were less than 0.25 for all of the compounds, whereas the values for the remaining compounds were higher than this cutoff. All compounds' rotatable bonds fell inside the permitted range.

The results of the boiled egg image (Figure 10) show the presence of the phytocompounds diosgenin (PubChem CID: 99474), hispaglabridin A (PubChem CID: 442774), and glabridin (PubChem CID: 124052) inside the egg yolk region, indicating that these phytocompounds can pass through the blood-brain barrier. The gastrointestinal tract is expected to passively absorb the phytocompounds agapanthagenin (PubChem CID: 15558507) and liqueritic acid (PubChem CID: 112111) that are found in the BOILED-Egg's white.

Furthermore, it is predicted that the P-glycoprotein will not remove certain phytochemicals from the central nervous system, including Diosgenin (PubChem CID: 99474), Hispaglabridin A (PubChem CID: 442774), Oleanolic Acid (PubChem CID: 10494), Daucosterol (PubChem CID: 5742590), (-)-Epicatechin gallate (PubChem CID: 107905) and Isovitexin (PubChem CID: 162350) whereas it is anticipated that the P glycoprotein will remove the phytochemicals Glabridin (PubChem CID: 124052), Agapanthagenin (PubChe m CID: 15558507), Liquiritic acid (PubChem CID: 112111), and the synthetic drug Bedaquiline (PubChem CID: 5388906) from the central nervous system.

The majority of the substances do not inhibit the CYP450 enzymes or cause any negative side effects, according to the results of CYP characteristics (Table

3). The phytocompounds Hispaglabridin A inhibited the CYP450 enzymes CYP2C19, CYP2C9 and CYP3A4. The phytocompound Glabridin inhibited the CYP450 enzymes CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4. The value of log K_p (Skin Permeant) is good for all compounds and A Bioavailability Score (ABS) is good for the most of the compounds.

From the results, (Table3) the compounds Diosgenin, Agapanthagenin, Liquiritic acid, Daucosterol, Glycyrrhetol, (-)-Epicatechin gallate, Isovitexin, Oleanolic acid did not inhibit any CYP450 enzymes. Compounds with a high log Kp negative value have limited ability to penetrate skin. According to this statement, the compounds Isovitexin, (-)-Epicatechin gallate, Agapanthagenin and Glabridin have less skin permeation ability.

Table 2: ADMET Properties of Phytocompounds

S. No	PubChem (CID)	Compound Name	Lipinski	BBB	HIA	PGP-	XLOGP3	TPSA (Å)	Log S (ESOL)	Fraction Csp3	Rotatable Bonds
1	99474	Diosgenin	Yes	Yes	High	Yes	5.67	38.69	-5.98	0.93	0
2	15558507	Agapanthagenin	Yes	No	High	No	4.09	79.15	-5.20	1.00	0
3	112111	Liquiritic acid	Yes	No	High	No	5.49	74.60	-6.15	0.87	1
4	442774	Hispaglabridin A	Yes	Yes	High	Yes	5.82	58.92	-6.05	0.36	3
5	5742590	Daucosterol	Yes	No	Low	Yes	7.74	99.38	-7.70	0.94	9
6	12310283	Glycyrrhetol	Yes	No	High	Yes	5.57	57.53	-6.11	0.90	1
7	107905	(-)-Epicatechin gallate	Yes	No	Low	Yes	1.53	177.14	-3.70	0.14	4
8	162350	Isovitexin	Yes	No	Low	Yes	0.21	181.05	-2.84	0.29	3
9	10494	Oleanolic Acid	Yes	No	Low	Yes	7.49	57.53	-7.32	0.90	1
10	124052	Glabridin	Yes	Yes	High	No	3.89	58.92	-4.61	0.30	1
Synthetic Drug											
11.	5388906	Bedaquiline	No	No	Low	No	7.21	45.59	-7.82	0.22	8

Note: Obey Lipinski: yes, that's fantastic, no violations, Blood-Brain arrier: Yes denotes favor, Human Intestinal Absorption (HIA): High indicates favorable PGP- (Molecules expected not to be excreted from the CNS by P-glycoprotein): XLOGP3 score between 0.7 and +5.0 indicates good lipophilicity. Polarity: Good is defined as TPSA between 20 and 130 $Å^2$. Water Solubility (Log S scale: Insoluble = -10, Poor = -6, Moderate = -4, Soluble = -2, Very = 0, Highly): Log S value less than 6 indicates good, Saturation (Fraction Csp3): Good saturation is defined as a fraction of carbons in the sp3 hybridization that is not less than 0.25. Flexibility (Rotatable Bonds): Good if there are no more than 9 rotatable bonds.

Table 3: Cytochrome P450 Properties of Phytocompounds

S. No.	PubChem (CID)	Compound Name	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log K_p (Skin permeation) (cm/s)	A Bioavailability Score (ABS)
1	99474	Diosgenin	No	No	No	No	No	-4.80	0.55
2	15558507	Agapanthagenin	No	No	No	No	No	-6.13	0.55
3	112111	Liquiritic acid	No	No	No	No	No	-5.27	0.85
4	442774	Hispaglabridin A	No	Yes	Yes	No	Yes	-4.56	0.55
5	5742590	Daucosterol	No	No	No	No	No	-4.32	0.55
6	12310283	Glycyrrhetol	No	No	No	No	No	-5.13	0.55
7	107905	(-)-Epicatechin gallate	No	No	No	No	No	-7.91	0.55
8	162350	Isovitexin	No	No	No	No	No	-8.79	0.55
9	10494	Oleanolic Acid	No	No	No	No	No	-3.77	0.85
10	124052	Glabridin	Yes	Yes	Yes	Yes	Yes	-5.52	0.55
Synthetic Drug									
11.	5388906	Bedaquiline	Yes	No	No	Yes	Yes	-4.57	0.17

Note: Yes, which indicates that the substance inhibits the CYP450 enzymes and causes unexpected negative effects; No indicates that the substance has no negative effects and does not inhibit the CYP450 enzymes; The molecule is less skin permeable the more negative the log Kp is; ABS 0.55 indicates that it satisfies the rule of five, whereas 0.17 indicates that it does not.

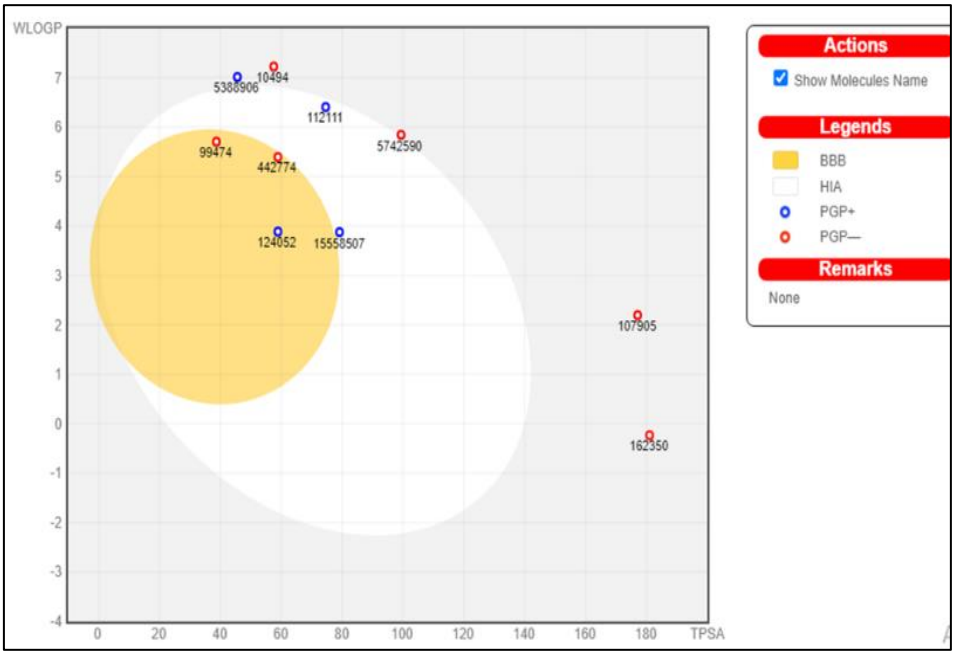

Figure 10: Boiled Egg for all compounds.

Note: BBB: It is envisaged that some chemicals in the yolk of the BOILED-Egg will passively flow over the blood-brain barrier. Molecules in the white of BOILED-Eggs called HIA-Points are thought to be passively absorbed by the gastrointestinal tract. PGP+: Blue dots indicate compounds that the P glycoprotein predicts will be eliminated from the central nervous system. PGP-: Red dots indicate compounds that the P-glycoprotein predicts won't be eliminated from the central nervous system.

DISCUSSION

A recent study reported that seven compounds (Arjunolic acid, Caffeic acid, Cinnamic acid, Epifriedelinol, Friedelin, Hexahydroxydiphenic acid, and Sinapic acid) from the Bark of *Syzygium cordatum* were identified as potential inhibitors for *Mycobacterium tuberculosis* because they exhibit better molecular interactions such as Arjunolic acid (−8.2 kcal/mol), Caffeic Acid (−5.8 kcal/mol), Cinnamic acid (−5.6 kcal/mol), Epifriedelinol (−8.9 kcal/mol), Friedelin (−8.8 kcal/mol), Hexahydroxydiphenic acid (−6.6 kcal/mol) and Sinapic acid (−5.3 kcal/mol) [37].

According to another study, stigmasterol and triterpenoid glycoside had strong binding affinities and were successfully docked with the five possible targets. which Triterpenoid Glycoside binds to in order to inhibit the function of MAPK1 and MAPK14. Tuberculosis is inhibited by stigmasterol when MAPK1 and TNF are present [38].

The results from a study conducted by Arulmozhi (2018) revealed that *Staphylococcus epidermidis*, *Enterococcus faecallis*, *Salmonella paratyphi*, *Shigella dysenteriae*, *Candida albicans* and *Mycobacterium tuberculosis* inhibited efficiently by the ethyl acetate extract of *Capparis zeylanica* leaves and it shows better activity when compared to standard drugs Gentamycin and Ketocozole[39]. The analysis done by Das (2020) showed the phytochemicals in *Mucuna pruriens* can stop the oxidation of fatty acids in the microbial cell, effectively deactivating the enzymatic metabolic activity and ending the life cycle of Mycobacterium TB [40]. According to a study by El Omari (2019), the development of *Mycobacterium spp.* Strains was completely prevented by the essential oils from *Micromeria barbata*, *Eucalyptus globulus*, and *Juniperus excelsa* [41].

In a research study conducted by Gupta (2018), Significant anti-mycobacterial activity was observed for eleven plants collected around Madhya Pradesh (MP), India viz., *Alstonia scholaris, Glycyrrhiza glabra, Holorrhena antidysentrica, Mallotus philippensis, Eulophia nuda, Cocculus hirsutus, Pueraria tuberosa, Cyperus rotundus, Curcuma caesia, Sphaeranthus indicus* and *Plumbago zeylanica* thus supporting the fact that these plants are used for anti-TB activity in the tribal areas of M.P., India [42]. The research analysis done by Hernández-García (2018) justified the ethnomedical use of isolated compounds from *Acacia farnesiana* fruits for the treatment of tuberculosis and dysentery [43].

According to the findings of Jethva's (2020) study effort Aqueous extracts of *O. sanctum, A. vasica, L. reticulata,* and *C. hirsutus* exhibit strong antimycobacterial TB activity, with respective *Mycobacterium tuberculosis* inhibition percentages of 71.26%, 74.58%, 75.21%, and 80.26% [44]. For the first time, it was demonstrated in a study by Martini (2020) that Artemisia extracts have a potent bactericidal effect against *Mycobacterium tuberculosis* (Mtb). It appears that *Artemisia annua* extracts kill Mtb through a mixture of Artemisinin (AN) and other biochemicals since their killing impact was significantly stronger than equal doses of pure Artemisinin (AN) [45]. According to Ngadino (2018), *Curcuma xanthorrhiza* ethanol extract had antimycobacterial activities with a Minimal Inhibitory Concentration (MIC) value of 1600 g/ml and a Minimal Bactericidal Concentration (MBC) value of 3200 g/ml for *Mycobacterium tuberculosis* H37Rv [46].

Similarly, according to the current *in silico* docking research, the phytocompounds Diosgenin from *Allium cepa*, Agapanthagenin from *Allium sativum*, and Liquiritic acid from *Glycyrrhiza glabra* interacted with the target protein Serine/Threonine Protein Kinase and gave very good binding affinity. Hence, the present study concludes that the above Indian medicinal plants may have the potential to act as a remedy for treating Tuberculosis.

CONCLUSION

In the present study, the phytocompounds from different Indian medicinal plants and the target protein Serine/Threonine Protein Kinase were subjected for *in silico* docking analysis to find the potential inhibitors for Tuberculosis. In which, ten compounds showed better results than the Synthetic drug Bedaquiline. Toxicity studies were done for the 10 best-interacted phytocompounds and the results showed that the compounds had very less toxicity. Of which, the phytocompounds Diosgenin, Agapanthagenin, and Liquiritic acid showed highest binding affinity among the other phytocompounds.

Hence, the present study concludes that the Diosgenin from *Allium cepa*, Agapanthagenin from *Allium sativum* and Liquiritic acid from *Glycyrrhiza glabra* may give a potential effect in the treatment of Tuberculosis.

Abbreviations

Mtb: *Mycobacterium tuberculosis*; LTBI: Latent TB Infection; BBB: Blood - Brain Barrier; HIA: Human Intestinal Absorption; PGP: P-glycoprotein; TPSA: Topological Polar Surface Area; CNS: Central Nervous System.

Conflict of Interest

The authors declare that they have no conflict of interest.

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